

Health Technology Review

Dosing of Immune Checkpoint Inhibitors

Authors: Shahab Sayfi, Quenby Mahood, Yonda Lai, Jasmeen Dourka, Rodrigue Ndabashinze, Rebecca Raj, Dipika Neupane, Kelvin Chan, Andrea C. Tricco

PROSPERO registration number: 1071290

This health technology review was conducted by the Knowledge Translation Program through the Post-Market Drug Evaluation CoLab Network.

Key Messages

What Is the Issue?

- Immune checkpoint inhibitors (ICIs) are cancer therapies that boost the immune system's ability to fight cancer cells.
- ICIs differ in their dosing regimens (e.g., in terms of the use of fixed versus weight-based dosing and the length of dosing intervals). The dosing approach may influence patient outcomes.
- This report assessed clinical outcomes for the following ICIs: atezolizumab, avelumab, cemiplimab, dostarlimab, durvalumab, ipilimumab, nivolumab, pembrolizumab, and tremelimumab.

What Did We Do?

- We reviewed and summarized the best available evidence comparing different dosing regimens for eligible ICIs.
- We summarized the clinical safety, efficacy, and effectiveness outcomes, and the pharmacokinetic and pharmacodynamic outcomes.
- We employed a narrative (descriptive) approach, rather than a quantitative synthesis (meta-analysis), because of the large variation in design, populations, and outcomes across the studies.

What Did We Find?

- Most comparative evidence in our data relates to pembrolizumab and nivolumab, with less evidence available for the other ICIs and comparators.
- Across studies evaluating fixed dosing versus weight-based dosing, survival and progression outcomes were often similar, and toxicity rates were usually comparable.
- Evidence for pharmacokinetic and pharmacodynamic outcomes suggests that fixed-dose regimens may result in average drug exposure similar to that achieved with weight-based dosing, whereas extended-interval regimens may produce higher peak concentrations and lower trough concentrations.

What Does It Mean?

- For several ICIs, particularly pembrolizumab and nivolumab, different dosing regimens (fixed versus weight-based) may result in similar overall outcomes. However, our confidence in these findings is limited due to the limited availability of evidence from large randomized controlled

Key Messages

trials and the considerable amount of evidence from inconclusive nonrandomized studies.

- Across multiple ICIs (e.g., avelumab, cemiplimab, durvalumab, pembrolizumab, nivolumab), the available evidence generally suggests no consistent or clinically meaningful differences in safety or efficacy between fixed and weight-based dosing, although this conclusion is limited by risk of bias.
- Pharmacokinetic and pharmacodynamic evidence indicates that differences in average drug exposure between fixed dosing and weight-based dosing are mainly peak and trough concentration differences that are unlikely to be clinically meaningful.
- For some ICIs (e.g., atezolizumab, dostarlimab, tremelimumab), evidence remains sparse or insufficient, and no firm conclusions can be drawn regarding comparative efficacy or safety between dosing strategies.

Table of Contents

Abbreviations.....	7
Introduction and Rationale	9
Background.....	9
Policy Issue.....	9
Purpose	10
Research Questions.....	10
Protocol Development	11
Opportunities for Feedback.....	11
Methods.....	11
Literature Search	11
Selection Criteria.....	12
Population and Subgroups.....	13
Intervention and Comparators	13
Outcomes Definition.....	13
Study Designs.....	13
Exclusion Criteria	13
Study Selection Process	14
Quality Assessment	14
Data Extraction	15
Data Analyses and Synthesis	15
Results.....	16
Selection of Primary Studies.....	16
Study and Patient Characteristics.....	18
Critical Appraisal	19
Findings	22
Limitations	47
Conclusions and Implications for Decision- or Policy-Making.....	48

Conclusions	48
Comparison With the Previous INESSS Report: Key Differences and Similarities.....	49
ICI-Specific Conclusions and Synthesis With Findings From the INESSS Report	50
Authors and Contributors.....	64
Authors.....	64
Contributors	65
Conflicts of Interest	65
References	66
Appendix 1: Literature Search Methods.....	70
Appendix 2: Study Characteristics	77
Appendix 3: Summary of Efficacy, Effectiveness, and Safety Outcomes.....	86
Appendix 4: Summary of Pharmacodynamic and Pharmacokinetic Outcomes	122
Appendix 5: List of Included Studies	141
Appendix 6: List of Excluded Studies	145
Appendix 7: PRISMA Checklist.....	165
Appendix 8: Overlap Between Flagged Systematic Reviews.....	168

List of Tables

Table 1: Selection Criteria.....	12
Table 2: Summary of Intervention and Patient Characteristics From Primary Studies (n = 38)	18
Table 3: Risk-of-Bias Assessment Using RoB 2 for the Included RCTs	20
Table 4: Risk-of-Bias Assessment Using ROBINS-I for the Included Nonrandomized Studies.....	20
Table 5: Comparison of INESSS Recommendations and CDA-AMC Findings on ICI Dosing Strategies	59
Table 6: Search Strategy Yield Summary	70
Table 7: Search Strategy — Ovid MEDLINE(R) ALL — 1946 to July 29, 2025	70
Table 8: Search Strategy — Embase Classic+Embase — 1947 to July 25, 2025	72
Table 9: Search Strategy — Cochrane Database of Systematic Reviews — 2005 to July 23, 2025	73
Table 10: Search Strategy — Cochrane Central Register of Controlled Trials — June 2025	75
Table 11: Legends Within the Search Strategies Across the Databases.....	76
Table 12: Study Characteristics	77
Table 13: Summary of Efficacy, Effectiveness, and Safety Outcomes	86
Table 14: Summary of Pharmacodynamic and Pharmacokinetic Outcomes.....	122
Table 15: Included Studies	141
Table 16: Excluded Studies	145
Table 17: PRISMA Checklist.....	165
Table 18: Overlap in Relevant Primary Studies Between Selected Systematic Reviews.....	168

List of Figures

Figure 1: PRISMA Flow Chart of Selected Reports.....	17
Figure 2: Risk-of-Bias Assessment Using AMSTAR 2 for the Included Reviews	22

Abbreviations

AE	adverse event
AMSTAR 2	A MeaSurement Tool to Assess Systematic Reviews 2
AUC	area under the concentration–time curve
AUC_{0–t}	area under the concentration–time curve from time 0 to last measurable time point
AUC_{ss}	area under the concentration–time curve at steady state
C_{avg}	average (mean) concentration
C_{avgd28}	average concentration over 28 days
C_{avgss}	average concentration at steady state
CDA-AMC	Canada’s Drug Agency
C_{max}	maximum concentration
C_{max1}	maximum concentration after first dose or first cycle
C_{maxss}	maximum concentration at steady state
C_{min}	minimum (trough) concentration
C_{min-d28}	minimum concentration over 28 days (study-defined)
C_{minss}	minimum (trough) concentration at steady state
CR	complete response
C_{trough}	trough concentration
CV	coefficient of variation
DL	dose level
ER	exposure-response
FDT	fixed-dose therapy, or fixed-dose treatment (study-defined)
ICI	immune checkpoint inhibitor
INESSS	Institut national d’excellence en santé et en services sociaux
IO	immuno-oncology
irAE	immune-related adverse event
IRR	infusion-related reaction
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	pharmacodynamics
pERC	pan-Canadian Oncology Drug Review Expert Review Committee
PFS	progression-free survival
PK	pharmacokinetics

PK/PD	pharmacokinetics and pharmacodynamics
PopPK	population pharmacokinetic
PR	partial response
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCC	renal cell carcinoma
RCT	randomized controlled trial
ROBINS-I	Risk Of Bias In Non-randomized Studies - of Interventions
rHuPH20	recombinant human hyaluronidase PH20
SC	subcutaneous
SD	standard deviation
TRAE	treatment-related adverse event
UC	urothelial carcinoma
WAT	weight-adjusted therapy (study-defined)

Introduction and Rationale

Background

Main Take-Aways

Immune checkpoint inhibitors are cancer therapies that enhance the immune system's ability to detect and destroy tumour cells. They are used to effectively treat many cancers but may also cause immune-related side effects. Immune checkpoint inhibitor dosing strategies are not limited to a single approach — they may be administered in fixed doses or weight-based doses, and the amount of time between each dose can vary. The dosing strategy used may impact clinical outcomes.

The burden of cancer in Canada remains considerable, with approximately 247,100 new cases and roughly 88,100 deaths estimated in 2024.¹ Cancer care, in practice, often involves combinations of surgery, radiation, systemic therapies (such as chemotherapy and targeted therapies), and immunotherapy, depending on the cancer type, stage, and patient values and preferences.²

Immune checkpoint inhibitors (ICIs), a subclass of immunotherapy or immuno-oncology (IO) drugs, have revolutionized the treatment strategies for various cancers. ICIs restore the immune system's ability to recognize and subsequently destroy tumour cells.³ The mechanism of action of ICIs, which are typically a type of monoclonal antibody, involves blocking the PD-1/PD-L1 and CTLA-4 immune checkpoint pathways — mechanisms that tumours exploit to suppress immune responses. Key agents include anti-PD-1 drugs (e.g., nivolumab, pembrolizumab, cemiplimab, dostarlimab), anti-PD-L1 drugs (e.g., atezolizumab, avelumab, durvalumab), and anti-CTLA-4 drugs (e.g., ipilimumab, tremelimumab). These therapies are used across various settings of cancer care (neoadjuvant, adjuvant, and metastatic) for malignancies such as melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and Hodgkin lymphoma.⁴

There are, however, immune-related adverse events (irAEs) and autoimmune complications associated with the use of ICIs that could impact patients with pre-existing autoimmune conditions.⁵ Dosing regimens for ICIs are diverse, with some drugs approved for fixed dosing, others for weight-based dosing, and some offering both options. This variability, as shown by the evidence in the literature, has led to differences in pharmacoeconomic implications, clinical effectiveness, and safety in different patient populations.

Policy Issue

Main Take-Aways

Policies on ICI dosing in Canada have evolved with the emergence of novel ICIs and combination therapies. Jurisdictions have requested a review of the most recent evidence to inform ICI dosing policies, specifically comparing fixed doses with weight-based doses (with or without a weight cap).

Before 2019, there was inconsistency in the dosing of ICIs recommended by the pan-Canadian Oncology Drug Review Expert Review Committee (pERC), which usually mirrored what the pivotal trials used.

Jurisdictions asked Canada's Drug Agency (CDA-AMC) to review the evidence comparing weight-based and fixed dosing for nivolumab and pembrolizumab, which resulted in the publication of a Technology Review on the dosing and timing of IO drugs.⁶ This led to broad policy changes implementing the use of weight-based dosing up to a cap for nivolumab and pembrolizumab.

Since then, more ICIs have been recommended for public reimbursement by pERC, and various combinations have also become available. To further inform their policy, jurisdictions used a review prepared by l'Institut national d'excellence en santé et en services sociaux (INESSS)⁷ that encompassed additional ICIs and indications. The evidence reviewed in this report was dated up to June 2022. Jurisdictions are requesting that CDA-AMC update this review to synthesize the latest evidence to inform the deliberations of local expert committees regarding optimal dosing of ICIs.

Policy Question

1. Should a weight-based dose (with or without a cap) or a fixed dose of ICIs be used for some or all oncology indications?

Purpose

Main Take-Aways

This report summarizes the best available evidence published since 2020 comparing weight-based and fixed-dose ICI regimens in oncology. It evaluates both clinical and health system outcomes (benefits, harms, and system impacts), in addition to pharmacokinetics and pharmacodynamics and exposure-response evidence that helps compare dosing approaches, including studies of subcutaneous formulations if available.

1. Through a review of the literature since 2020, assess the clinical evidence comparing weight-based versus fixed-dose regimens of oncology ICIs, including studies evaluating subcutaneous formulations.
2. Through a review of the literature since 2020, assess the pharmacometric properties, including pharmacokinetic parameters and exposure-response models, that allow comparison of weight-based and fixed dosing for oncology ICIs, including studies evaluating subcutaneous formulations.

Research Questions

The project addressed the following research questions:

1. What are the comparative clinical efficacy, effectiveness, and safety of dosage regimens (weight-based with or without a cap versus fixed-dose, considering various dosing frequencies) for ICI drugs across all funded indications?

2. What are the comparative pharmacokinetics and pharmacodynamics of dosage regimens (weight-based with or without a cap versus fixed-dose, considering various dosing frequencies) for ICI drugs across all funded indications?

Protocol Development

A review protocol was developed a priori and was followed throughout the review process. The protocol and review followed the methods of the Cochrane Handbook for Systematic Reviews for Interventions, and the reporting followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist for systematic reviews.⁸

We registered the project in advance in PROSPERO (Centre for Reviews and Dissemination, University of York) (PROSPERO registration number: CRD1071290).⁹

Opportunities for Feedback

Interested parties were given the opportunity to comment on the proposed project scope that informed this report. They were also given the opportunity to provide feedback on the draft included studies list and the draft report. Unpublished data identified as part of the feedback process was only included if the source of data was in the public domain.

Methods

Literature Search

We conducted a comprehensive literature search in July 2025 across MEDLINE, Embase, and the Cochrane Library to identify relevant studies on weight-based versus fixed-dose IO therapies. The search was informed by a previous search as described in an INESSS report⁷ and a CDA-AMC (formerly CADTH) Optimal Use report.⁶ The literature searches were comprised of concepts related to IO therapies, dosage, and pharmacokinetics (available in [Appendix 1](#)). While the INESSS report⁷ was updated to June 2022, we extended the searches to publications from January 2020, which was when the original INESSS search was conducted, to the present. While the INESSS report⁷ was updated to June 2022, it did not include 2 additional drugs of interest — ipilimumab and tremelimumab. Because these 2 drugs were not included in the original search, a secondary search focusing on these drugs was conducted and limited to publication dates from January 1, 2020, to the present. The searches were limited to English- and French-language documents. Conference abstracts were excluded from the Embase search. The searches were executed by an experienced information specialist and peer-reviewed by another using the PRESS (Peer Review of Electronic Search Strategies) checklist, and refined accordingly.¹⁰ Complete literature searches for each database are available in [Appendix 1](#).

We identified grey literature using the CDA-AMC Grey Matters checklist,¹¹ covering health technology assessments, regulatory reports, and clinical trial registries. Additional sources were identified by handsearching references and preprint repositories.

We searched MEDLINE, Embase, and the Retractions Watch Database in January 2026 to identify retracted publications. None of the included studies were identified as retractions.

Selection Criteria

We included studies that met the population, intervention, comparator, and study design criteria. Studies were not included or excluded only on the basis of reported outcomes.

Table 1: Selection Criteria

Criteria	Description
Population	Adult patients with cancer matching 1 of the approved indications for which ICIs are recommended for reimbursement.
Interventions	Fixed dosing with: • atezolizumab • avelumab • cemiplimab • dostarlimab • durvalumab • ipilimumab • nivolumab • pembrolizumab • tremelimumab • any route of administration (including IV and subcutaneous) and any dosing schedule Combinations of an ICI with 1 or more other anticancer drugs are in scope if they are recommended by pERC.¹² Note: For ipilimumab, dosing is tumour-specific and based on findings from phase II dose-finding trials. As such, studies evaluating fixed vs. weight-based dosing may be limited or unavailable. Inclusion will depend on whether eligible comparative data exist.
Comparators	Weight-based dosing (with or without a cap) of the same drugs as listed previously.
Outcomes	RQ1: • Clinical efficacy and effectiveness (e.g., overall response rate, progression-free survival, overall survival) • Safety (e.g., all-grade AEs, grade 3+ AEs, all-grade SAEs, grade 3+ SAEs, withdrawals due to AEs, or deaths due to AEs) • Exposure-response relationship • Exposure-safety relationship • System- and implementation-related outcomes (e.g., preparation time, risk of repetitive strain injuries for staff, resource use, staff workflow or satisfaction) RQ2: • Drug exposure (e.g., AUC_{ss}, C_{avg1}) • Pharmacodynamic parameters (e.g., receptor or target occupancy)

Criteria	Description
Study design	RQ1: • Phase I to IV randomized controlled trials • Nonrandomized studies • Dose- or exposure-response analyses • Systematic reviews of these studies RQ2: • Phase I to II studies with PK/PD analyses • Population pharmacokinetic modelling or simulation studies • Systematic reviews of these studies • Non-English publications and conference abstracts are excluded

AE = adverse event; AUC_{ss} = area under the concentration–time curve at steady state; C_{avg1} = average concentration after first dose or first cycle (study-defined); ICI = immune checkpoint inhibitor; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PK/PD = pharmacokinetic and pharmacodynamic; RQ = research question; SAE = serious adverse event; vs. = versus.

Population and Subgroups

We included studies that enrolled adult patients with cancer receiving an eligible ICI drug for an approved indication for which the drug is recommended for reimbursement.

Intervention and Comparators

We compared fixed (“flat”) dosing versus weight-based dosing (with or without a cap) for eligible ICIs (any route and schedule), including in-scope, pERC-recommended combination regimens. We excluded studies not directly comparing fixed versus weight-based dosing, non-English publications, and conference abstracts

Outcomes Definition

For research question 1, we assessed clinical efficacy, effectiveness and safety (e.g., overall survival [OS], progression-free survival [PFS], objective response rate [ORR], and adverse events [AEs]), plus exposure-response (ER) and/or safety and system outcomes when reported. For research question 2, we assessed pharmacokinetics and pharmacodynamics (PK/PD) outcomes (drug exposure measures and pharmacodynamic parameters) when reported.

Study Designs

For research question 1, we included randomized controlled trials (RCTs) and comparative nonrandomized studies (and relevant systematic reviews), plus dose-response and ER analyses. For research question 2, we included PK/PD studies and population pharmacokinetic (PopPK) modelling and/or simulation studies (and relevant systematic reviews).

Exclusion Criteria

We excluded articles if they did not meet the selection criteria ([Table 1](#)), were duplicate records or publications, were published before 2020, were non-English, or were conference abstracts.

Study Selection Process

Search results were imported into DistillerSR, online software for systematic review management.¹³ The research team pilot-tested the inclusion criteria ([Table 1](#)) on a random sample of 50 titles and abstracts (or citations) for the first level of screening, and 25 full-text articles for the second level. Once a minimum agreement of 75% was achieved, 2 reviewers independently screened titles and abstracts for relevance to the clinical research questions. Full-texts of potentially relevant articles were retrieved and independently assessed for possible inclusion based on the predetermined selection criteria. The 2 reviewers then compared their chosen included and excluded studies and discussed their conflicts until consensus was reached. If a consensus was not reachable, a third person (the principal investigator and a clinical expert) helped with the judgment. The study selection process was presented in a PRISMA 2020 flow chart ([Figure 1](#)).⁸

Quality Assessment

We applied the revised Cochrane risk of bias tool for randomized trials (ROB 2) to each of the included RCTs that reported at least 1 outcome of interest.¹⁴ The ROB 2 tool contains 6 unique domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other issues.

In a ROB table, each domain includes 1 or more signalling questions, and we created a form that was consistent with the ROB 2 template. The first part of the form characterizes the study's information; the second part involves judgments related to methodological quality of the study by answering prespecified questions about the adequacy of the study in relation to the item, including a judgment of low, high, or unclear risk of bias.

For each unique RCT, we evaluated the quality of the original primary publication while consulting details from supporting literature (e.g., published protocol, ClinicalTrials.gov records, and appendices), as necessary.

We applied the Risk Of Bias In Nonrandomized Studies - of Interventions (ROBINS-I) tool for nonrandomized intervention studies.¹⁵ The tool assesses risk of bias across 7 domains: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result. Judgments were made for each domain and summarized as an overall ROBINS-I risk-of-bias judgment for each study.

We employed the updated version of A MeaSurement Tool to Assess Systematic Reviews (AMSTAR 2) tool for systematic reviews.¹⁶ This tool contains 16 items and allows a thorough methodological evaluation of systematic reviews, from early stages (e.g., research question development and the defining of Population, Intervention, Comparator, Outcome [PICO] elements) through to the conduct of searching and screening, as well as data analysis and interpretation.

Before full assessment, we pilot-tested each risk-of-bias tool on a sample of 1 or 2 included studies to ensure consistent interpretation of criteria and clarify uncertainties. To promote agreement, we discussed the

conflicts in detail. All quality assessments were conducted by 1 reviewer and verified by a second reviewer. Conflicts were resolved by discussion or the involvement of a third reviewer.

Following the risk-of-bias assessments, we used ROBINS-I-style tables ([Table 3](#), [Table 4](#), and [Figure 2](#)) to visualize the judgments using traffic-light displays.¹⁷

Data Extraction

We extracted the information using a standardized data abstraction form. We pilot-tested the data extraction form using a sample of 5 included studies to ensure consistency in data interpretation, refine the abstraction items, and improve clarity. We used the feedback from the pilot test to revise the form before commencing full data extraction.

For each included study, we primarily extracted data from the original publication, with supplementary information obtained from companion reports and trial registry records, when needed. When multiple publications for a single study were available (e.g., online appendices or companion publications reporting different outcomes or follow-up), the most recently adjudicated results for each outcome were extracted, with preference given to peer-reviewed sources.

The abstraction form captured data across 5 domains: study characteristics, participant characteristics, dosing and intervention characteristics, clinical efficacy and safety outcomes, and PK/PD outcomes. Extracted items encompassed information on study design, setting, cancer indication, and line of therapy; eligibility criteria and baseline characteristics (e.g., age; sex; Eastern Cooperative Oncology Group performance status; weight, body mass index, or body surface area; comorbidities; prior therapies); intervention and comparator details (drug, dose, route, frequency, duration, cotreatments, and dosing strategy); clinical outcomes (e.g., ORR, PFS, OS) and safety outcomes (e.g., AEs/SAEs, grade ≥ 3 events, discontinuations, treatment-related deaths) with measurement time points, including arm-level results and comparative effect estimates when reported; and PK/PD parameters (e.g., minimum (trough) concentration [$C_{\min}$] and maximum concentration [$C_{\max}$], area under the concentration–time curve [AUC] and area under the concentration–time curve at steady state [AUC_{ss}], average [mean] concentration [C_{avg}], half-life, target occupancy) and ER/exposure-safety findings, if available.

Data Analyses and Synthesis

We synthesized the studies descriptively by summarizing study characteristics, patient characteristics, risk-of-bias assessments, and outcome results.

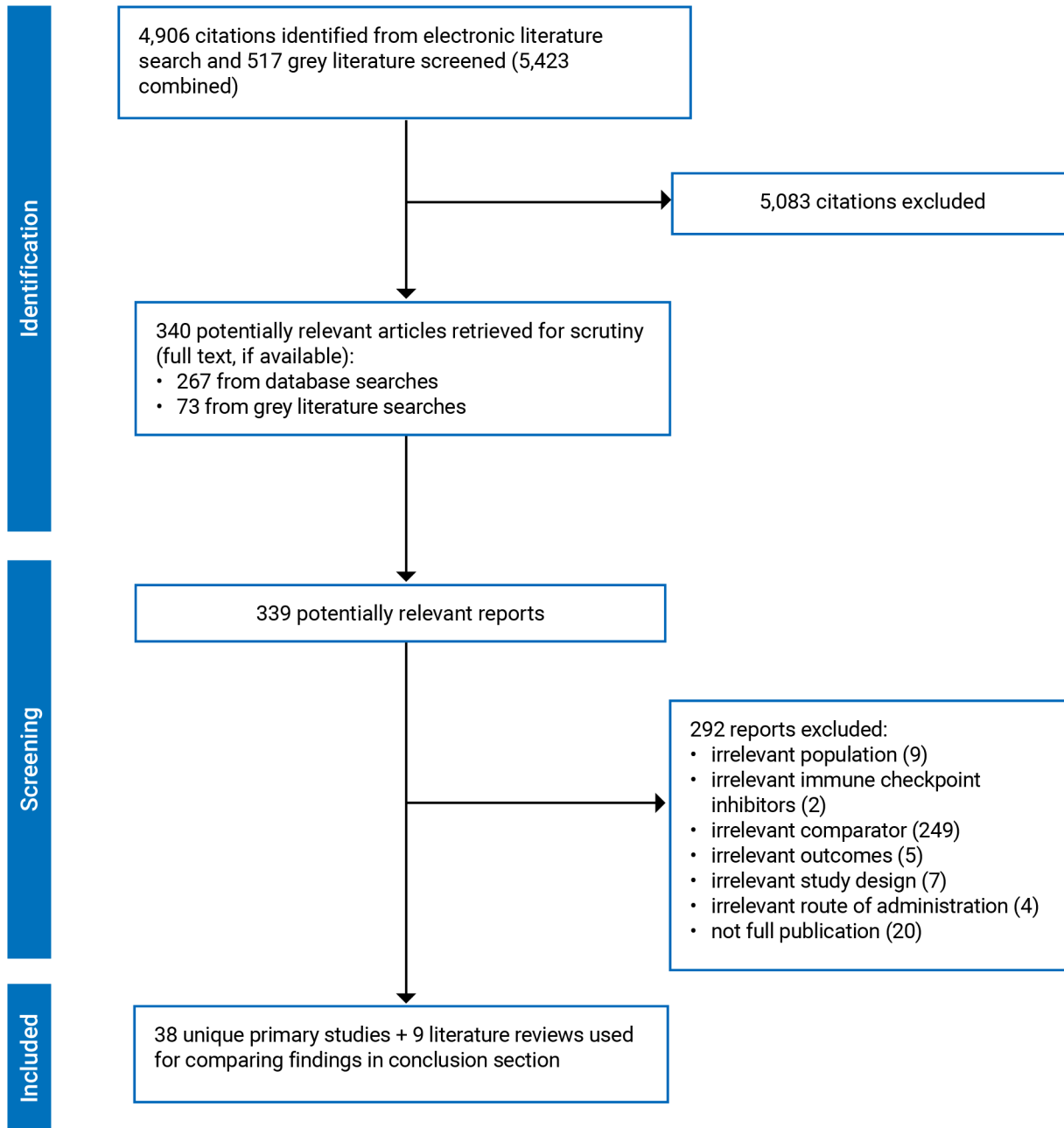
Results

Selection of Primary Studies

Main Take-Aways

We screened 5,423 records at the title and abstract level and reviewed 339 articles in full text. A total of 38 unique studies met the eligibility criteria and were included in this report.

Following deduplication, 5,423 records were screened based on title and abstract, and 339 records were assessed in full text. Of the full-text records, 292 were excluded with reasons (irrelevant population; irrelevant ICI; irrelevant comparator; irrelevant outcomes; irrelevant study design; published in a language other than English or French; full publication not available), and 38 unique primary studies were included in the final synthesis. We tabulated lists of included and excluded full-text records in [Appendix 5](#) and [6](#), respectively. The study selection process is summarized in the PRISMA flow chart ([Figure 1](#)).

Figure 1: PRISMA Flow Chart of Selected Reports

Study and Patient Characteristics

Main Take-Aways

The evidence in the 38 included studies was dominated by real-world nonrandomized studies and PK/PD modelling, with only 2 RCTs ([Table 2](#)). Most studies were conducted in high-income settings and largely focused on nivolumab and pembrolizumab in advanced cancers (especially NSCLC and melanoma).

Of the 38 primary studies, there were 2 RCTs, 22 nonrandomized studies, and 14 modelling and/or simulation studies. Most studies were conducted in high-income countries, with multicentre designs being most common in RCTs and nonrandomized studies. Nivolumab was the most frequently evaluated ICI across all study designs, followed by pembrolizumab. Hospital settings were most common in RCTs and nonrandomized studies. Most studies predominantly included male participants. Eastern Cooperative Oncology Group performance status and prior therapies were often reported, yet comorbidities were frequently not reported, especially in nonrandomized studies. In addition, we found 9 review articles, assessed their methodological quality, and compared their findings with our results in the Conclusions and Implications for Decision- or Policy-Making section.¹⁸⁻²⁶ Study characteristics are available in [Table 8 Appendix 2](#).

Table 2: Summary of Intervention and Patient Characteristics From Primary Studies (n = 38)

Characteristics	Summary: n (%)		
	RCTs (n = 2)	Nonrandomized studies (n = 22)	Modelling and/or simulation studies (n = 14)
Country income classification^a	- High-income: 1 (50%) - Mixed: 1 (50%)	- High-income: 17 (77.3%) - Lower- to middle-income: 1 (4.5%) - Mixed: 4 (18.2%)	- High-income: 1 (7.1%) - Lower- to middle-income: 1 (7.1%) - Mixed: 3 (21.4%) - NA: 9 (64.3%)
Centre	Multicentre: 2 (100%)	- Multicentre: 14 (63.6%) - Single-centre: 8 (36.4%)	- Multicentre: 4 (28.6%) - Single-centre: 1 (7.1%) - NA: 9 (64.3%)
Reported ICI(s)	- Nivolumab: 1 (50%) - Avelumab: 1 (50%)	- Nivolumab: 10 (45.5%) - Pembrolizumab: 8 (36.4%) - Durvalumab: 4 (18.2%) - Cemiplimab: 3 (13.6%) - Tremelimumab: 2 (9.1%) - Atezolizumab: 1 (4.5%) - Dostarlimab: 1 (4.5%)	- Nivolumab: 8 (57.1%) - Pembrolizumab: 3 (21.4%) - Cemiplimab: 2 (14.3%) - Avelumab: 2 (14.3%) - Durvalumab: 2 (14.3%) - Tremelimumab: 1 (7.1%) - Atezolizumab: 1 (7.1%) - Ipilimumab: 1 (7.1%)
Study setting	Hospital: 2 (100%)	- Hospital: 18 (81.8%) - Outpatient: 2 (9.1%)	- Modelling: 11 (78.6%) - Hospital: 1 (7.1%) - NA: 2 (14.3%)

Characteristics	Summary: n (%)		
	RCTs (n = 2)	Nonrandomized studies (n = 22)	Modelling and/or simulation studies (n = 14)
		- Registry: 2 (9.1%) - Modelling: 0 (0%)	
Funding source type	Industry: 2 (100%)	- Industry: 9 (40.9%) - Public: 2 (9.1%) - None: 8 (36.4%) - NR: 3 (13.6%)	- Industry: 12 (85.7%) - Public: 1 (7.1%) - None: 1 (7.1%)
Sex^b	- Female > 50%: 0 (0%) - Male > 50%: 2 (100%)	- Female > 50%: 4 (18.2%) - Male > 50%: 17 (77.3%) - NR: 1 (4.5%)	- Female > 50%: 0 (0%) - Male > 50%: 6 (42.9%) - NA: 8 (57.1%)
Age	< 60 years: 1 (50%) - NR: 1 (50%)	< 60 years: 1 (4.5%) 60 to 64.9 years: 5 (22.7%) 65 to 69.9 years: 8 (36.4%) ≥ 70 years: 4 (18.2%) - NR: 4 (18.2%)	< 60 years: 3 (21.43%) 65 to 69.9 years: 3 (21.43%) - NA: 8 (57.14%)
ECOG performance status reported	Reported: 2 (100%)	- Reported: 19 (86.4%) - NR: 3 (13.6%)	- Reported: 9 (64.3%) - NR: 2 (14.3%) - NA: 3 (21.4%)
Weight, BSA, or BMI range	- Reported: 1 (50%) - NR: 1 (50%)	- Reported: 13 (59.1%) - NR: 9 (40.9%)	- Reported: 11 (78.6%) - NR: 1 (7.1%) - NA: 2 (14.3%)
Comorbidities	NR: 2 (100%)	- Reported: 8 (36.4%) - NR: 14 (63.6%)	- NR: 12 (85.7%) - NA: 2 (14.3%)
Prior therapies	Reported: 2 (100%)	- Reported: 18 (81.8%) - NR: 4 (18.2%)	- Reported: 6 (42.86%) - NR: 6 (42.86%) - NA: 2 (14.28%)

BMI = body mass index; BSA = body surface area; ECOG = Eastern Cooperative Oncology Group; GNI = gross national income; ICI = immune checkpoint inhibitor; NA = not applicable; NR = not reported; RCT = randomized controlled trial.

^aHigh-income = GNI per capita ≥ US\$13,935 USD; middle-income = GNI per capita between US\$1,136 and US\$13,935.²⁷

^bValues represent the number (%) of studies in which more than 50% of participants were female or male.

Critical Appraisal

Main Take-Aways

Most of the included studies had important limitations (missing data, confounding, and incomplete reporting), which means their results may not be fully reliable.

Overall, methodological quality for the included studies was generally at serious risk of bias. The included reviews commonly had weaknesses in prespecification of their methodology and in the search, selection,

and extraction processes, and there was a limited assessment of heterogeneity and publication bias — factors that can deviate the effect estimates from the true effects.

For the RCTs, both included studies were judged to have some concerns, particularly due to the absence of prespecified analysis plans in their protocols, the open-label design that may have introduced assessment bias, and nonrigorous statistical approaches (e.g., analyzing treated rather than randomized patients).

Similarly, the included nonrandomized studies were characterized by serious risk of bias, largely due to confounding.

Regarding relevance to Canada, populations, interventions, comparators, and outcomes were generally clinically applicable, but generalizability is constrained by several factors. For example, some evidence came from settings outside of Canada where treatment access, monitoring practices, and supportive care may differ from oncology practice in Canada. Furthermore, factors such as tumour type, baseline prognosis, patient characteristics, and variation in care delivery and monitoring may impact clinical outcome results.

Table 3: Risk-of-Bias Assessment Using RoB 2 for the Included RCTs

First author (year)	Risk of bias domain					Overall risk-of-bias
	Randomization ^a	Deviation ^b	Missing data ^c	Measurement ^d	Results selection ^e	
Albiges (2025) ²⁸	Low	Low	Low	Low	Some	Some
Herrera (2021) ²⁹	Low	Some	Low	Some	Low	Some

RCT = randomized controlled trial.

^aIndicates bias arising from the randomization process.

^bIndicates bias due to deviations from the intended intervention.

^cIndicates bias due to missing outcome data.

^dIndicates bias in the measurement of the outcome.

^eIndicates bias in the selection of the reported results.

Table 4: Risk-of-Bias Assessment Using ROBINS-I for the Included Nonrandomized Studies

First author (year)	Risk-of-bias domain							Overall risk of bias
	Confounding ^a	Participant selection ^b	Classification ^c	Deviation ^d	Missing data ^e	Measurement ^f	Results selection ^g	
Campo Le Brun (2025) ³⁰	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Serious
Horisaki (2025) ³¹	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Serious
Hughes (2025) ³²	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Serious
Smeenk (2025) ³³	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Serious
Staender (2025) ³⁴	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Serious

First author (year)	Risk-of-bias domain							
	Confound- ing ^a	Participant selection ^b	Classifica- tion ^c	Deviation ^d	Missing data ^e	Measure- ment ^f	Results selection ^g	Overall risk of bias
Chaitesipaseut (2024) ³⁵	Serious	Serious	Low	Moderate	Moderate	Low	Moderate	Serious
Grit (2024) ³⁶	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Serious
Leroy (2024) ³⁷	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Serious
Patel (2024) ³⁸	Serious	Serious	Low	Moderate	Moderate	Moderate	Moderate	Serious
Rischin (2024) ³⁹	Serious	Low	Low	Moderate	Low	Moderate	Moderate	Serious
Berard (2023) ⁴⁰	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Serious
Samłowski (2023) ⁴¹	Serious	Serious	Low	Moderate	Moderate	Moderate	Moderate	Serious
Fujiwara (2022) ⁴²	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Serious
Hijmering- Kappelle (2022) ⁴³	Serious	Serious	Low	Moderate	Low	Moderate	Moderate	Serious
Iikura (2022) ⁴⁴	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Okada (2022) ⁴⁵	Serious	Low	Low	Moderate	Low	Moderate	Moderate	Serious
Patnaik (2022) ⁴⁶	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Serious
To (2022) ⁴⁷	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Serious
Juergens (2020) ⁴⁸	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Serious
Kato (2020) ⁴⁹	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Serious
Rischin (2020) ⁵⁰	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Serious

^aIndicates bias due to confounding.

^bIndicates bias in the selection of the participants.

^cIndicates bias in the classification of the interventions.

^dIndicates bias due to deviations from the intended interventions.

^eIndicates bias due to missing data.

^fIndicates bias in the measurement of the outcomes.

^gIndicates bias in the selection of the reported results.

Figure 2: Risk-of-Bias Assessment Using AMSTAR 2 for the Included Reviews

Study	Risk of bias																	Overall
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	
Hoyek (2025)	+	×	+	+	+	×	-	+	-	×	×			+	+		+	+
Tan (2025)	×	×	+	-	×	×	×	+	×	×	×			×	+		+	×
Mao (2024)	+	-	×	-	+	+	×	+	+	×	+	+	+	+	+	+	+	×
Hong (2023)	+	+	+	+	+	+	×	+	+		×	+	×	+	+	+	+	-
Li (2023)	+	+	×	-	+	×	×	-	+	×	×	+	×	×	+	+	+	×
Wesevich (2023)	×	×	×	×	×	×	×	-	×	×	×			×	×		+	×
Jiang (2022)	+	×	+	-	×	×	×	+	×	×	×			×	×		+	×
Seghal (2020)	×	×	×	×	×	×	×	-	×	×	×			×	×		+	×
Lee (2020)	×	×	×	-	×	×	×	+	×	×	×			×	×		+	×

D1: 1 Did the research questions and inclusion criteria for the review include the components of PICO?
 D2: 2 Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
 D3: 3 Did the review authors explain their selection of the study designs for inclusion in the review?
 D4: 4 Did the review authors use a comprehensive literature search strategy?
 D5: 5 Did the review authors perform study selection in duplicate?
 D6: 6 Did the review authors perform data extraction in duplicate?
 D7: 7 Did the review authors provide a list of excluded studies and justify the exclusions?
 D8: 8 Did the review authors describe the included studies in adequate detail?
 D9: 9a Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review? For included RCTs
 D10: 9b Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review? For included NRSIs
 D11: 10 Did the review authors report on the sources of funding for the studies included in the review?
 D12: 11 If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?
 D13: 12 If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis?
 D14: 13 Did the review authors account for RoB in individual studies when interpreting and discussing the results of the review?
 D15: 14 Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
 D16: 15 If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
 D17: 16 Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Judgement
 + High
 - Unclear
 × Low
 Not applicable

NRSI = nonrandomized study of interventions; PICO = population, intervention, comparator, and outcomes; RCT = randomized controlled trial; RoB = risk of bias.

Findings

Main Take-Aways

- Limited direct “head-to-head” clinical evidence comparing fixed versus weight-based (or alternative) dosing makes the interpretation and clinical decisions more challenging; therefore, definitive conclusions cannot be made.
- Studies on nivolumab and pembrolizumab generally suggest that fixed dosing results are similar to those of weight-based dosing for survival and cancer control, and serious immune-related side effects are usually similar across dosing regimens.
- Evidence for PK/PD outcomes suggests that fixed-dose regimens may result in average drug exposure similar to that achieved with weight-based dosing, whereas extended-interval regimens may produce higher peak concentrations and lower trough concentrations.

Efficacy, Effectiveness, and Safety Outcomes

Safety, efficacy, and effectiveness outcomes are summarized by publication in [Table 13 Appendix 3](#).

Atezolizumab

Only 1 study reported on this ICI.

Patel³⁸ was a retrospective cohort study including 100 patients treated with nivolumab (n = 47), pembrolizumab (n = 36), durvalumab (n = 9), or atezolizumab (n = 8). The study included 3 dosing groups — arm 1 (conventional dose; fixed approved dosing), arm 2 (per-body-weight dose), and arm 3 (low dose) — with low-dose atezolizumab defined as 1 mg/kg every 3 weeks. The study is at serious risk of bias, mainly

because of serious confounding, given that the nonrandomized dosing groups differed in ICI type, tumour type, clinical setting, and concomitant treatments, and no adjusted analysis was reported. Clinical outcomes were presented only at the overall dosing-group level, not separately by drug. In the palliative setting, arm 1 had complete response (CR) in 2 of 18 patients (11.1%), partial response (PR) in 11 of 18 patients (61.1%), and progressive disease in 5 of 18 patients (27.8%), corresponding to an ORR of 72.2%. Arm 2 had CR in 2 of 23 patients (8.7%), PR in 12 of 23 patients (52.2%), and progressive disease in 9 of 23 patients (39.1%), corresponding to an ORR of 60.9%. Arm 3 had CR in 0 of 37 patients (0%), PR in 28 of 37 patients (75.7%), and progressive disease in 9 of 37 patients (24.3%), corresponding to an ORR of 75.7%. Median follow-up was 10.2 months for conventional, fixed dosing, 9.8 months for per-weight dosing, and 3.9 months for low-dose treatment. Median OS was reported only for the overall cohort (6.8 months, range 4.6 to 9.0), with no arm-specific OS estimates provided. Safety outcomes, including AEs and irAEs, were not reported.

Overall, the study suggests that weight-based and lower-dose ICI regimens may provide similar safety and efficacy outcomes to fixed-dose regimens.

Avelumab

A total of 3 studies (Herrera, Masters, and Novakovic)^{29,51,52} reported on this ICI.

Herrera²⁹ was a phase Ib randomized, open-label, parallel-arm PK/PD clinical trial including 31 patients. It evaluated IV avelumab (1-hour infusion) across 4 fixed-dose regimens (70 mg every 2 weeks, 350 mg every 2 weeks, 500 mg every 2 weeks, and 500 mg every 3 weeks) and 1 weight-based dosing regimen (10 mg/kg every 2 weeks). The overall methodological quality of the trial was judged to have some concerns due to deviations from intended interventions (i.e., inclusion of dosing schedules that are lower intensity than those used in clinical practice), including inconsistent appropriate analyses across outcomes, and potential bias in outcome measurement arising from the unblinded open-label design.

Overall, the ORR across all randomized patients was 41.9%, with a median PFS of 5.7 months and a 1-year PFS rate of 18.2%. Among treated patients, any-grade treatment-related AEs (TRAEs) occurred in 86.7%, grade 3 or higher TRAEs in 43.3%, grade 3 or higher irAEs in 16.7%, and treatment discontinuation due to AEs in 19.4%; 1 treatment-related death due to pneumonitis was reported. Because each treatment arm was very small, arm-level efficacy comparisons should be interpreted cautiously; numerically, the 10 mg/kg every-2-weeks arm had a higher ORR than the 70 mg every-2-weeks, 350 mg every-2-weeks, and 500 mg every-2-weeks arms, but had a lower ORR than the 500 mg every-3-weeks arm.

Masters⁵¹ was a model-informed drug development study using PopPK modelling, simulation, and ER logistic regression analyses based on trial datasets, including 2,315 patients in the pooled PopPK dataset. The study compared weight-based avelumab 10 mg/kg IV every 2 weeks with flat-dose avelumab 800 mg IV every 2 weeks using simulated or reference flat-dose exposures. Safety outcomes were modelled for grade 3 and higher TRAEs, any-grade irAEs, and any-grade infusion-related reactions (IRRs). Overall, the ER analyses suggested a relatively flat relationship between avelumab exposure and these safety outcomes. For example, for any-grade irAEs, no exposure metric was statistically significantly associated with risk; the strongest, though still nonstatistically significant, association was for C_{max} after a single dose, with an odds ratio of 1.000 (95% confidence interval [CI], 0.999 to 1.010) per mcg/mL increase.

Novakovic et al.⁵² was a pharmacometric study using PopPK modelling and simulation based on data from 3 clinical trials (1,827 patients enrolled). The study compared avelumab 10 mg/kg IV every 2 weeks (weight-based dosing) with avelumab 800 mg IV every 2 weeks (fixed dose). Model-based analyses suggested similar ER relationships between dosing strategies. The predicted probability of any-grade irAEs was slightly higher with fixed dosing compared with weight-based dosing (12.6% versus 11.4%). IRR probability was similar between regimens (approximately 24.7% with weight-based dosing, with comparable estimates for fixed dosing). Predicted objective response probabilities based on exposure metrics were 31.8% in metastatic Merkel cell carcinoma and 17.3% in urothelial carcinoma (UC) for the weight-based regimen, with no meaningful differences reported between dosing strategies.

Cemiplimab

Three studies reported on this ICI. **Hughes et al.**³² was a phase II, open-label, multicohort study evaluating cemiplimab in patients with metastatic cutaneous squamous cell cancer. The study included a weight-based regimen (3 mg/kg IV every 2 weeks; n = 59) and a fixed-dose regimen (350 mg IV every 3 weeks; n = 56). This study has a serious risk of bias mostly due to confounding and lack of adjusted analyses to control for baseline prognostic differences between groups. ORRs were similar between the weight-based and fixed-dose groups (50.8% versus 46.4%), with comparable CR rates (20.3% versus 19.6%) and PR rates (30.5% versus 26.8%). Median PFS was 18.4 months for the weight-based regimen and 21.7 months for the fixed-dose regimen, while median OS was 57.7 months and 48.4 months, respectively. Durability of response was also similar, with 12-month duration-of-response estimates of 89.5% and 88.5%. Safety outcomes were broadly comparable across dosing strategies, with grade ≥ 3 TRAEs reported in 50.8% of patients receiving weight-based dosing and 42.9% receiving fixed dosing.

Overall, these findings suggest similar efficacy and safety profiles between fixed-dose and weight-based cemiplimab in metastatic cutaneous squamous cell carcinoma.

Rischin et al. (2024)³⁹ was an open-label, nonrandomized phase II sequential cohort study that compared pooled earlier cohorts (groups 1 to 3, including weight-based cemiplimab 3 mg/kg every 2 weeks and fixed 350 mg every 3 weeks; n = 193) with fixed-dose cemiplimab 600 mg every 4 weeks (group 4; n = 63) in advanced cutaneous squamous cell carcinoma. Methodological quality was at serious risk of bias for fixed-versus-weight-based inference because the comparison involved nonrandomized sequential cohorts and a mixed pooled comparator rather than a pure weight-based arm, and acknowledged baseline imbalances without adjusted head-to-head analyses. Safety outcomes were similar overall: any treatment-emergent adverse event occurred in 100% of both groups, grade 3 or higher treatment-emergent adverse events in 49% versus 54%, any TRAEs in 77% versus 83%, and grade 3 or higher TRAEs in 17% versus 16% for groups 1 to 3 versus group 4, respectively. Discontinuations and deaths due to AEs were somewhat more frequent in the fixed 600 mg every 4 weeks group. Efficacy for earlier groups was only reported contextually, with an integrated ORR of 46.1% (95% CI, 38.9 to 53.4), whereas the fixed 600 mg every 4 weeks group had an ORR of 61.9% (95% CI, 48.8 to 73.9), disease control of 77.8% (95% CI, 65.5 to 87.3), durable disease control of 76.2% (95% CI, 63.8 to 86.0), 12-month PFS of 65% (95% CI, 51 to 76), and 12-month OS of 73% (95% CI, 60 to 83).

Overall, the study concluded that cemiplimab 600 mg IV every 4 weeks showed strong and durable antitumour activity with acceptable safety in advanced cutaneous squamous cell carcinoma.

Rischin et al. (2020)⁵⁰ was a phase II, open-label, nonrandomized, multicentre international study including 115 patients. It reported outcomes for fixed-dose cemiplimab 350 mg IV every 3 weeks (group 3, n = 56) and weight-based cemiplimab 3 mg/kg IV every 2 weeks (group 1, n = 59). The study was at serious risk of bias for fixed-versus-weight-based inference because it compared sequential, nonrandomized cohorts: group 3 opened only after group 1 had fully enrolled, the primary analyses for the 2 groups were statistically independent, and no adjusted direct head-to-head comparison was performed. In the fixed-dose group, ORR per independent central review was 41.1% (95% CI, 28.1 to 55.0), disease control rate was 64.3% (95% CI, 50.4 to 76.6), durable disease control rate was 57.1% (95% CI, 43.2 to 70.3), the 8-month Kaplan-Meier estimate for duration of response was 95.0% (95% CI, 69.5 to 99.3), and median time to response was 2.1 months (range 2.0 to 8.3). In the weight-based group, the corresponding values were ORR 49.2% (95% CI, 35.9 to 62.5), disease control rate 71.2% (95% CI, 57.9 to 82.2), durable disease control rate 61.0% (95% CI, 47.4 to 73.5), 12-month Kaplan-Meier duration-of-response estimate 88.9% (95% CI, 69.3 to 96.3), and median time to response 1.9 months (range 1.7 to 9.1). Safety outcomes showed that TRAEs occurred in 36 of 56 (64.3%) patients in the fixed-dose group and 46 of 59 (78.0%) patients in the weight-based group; grade 3 or higher TRAEs occurred in 7 of 56 (12.5%) and 9 of 59 (15.3%) patients, respectively. irAEs occurred in 32 of 56 (57.1%) versus 40 of 59 (67.8%) patients, with grade 3 or higher irAEs in 7 of 56 (12.5%) versus 8 of 59 (13.6%) patients. Overall, the study concluded that cemiplimab 350 mg IV every 3 weeks showed strong antitumour activity, with durable responses seen in both the fixed-dose and weight-based cohorts and a broadly similar safety profile across groups.

Dostarlimab

Only 1 study reported on this ICI.

Patnaik et al.⁴⁶ was an open-label, first-in-human phase I cohort study evaluating weight-based and fixed dosing of dostarlimab. Part 1 assessed weight-based dose escalation using a 3 + 3 design (1, 3, and 10 mg/kg every 2 weeks), while part 2A evaluated fixed dosing using a modified 6 + 6 design (500 mg every 3 weeks and 1,000 mg every 6 weeks). The overall methodological quality is at serious risk of bias mainly due to lack of adjustment for important prognostic differences across groups, introducing potential confounding across the weight-based cohorts. PRs were observed in the 3 mg/kg (1 of 3, 33.3%) and 10 mg/kg (1 of 12, 8.3%) groups, whereas the 1 mg/kg cohort demonstrated stable disease in 2 of 6 patients (33.3%). In the fixed-dose cohorts, no PRs were reported; stable disease occurred only in the 1,000 mg every 6 weeks group (2/7, 28.6%). Safety outcomes were generally comparable across dosing strategies, with TRAEs reported in all participants and events of grade 3 or higher occurring in 14% to 50% of patients across cohorts.

Overall, the early-phase findings did not demonstrate a clear dose-response relationship in efficacy or major differences in safety between weight-based and fixed-dosing regimens.

Durvalumab

Four studies reported on this ICI.

Patel³⁸ was a retrospective cohort study including 100 patients treated with nivolumab (n = 47), pembrolizumab (n = 36), durvalumab (n = 9), or atezolizumab (n = 8). The study included 3 dosing groups: arm 1 (conventional dose; fixed approved dosing), arm 2 (per-body-weight dose), and arm 3 (low dose), with low-dose atezolizumab defined as 1 mg/kg every 3 weeks. The study is at serious risk of bias, mainly because of serious confounding, given that the nonrandomized dosing groups differed in ICI type, tumour type, clinical setting, and concomitant treatments, and no adjusted analysis was reported. Clinical outcomes were pooled across ICI agents, tumour types, dosing regimens, and concomitant therapies and were presented only at the overall dosing-group level, not separately by drug. In the palliative setting, arm 1 had CR in 2 of 18 (11.1%) patients, PR in 11 of 18 (61.1%) patients, and PD in 5 of 18 (27.8%) patients, corresponding to an ORR of 72.2%. Arm 2 had CR in 2 of 23 (8.7%) patients, PR in 12 of 23 (52.2%) patients, and PD in 9 of 23 (39.1%) patients, corresponding to an ORR of 60.9%. Arm 3 had CR in 0 of 37 (0%), PR in 28 of 37 (75.7%) patients, and PD in 9 of 37 (24.3%) patients, corresponding to an ORR of 75.7%. Median follow-up was 10.2 months for conventional, fixed dosing, 9.8 months for per-weight dosing, and 3.9 months for low-dose treatment. Median OS was reported only for the overall cohort (6.8 months, range 4.6 to 9.0), with no arm-specific OS estimates provided. Safety outcomes, including AEs and irAEs, were not reported.

Overall, the study suggests that weight-based and lower-dose ICI regimens may provide comparable outcomes to fixed-dose regimens.

Fujiwara⁴² was a phase I, open-label trial with 65 participants. For the relevant part 2 cohorts, the study included 2 weight-based combination regimens — cohort 1: tremelimumab administered in 6 doses of 10 mg/kg every 4 weeks then 3 doses every 12 weeks plus 13 doses of durvalumab 15 mg/kg every 4 weeks, and cohort 2: 4 doses of tremelimumab 1 mg/kg every 4 weeks plus 4 doses of durvalumab 20 mg/kg every 4 weeks then 10 mg/kg every 2 weeks — compared with 1 fixed-dose combination regimen, cohort 3: 4 doses of tremelimumab 75 mg every 4 weeks plus 13 doses of durvalumab 1,500 mg every 4 weeks. The study is at serious risk of bias, mainly due to confounding, because the cohorts were small, nonrandomized, sequential, and unadjusted for baseline prognostic differences. This should also not be interpreted as a clean fixed- versus weight-based durvalumab comparison, given that the accompanying tremelimumab regimens also differed across cohorts. Using a crude pooled comparison of the 2 weight-based cohorts versus the fixed-dose cohort, objective response was lower in the fixed-dose arm (0 of 6 patients, 0%) than in the pooled weight-based arms (2 of 10 patients, 20.0%). Disease control was 33.3% (2 of 6 patients) in the fixed-dose arm versus 20.0% (2 of 10 patients) in the pooled weight-based arms. Incidence of AEs was similar with either dosing option: any AE occurred in 100% versus 90.0%, grade 3 or higher AEs in 50.0% versus 50.0% of patients, and serious AEs in 50.0% versus 50.0% of patients, respectively. Adverse events leading to discontinuation occurred in 16.7% of fixed-dose patients versus 40.0% of pooled weight-based patients. The available data suggest that both weight-based and fixed-dose tremelimumab plus durvalumab regimens were safe and tolerable.

Juergens et al.⁴⁸ was a phase Ib, multicentre, multicohort dose-escalation trial (Rolling Six design) with 136 participants. The study evaluated both weight-based and fixed-dose durvalumab regimens across sequential dose-escalation cohorts, including 15 mg/kg every 3 weeks and fixed doses of 1,125 mg every 3 weeks and 1,500 mg every 3 weeks. The study is at serious risk of bias overall, largely due to confounding, because dosing strategies were implemented in nonrandomized, sequential cohorts and were combined with varying tremelimumab regimens, without adjustment for baseline or clinical differences. Clinical outcomes were reported according to treatment regimen rather than dosing strategy. Durvalumab monotherapy (N = 24) achieved an ORR of 29% (CR 4%; PR 25%), while combination therapy with tremelimumab (N = 112) showed a higher ORR of 42% (CR 2%; PR 40%). Safety outcomes also differed by regimen, with irAEs occurring in 46% (grade $\geq$ 3: 4%) of monotherapy patients and 77% (grade $\geq$ 3: 24%) of combination therapy patients. However, outcomes were not stratified by dosing strategy (fixed versus weight-based), and the presence of cointerventions and sequential cohort design precludes a valid comparison between dosing approaches.

Hijmering-Kappelle et al.⁴³ was a retrospective single-centre cohort study of 66 patients comparing weight-based durvalumab (10 mg/kg every 2 weeks) with fixed extended-interval durvalumab (1,500 mg every 4 weeks) in stage III NSCLC. The study is at serious risk of bias due to nonrandomized escalation to fixed dosing after patients remained free of early toxicity, causing confounding and selection bias without adjusted analyses. Fixed and weight-based durvalumab showed broadly similar safety and efficacy: grade 3 or higher AEs were similar overall (11.5% versus 7.6%) and in the escalation window (10.5% versus 10.9%), treatment discontinuation was somewhat lower with fixed dosing (3 versus 5 patients), and median PFS and OS were not reached in either group.

Ipilimumab

None of the included studies reported on this ICI.

Nivolumab

Fifteen studies provided data on this ICI.

Albiges et al.,²⁸ the largest trial in our included studies for this ICI, was a phase III, open-label, randomized, noninferiority trial (CheckMate 67T; NCT04810078) with 495 patients. The study is at some risk of bias, mostly due to a lack of analysis plans in the protocol. It evaluated subcutaneous (SC) nivolumab 1,200 mg plus 20,000 units of recombinant human hyaluronidase PH20 (rHuPH20) every 4 weeks versus IV nivolumab 3 mg/kg every 2 weeks. SC nivolumab plus rHuPH20 (1,200 mg every 4 weeks) and IV nivolumab (3 mg/kg every 2 weeks) had similar efficacy. ORR was higher with SC (24.2% versus 18.2% at 8 months or more; 26.6% versus 20.6% at 15 months or more), while disease control rate (DCR) (approximately 63%), time to response (approximately 3.7 months), PFS (hazard ratio [HR] = 1.06), and 6- and 12-month OS rates were broadly similar. AEs, on the other hand, were common in both arms, but grade 3 or 4 TRAEs and discontinuations were slightly lower with SC (grade 3 or 4 TRAE 11.7% versus 17.1% IV). Immune-mediated AEs were generally similar with no new safety signals, and treatment-related deaths were rare ($\leq$ 1.2%). SC nivolumab demonstrated comparable pharmacokinetic profiles and ORRs to IV administration, meeting noninferiority criteria.

Campo le Brun³⁰ was a prospective cohort study with 348 patients. The study is at serious risk of bias mostly due to residual confounding and selection bias. Dosing strategy was closely linked to calendar time (weight-adjusted nivolumab was used before 2018, whereas flat-dose nivolumab was used after the dosing regimen changed in 2018), baseline imbalances existed before weighting, BRAF status differed between groups, and the authors explicitly acknowledge temporal bias and exclusion bias from removing patients who changed dosing regimen. Grade 3 or 4 irAEs occurred in 13.1% (21 of 160) of patients receiving weight-adjusted dosing and 11.7% (22 of 188) receiving fixed dosing ($P = 0.8$). Any-grade irAEs occurred in 63.1% of the weight-adjusted group and 67.0% of the fixed-dose group ($P = 0.5$). No grade 5 toxicities were reported. Efficacy outcomes numerically favoured the fixed-dose strategy. ORR was 48.4% with fixed dosing versus 40.0% with weight-adjusted dosing ($P = 0.14$), and DCR was 66.0% versus 61.2% ($P = 0.42$). After inverse probability of treatment weighting, median OS was 37.0 months with fixed dosing compared with 24.8 months with weight-adjusted dosing. Median PFS was 3.7 months versus 3.1 months, respectively. The HR for OS comparing fixed versus weight-adjusted dosing was 0.74 (95% CI, 0.54 to 1.01), and for PFS, it was 0.84 (95% CI, 0.65 to 1.07). Landmark survival estimates at 6, 12, 18, and 24 months were also consistently higher in the fixed-dose group. Safety outcomes were similar between dosing strategies.

Overall, there were no differences in the rates of severe irAEs or median PFS between patients receiving weight-based versus fixed-dose nivolumab. Similarly, median OS was not statistically significantly different between the groups.

Horisaki³¹ was a retrospective cohort study of 153 patients with advanced melanoma and is best judged to be at a serious overall risk of bias, primarily due to confounding. Although the authors measured several baseline characteristics and performed multivariable analyses, important residual confounding remains likely, especially from treatment line, prior therapies, melanoma subtype or severity, body weight, and possible calendar-time effects related to evolving uptake of fixed-dose regimens. The study included both fixed-dose nivolumab (240 mg every 2 weeks; 480 mg every 4 weeks) and weight-based nivolumab (2 mg/kg every 3 weeks; 3 mg/kg every 2 weeks). However, the reported direct outcome comparisons were limited. The study reported a fixed-dose versus fixed-dose comparison for 480 mg every 4 weeks versus 240 mg every 2 weeks, and a weight-based versus weight-based comparison for 3 mg/kg every 2 weeks versus 2 mg/kg every 3 weeks. For the latter, outcomes were broadly similar: ORR was 24.3% versus 14.6% ($P = 0.278$), DCR was 40.5% versus 46.3% ($P = 0.606$), median PFS was 2.6 versus 3.1 months ($P = 0.753$), and median OS was 18.9 versus 11.8 months ($P = 0.892$). Any-grade irAEs occurred in 48.6% versus 46.3%, and grade 3 or higher irAEs occurred in 10.8% versus 19.5%, respectively.

The study concluded that more frequent nivolumab dosing may provide short-term benefits in patients living in Japan with advanced melanoma, but long-term efficacy and safety outcomes were comparable across the different dosing regimens.

Staender³⁴ was a retrospective cohort study with 47 patients. The study has an overall serious risk of bias, primarily due to confounding, because treatment allocation was related to changes in dosing practice over time (weight-adapted dosing used earlier and fixed dosing introduced later), and the analysis did not adequately adjust for baseline differences between groups. Weight-adapted therapy (study-defined)

(WAT) was compared with fixed-dose therapy (FDT) for anti-PD-1 monotherapy using nivolumab or pembrolizumab. WAT used nivolumab 3 mg/kg every 2 weeks or pembrolizumab 2 mg/kg every 3 weeks, while FDT used nivolumab 240 mg every 2 weeks or 480 mg monthly and pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks. Median PFS was 174 days in the WAT group and 208 days in the FDT group; median OS was 980 days in the WAT group and not reached in the FDT group. However, there were no statistically significant differences between groups for either PFS (log-rank $P = 0.595$) or OS (log-rank $P = 0.502$), and HRs with confidence intervals were not reported. The authors reported no difference in irAEs between WAT and FDT.

Leroy³⁷ was a retrospective cohort study including 337 patients. The study is at serious risk of bias, primarily due to potential confounding from differences in calendar period, given that the cohorts were treated during different, partly overlapping time periods, and baseline patient characteristics were not fully adjusted in the analysis. The study compared weight-based nivolumab (3 mg/kg every 2 weeks) with fixed dosing (480 mg every 4 weeks). The cumulative incidence of grade 3 or higher irAEs at 12 months was 6.1% in both groups, with no statistically significant difference (HR = 0.54; 95% CI, 0.21 to 1.36; $P = 0.19$). Discontinuation due to irAEs occurred in 14.3% (10 of 70) of patients receiving weight-based dosing and 21.3% (57 of 267) receiving fixed dosing. In terms of efficacy, 12-month OS was higher in the fixed-dose group (88.0%) compared with the weight-based group (52.6%), with a statistically significant difference (log-rank $P < 0.001$; HR not reported). The findings showed no meaningful difference between the weight-based and fixed-dose groups in the rate of severe irAEs. However, OS appeared to be higher in the fixed-dose group.

Patel³⁸ was a retrospective cohort study including 100 patients treated with nivolumab ($n = 47$), pembrolizumab ($n = 36$), durvalumab ($n = 9$), or atezolizumab ($n = 8$). The study included 3 dosing groups: arm 1 (conventional dose; fixed approved dosing), arm 2 (per-body-weight dose), and arm 3 (low dose), with low-dose atezolizumab defined as 1 mg/kg every 3 weeks. The study is at serious risk of bias, mainly because of serious confounding, given that the nonrandomized dosing groups differed in ICI type, tumour type, clinical setting, and concomitant treatments, and no adjusted analysis was reported. Clinical outcomes were presented only at the overall dosing-group level, not separately by drug. In the palliative setting, arm 1 had CR in 2 of 18 (11.1%) patients, PR in 11 of 18 (61.1%) patients, and PD in 5 of 18 (27.8%) patients, corresponding to an ORR of 72.2%. Arm 2 had CR in 2 of 23 (8.7%) patients, PR in 12 of 23 (52.2%) patients, and PD in 9 of 23 (39.1%) patients, corresponding to an ORR of 60.9%. Arm 3 had CR in 0 of 37 (0%) patients, PR in 28 of 37 (75.7%) patients, and PD in 9 of 37 (24.3%) patients, corresponding to an ORR of 75.7%. Median follow-up was 10.2 months for conventional, fixed dosing, 9.8 months for per-weight dosing, and 3.9 months for low-dose treatment. Median OS was reported only for the overall cohort (6.8 months, range 4.6 to 9.0), with no arm-specific OS estimates provided. Safety outcomes, including AEs and irAEs, were not reported.

Overall, the study suggests that weight-based and lower-dose ICI regimens may provide similar safety and efficacy outcomes to fixed-dose regimens.

Samlowski⁴¹ was a retrospective cohort study with 191 patients. This study is at serious risk of bias, mainly because treatment allocation was not randomized and important residual confounding likely remains despite

propensity score matching. This study evaluated 4 real-world adjuvant nivolumab dosing arms in melanoma: de novo fixed-dose 480 mg every 4 weeks (C1), switch to 480 mg every 4 weeks after prior 240 mg or 3 mg/kg every 2 weeks (C2), de novo weight-based 3 mg/kg every 2 weeks (C3), and de novo fixed-dose 240 mg every 2 weeks (C4). Compared with the weight-based 3 mg/kg every 2 weeks arm, the fixed-dose arms showed broadly similar treatment duration and safety. Median treatment duration was 10.2 months with fixed 480 mg every 4 weeks, 10.7 months with fixed 240 mg every 2 weeks, and 8.3 months with weight-based 3 mg/kg every 2 weeks. The proportion with at least 1 TRAE was also similar across groups (60.0%, 58.2%, and 54.5%, respectively), as were premature discontinuation rates (32.5%, 41.8%, and 40.9%). Although significant TRAEs appeared somewhat lower with fixed 480 mg every 4 weeks (17.5%) and fixed 240 mg every 2 weeks (20.0%) than with weight-based dosing (27.3%), the small size of the weight-based cohort limits strong conclusions.

Overall, the study suggests that fixed-dose nivolumab was generally comparable to weight-based dosing in this adjuvant melanoma setting.

likura⁴⁴ was a retrospective cohort study with 113 patients. This study is at serious overall risk of bias, driven mainly by confounding, because treatment allocation was nonrandomized and the groups differed in baseline characteristics, particularly prior treatment burden, without multivariable adjustment. The study compared weight-based nivolumab 3 mg/kg every 2 weeks with fixed-dose nivolumab 240 mg every 2 weeks. Overall, fixed dosing showed safety outcomes that were broadly similar to weight-based dosing, with no statistically significant differences in overall immune-related toxicity or treatment discontinuation due to irAEs. Any-grade irAEs occurred in 19.4% of patients receiving fixed dosing versus 29.9% with weight-based dosing ($P = 0.264$), while grade 2 or higher irAEs occurred in 19.4% versus 23.3% of patients, respectively ($P = 0.808$). Discontinuation due to irAEs was also less frequent with fixed dosing (2.8% versus 9.1%), although this difference was not statistically significant. At the category level, most grade 2 or higher irAE types were infrequent and generally comparable across groups, except for rash, which was significantly more common in the 240 mg fixed-dose group ($P = 0.028$).

Overall, these findings suggest that fixed-dose nivolumab had a broadly similar safety profile to weight-based dosing, with the main notable difference being a higher rate of grade 2 or higher rash in the fixed-dose arm.

Okada⁴⁵ was a retrospective cohort study with 199 patients. The study is at serious risk of bias, primarily due to confounding, given that patients received nivolumab 3 mg/kg or 240 mg fixed dosing according to different calendar periods rather than random allocation, and the analysis did not adequately adjust for important prognostic factors or secular trends. The study compared weight-based nivolumab 3 mg/kg every 2 weeks with fixed-dose nivolumab 240 mg every 2 weeks. Overall, fixed dosing showed similar efficacy and safety to weight-based dosing, with no statistically significant differences between groups. The fixed-dose group had a numerically higher ORR (25% versus 15%) and DCR (57% versus 46%), but these differences were not statistically significant ($P = 0.15$ for both). Survival outcomes were also comparable: median OS was 10.9 months with fixed dosing versus 9.5 months with weight-based dosing (HR = 0.89; 95% CI, 0.57 to 1.37; $P = 0.59$), and median PFS was 3.8 versus 3.7 months (HR = 1.01; 95% CI, 0.71 to 1.44; $P = 0.95$). In terms of safety, any-grade irAEs occurred in 21% of patients receiving fixed dosing compared with 28% in

the weight-based group, with no statistically significant difference ($P = 0.24$). Grade 3 or higher irAEs were not reported by arm. There were no treatment-related deaths in the weight-based group, whereas 1 grade 5 event (0.9%) due to interstitial lung disease occurred in the fixed-dose group. Overall, these findings suggest that fixed-dose nivolumab 240 mg every 2 weeks provides comparable efficacy and broadly similar safety to weight-based dosing at 3 mg/kg every 2 weeks.

Kato⁴⁹ was a retrospective cohort study with 19 patients. This study is at serious risk of bias, driven primarily by confounding. Notably, serum albumin was significantly greater in the fixed-dose group compared to the weight-based group. Serum albumin is an indicator of the level of cachexia, with low serum albumin suggesting a worsened disease severity. Thus, the difference in serum albumin observed in this study suggests a source of residual confounding associated with prognosis and clinical status. The study compared 3 mg/kg every 2 weeks with 240 mg every 2 weeks. In this small study, the flat-dose group appeared to have numerically better survival and lower toxicity, whereas the weight-based group showed a numerically higher response rate, but none of the reported between-group differences were statistically significant. Specifically, ORR was 45.5% (5 of 11) with weight-based dosing versus 25.0% (2 of 8) with flat dosing ($P = 0.63$). Any-grade irAEs occurred in 72.7% (8 of 11) of the weight-based group and 50.0% (4 of 8) of the flat-dose group ($P = 0.38$), whereas grade 3 to 4 irAEs were reported in 54.6% (6 of 11) versus 12.5% (1 of 8), respectively ($P = 0.15$). For efficacy, the 12-month PFS rate was 53.0% with weight-based dosing compared with 87.5% with flat dosing, and the 12-month OS rate was 80.8% versus 100%, respectively. Median PFS and OS were not reached, and HRs were not reported, so the survival comparison is descriptive only.

Overall, this study suggests no clear statistically significant difference between fixed and weight-based nivolumab dosing for survival and toxicity, although the flat-dose regimen showed numerically lower toxicity and higher 12-month survival rates in this very small sample.

Gandhi⁵³ was a prospective comparative study including 25 patients. The study compared conventional weight-based nivolumab dosing (3 mg/kg IV every 2 or 3 weeks) with a low fixed dose of 40 mg IV every 2 or 3 weeks. Clinical outcomes appeared broadly similar between the 2 dosing strategies. At 3 months, the ORR was 18.2% (2 of 11) in the weight-based group and 11.1% (1 of 9) in the low fixed-dose group. Median PFS was 4.3 months (95% CI, 1.46 to 7.07) with weight-based dosing and 5.8 months (95% CI, 3.39 to 8.26) with low fixed dosing, with no statistically significant difference between groups ($P = 0.31$). Safety outcomes differed by end point. Any AEs occurred in 100% (14 of 14) of patients receiving weight-based dosing compared with 63.6% (7 of 11) in the low fixed-dose group. However, irAEs of any grade were more frequent in the low fixed-dose group (85.7% [6 of 11]) than in the weight-based group (64.3% [9 of 14]). Grade 3 or higher irAEs were reported only in the weight-based group (28.6% [4 of 14]) and not in the low fixed-dose group (0 of 11). No patients discontinued treatment because of AEs, and no treatment-related deaths were reported in either group.

Overall, this small study suggests broadly similar efficacy between weight-based and low fixed-dose nivolumab, with no statistically significant difference in PFS.

Sheng⁵⁴ was a model-informed benefit-risk assessment that incorporated PopPK modelling together with descriptive safety data from clinical trial datasets. The study evaluated nivolumab 3 mg/kg IV every 2 weeks, 240 mg IV every 2 weeks, and 10 mg/kg IV every 2 weeks. For this paper, the relevant comparison is fixed dosing at 240 mg every 2 weeks versus weight-based dosing at 3 mg/kg every 2 weeks. Chinese exposure simulations included patients receiving 240 mg every 2 weeks ($n = 314$) and 3 mg/kg every 2 weeks ($n = 294$). Chinese safety data came from the CheckMate 077 trial (240 mg, $n = 20$; 3 mg/kg, $n = 15$) and the CheckMate 078 trial (3 mg/kg, safety $n = 241$), whereas global pooled safety data included 3 mg/kg ($n = 1,375$) and 10 mg/kg ($n = 131$). In the Chinese CheckMate 077 cohort, any-grade AEs occurred in 90.0% of patients receiving 240 mg every 2 weeks and 100.0% receiving 3 mg/kg every 2 weeks; grade 3 or 4 AEs occurred in 10.0% and 6.7%, respectively. In the CheckMate 078 trial, 97.9% of patients who were living in China and receiving 3 mg/kg every 2 weeks had any-grade AEs, and grade 3 or 4 AEs occurred in 43.2%, grade 5 AEs in 4.1%, SAEs in 36.5%, and AEs leading to discontinuation in 16.6%. The study also reported model-predicted PK exposure metrics ($C_{\min}$, $C_{\max}$, and C_{avg} at first dose and steady state), which supported similar exposure between the 240 mg fixed-dose and 3 mg/kg weight-based regimens. The higher-dose 10 mg/kg every 2 weeks group showed greater toxicity, with grade 3 or 4 AEs in 50.4% of patients and grade 5 AEs in 13.7%.

Overall, the study suggests that nivolumab 240 mg every 2 weeks yields comparable predicted PK exposure to 3 mg/kg every 2 weeks, whereas descriptive safety findings do not suggest a major difference, although direct comparison is limited by small and unequal safety datasets.

Zhao⁵⁵ was a model-informed drug development study that used PopPK simulations, ER analyses for safety and efficacy, and intratumoral receptor occupancy modelling. The study included a PK simulation dataset of 3,203 patients, a safety ER dataset of 2,560 patients, and efficacy ER datasets of 1,615 patients for OS and 1,579 patients for ORR. The study evaluated nivolumab weight-based dosing (3 mg/kg every 2 weeks) alongside fixed dosing regimens of 240 mg every 2 weeks and 480 mg every 4 weeks across multiple tumour types. Model-based predictions suggested similar efficacy across regimens. Predicted ORR differed by no more than approximately 2 percentage points between dosing strategies, and predicted OS values were likewise very similar across melanoma, RCC, squamous NSCLC, and nonsquamous NSCLC. Predicted safety outcomes were also comparable. Time-to-event modelling showed similar cumulative probabilities of grade 2 or higher immune-mediated AEs (IMAEs), grade 2 or higher TRAEs, and TRAEs leading to discontinuation or death across regimens. Logistic ER models also predicted similar probabilities of grade 2 or higher IMAEs, grade 3 or higher AEs, and AEs leading to discontinuation or death.

Overall, the study found negligible differences between fixed-dose and weight-based nivolumab regimens in modelled safety and efficacy outcomes.

Sanghavi et al.⁵⁶ was a model-based ER and benefit-risk analysis with 448 patients in the adjuvant melanoma efficacy dataset from the CheckMate 238 trial and 3,008 patients in the pooled safety dataset across 14 studies. It compared weight-based nivolumab 3 mg/kg every 2 weeks with fixed dosing of 240 mg every 2 weeks and 480 mg every 4 weeks. Predicted efficacy was essentially identical across regimens: 1- and 2-year recurrence-free survival and distant metastasis-free survival were nearly the same for fixed

and weight-based dosing. Predicted safety was also very similar. For grade 3 and higher AEs, the 6-month probability was 0.206 with 3 mg/kg, 0.2056 with 240 mg, and 0.1967 with 480 mg; at 12 months, it was 0.2892, 0.2887, and 0.2769, respectively. For grade 2 and higher IMAEs, the 6-month probability was 0.2275 with 3 mg/kg, 0.2280 with 240 mg, and 0.2516 with 480 mg; at 12 months, it was 0.3135, 0.3142, and 0.3445, respectively.

Overall, fixed-dose nivolumab showed comparable predicted efficacy and broadly similar predicted safety to weight-based dosing, with only a small increase in predicted grade 2 and higher IMAEs for 480 mg every 4 weeks.

Bei et al.⁵⁷ conducted a model-based quantitative clinical pharmacology study incorporating PopPK modelling, ER analyses for safety and efficacy, and an overall benefit-risk assessment. The safety ER dataset included 273 patients living in Japan, the efficacy ER dataset included 134 patients living in Japan, and the PopPK modelling and simulation dataset included 3,939 patients in total, of whom 420 were living in Japan. The study compared nivolumab weight-based dosing (3 mg/kg every 2 weeks) with fixed dosing (240 mg every 2 weeks) using model-based predictions of efficacy and safety across multiple tumour types. Overall, the findings suggested that the fixed-dose and weight-based regimens produced similar outcomes, with no clinically meaningful differences. For efficacy, the predicted 1-year and 2-year OS probabilities were nearly identical between regimens across squamous NSCLC, nonsquamous NSCLC, and RCC; in melanoma, predicted survival was numerically slightly higher with 3 mg/kg, but the confidence intervals overlapped. Predicted ORR was also similar between dosing strategies, with no meaningful differences within tumour type. For safety, the study evaluated AEs leading to discontinuation or death, grade 3 or higher AEs, and grade 2 or higher IMAEs. Predicted safety event proportions were very similar between regimens across tumour types, and the authors concluded that 240 mg was associated with either no change or only negligible increases of up to 2%, which were not statistically significant. In summary, Bei et al. suggests that nivolumab 240 mg every 2 weeks provides similar predicted survival, response, and safety outcomes to 3 mg/kg every 2 weeks, supporting fixed dosing as an alternative to weight-based dosing.

Pembrolizumab

Eight studies reported on this ICI.

Smeenk³³ was a real-world, retrospective bicentre cohort study including 766 patients and is judged to have a serious overall risk of bias, primarily due to confounding. Treatment allocation was strongly associated with institution and calendar period, leaving substantial potential for residual confounding despite an inverse probability of treatment weighting adjustment. The study compared 2 pembrolizumab dosing strategies: a hybrid weight-banded fixed dosing approach (100, 150, or 200 mg every 3 weeks based on body weight, or doubled every 6 weeks) and standard flat dosing (200 mg every 3 weeks or 400 mg every 6 weeks). The hybrid dosing arm showed numerically improved outcomes compared with flat dosing, with longer median OS (17.7 versus 11.8 months), higher 1-year OS (61% versus 50%), and longer median PFS (6.4 versus 4.6 months). HRs also favoured hybrid dosing for both OS (HR = 0.76; 95% CI, 0.65 to 0.90) and PFS (HR = 0.82; 95% CI, 0.70 to 0.96).

Safety and treatment-course measures were broadly similar between groups. The study concluded that OS in the hybrid dosing group was comparable to that observed with flat dosing, demonstrating noninferiority.

Staender³⁴ was a retrospective cohort study with 47 patients. The study has an overall serious risk of bias, primarily due to confounding, because treatment allocation was related to changes in dosing practice over time (weight-adapted dosing used earlier and fixed dosing introduced later), and the analysis did not adequately adjust for baseline differences between groups. Weight-adapted dosing (WAT) was compared with FDT for anti-PD-1 monotherapy using nivolumab or pembrolizumab. WAT used nivolumab 3 mg/kg every 2 weeks or pembrolizumab 2 mg/kg every 3 weeks, whereas FDT used nivolumab 240 mg every 2 weeks or 480 mg monthly and pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks. Median PFS was 174 days in the WAT group and 208 days in the FDT group; median OS was 980 days in the WAT group and not reached in the FDT group. However, there were no statistically significant differences between groups for either PFS (log-rank $P = 0.595$) or OS (log-rank $P = 0.502$), and HRs with confidence intervals were not reported. The authors reported no difference in irAEs between WAT and FDT.

Chaitesipaseut et al.³⁵ was a retrospective cohort study including 1,413 patients and was determined to have a serious overall risk of bias, primarily due to residual confounding. The analysis adjusted for a limited set of covariates, while important clinical confounders were likely unmeasured, and treatment selection may have been influenced by prognostic factors. The study compared fixed-dose and weight-based pembrolizumab. The fixed-dose group received 200 mg every 3 weeks or 400 mg every 6 weeks, whereas the weight-based group received 2 mg/kg every 3 weeks or 4 mg/kg every 6 weeks. The OS rate at the end of follow-up was similar between groups (36.6% versus 37.7%), with an adjusted HR for mortality of 1.06 (95% CI, 0.84 to 1.32). All-cause emergency department visits (15.6% versus 14.5%) and hospitalizations (19.7% versus 17.4%) were also comparable. Composite irAEs were reported in 21.0% of the fixed-dose group and 23.2% of the weight-based group.

Results were consistent with noninferiority and suggested similar efficacy and safety between fixed-dose and weight-based pembrolizumab.

Grit et al.³⁶ was a retrospective cohort study with 1,966 participants. The study is at serious risk of bias, primarily due to residual confounding, given that several important prognostic variables (e.g., performance status, brain metastases, and body weight) were not fully accounted for. The study compared standard fixed dosing of pembrolizumab (200 mg every 3 weeks or 400 mg every 6 weeks) with a weight-banded fixed dosing strategy (< 65 kg: 100 mg every 3 weeks or 200 mg every 6 weeks; 65 kg to 90 kg: 150 mg every 3 weeks or 300 mg every 6 weeks; ≥ 90 kg: standard dosing). Median OS was 15.2 months (95% CI, 14.2 to 17.2) with standard dosing and 18.1 months (95% CI, 15.4 to 23.0) with weight-banded fixed dosing. The adjusted HR for OS was 0.83 (95% CI, 0.69 to 1.003; $P = 0.053$), consistent with noninferiority. Time to next treatment or death was also similar between groups (adjusted HR = 0.87; 95% CI, 0.74 to 1.03). No comparative safety outcomes were reported. The study concluded that a modified pembrolizumab dosing strategy using partially lower doses appears to preserve clinical effectiveness in NSCLC.

Patel³⁸ was a retrospective cohort study including 100 patients treated with nivolumab ($n = 47$), pembrolizumab ($n = 36$), durvalumab ($n = 9$), or atezolizumab ($n = 8$). The study included 3 dosing groups:

arm 1 (conventional dose; fixed approved dosing), arm 2 (per-body-weight dose), and arm 3 (low dose), with low-dose atezolizumab defined as 1 mg/kg every 3 weeks. The study is at serious risk of bias, mainly because of serious confounding, given that the nonrandomized dosing groups differed in ICI type, tumour type, clinical setting, and concomitant treatments, and no adjusted analysis was reported. Clinical outcomes were presented only at the overall dosing-group level, not separately by drug. In the palliative setting, arm 1 had CR in 2 of 18 (11.1%) patients, PR in 11 of 18 (61.1%) patients, and PD in 5 of 18 (27.8%) patients, corresponding to an ORR of 72.2%. Arm 2 had CR in 2 of 23 (8.7%) patients, PR in 12 of 23 (52.2%) patients, and PD in 9 of 23 (39.1%) patients, corresponding to an ORR of 60.9%. Arm 3 had CR in 0 of 37 (0%) patients, PR in 28 of 37 (75.7%) patients, and PD in 9 of 37 (24.3%) patients, corresponding to an ORR of 75.7%. Median follow-up was 10.2 months for conventional, fixed dosing, 9.8 months for per-weight dosing, and 3.9 months for low-dose treatment. Median OS was reported only for the overall cohort (6.8 months, range 4.6 to 9.0), with no arm-specific OS estimates provided. Safety outcomes, including AEs and irAEs, were not reported.

Overall, the study suggests that weight-based and lower-dose ICI regimens may provide similar efficacy and safety outcomes to fixed-dose regimens.

Berard⁴⁰ was a retrospective cohort study including 279 patients. The study is at serious risk of bias, mainly due to residual confounding, because the dosing strategy appears to have been influenced by evolving provincial guidance, likely calendar-time and centre effects, limited covariate adjustment, and treatment switching from fixed dosing to weight-based capped dosing. The study compared pembrolizumab fixed dosing (200 mg) with weight-based capped dosing (2 mg/kg up to a maximum of 200 mg). OS did not differ between strategies, with an adjusted HR for fixed-dose versus weight-based capped dose of 0.97 (95% CI, 0.61 to 1.53; $P = 0.88$). Across the overall cohort, median PFS was 9.4 months (95% CI, 6.6 to 11.2) and median OS was 17.3 months (95% CI, 12.9 to Not Reached). Landmark outcomes for the overall cohort were also reported at 6, 12, and 24 months. For toxicity, irAEs causing treatment delay or interruption occurred in 28.6% (14 of 49) of patients in the fixed-dose group and 27.4% (63 of 230) in the weight-based capped-dose group. The median number of cycles before an irAE-related delay or interruption was 5 (range 1 to 36) in the fixed-dose group and 6 (range 1 to 34) in the weight-based capped-dose group.

The study concluded that use of weight-based dosing does not appear to have a negative impact on patient outcomes.

To⁴⁷ was a retrospective chart review cohort study including 64 patients. The study is at serious risk of bias, primarily due to confounding, given that dose allocation was nonrandom and likely influenced by financial and clinical factors. Important baseline and treatment differences existed between groups, including body weight, line of therapy, and cointerventions, and not all key confounders appear to have been adequately controlled. The study compared a lower-dose, weight-based pembrolizumab strategy (2 mg/kg or 100 mg fixed every 3 weeks) with standard fixed-dose pembrolizumab 200 mg every 3 weeks. Median OS was 22.7 months in the lower-dose, weight-based group and not reached in the fixed-dose group, with no statistically significant difference between groups. The fixed-dose group showed higher PFS (6.1 versus 4.5 months; log-rank $P = 0.046$), although the adjusted analysis did not demonstrate a significant difference. ORR was

substantially higher with fixed dosing (53.6% versus 13.9%; $P = 0.001$), whereas DCR was numerically higher (78.6% versus 63.9%; $P = 0.202$). In terms of safety, any-grade irAEs were more frequent with fixed dosing (32% versus 11%; $P = 0.038$), whereas grade 3 or 4 irAEs were similar between groups (7.1% versus 2.8%; $P = 0.577$). Discontinuation due to toxicity was reported only overall (3 of 64, 5%) and not by treatment arm.

Overall, fixed-dose pembrolizumab showed higher observed PFS and ORR, no difference in OS, and more any-grade irAEs.

Lala (2020)⁵⁸ was a PK modelling and simulation (population PK + simulations) study with 2,799 patients. The study evaluated the safety of several pembrolizumab dosing strategies, including fixed dosing (200 mg every 3 weeks or 400 mg every 6 weeks) and weight-based dosing (2 mg/kg every 3 weeks, 10 mg/kg every 2 weeks, and 10 mg/kg every 3 weeks). Safety data were primarily reported for the weight-based dosing groups. In the 2 mg/kg every 3 weeks cohort ($N = 740$), any AEs occurred in 20.0%, grade 3 to 5 AEs in 5.0% of patients, SAEs in 5.5%, discontinuation due to AEs in 2.0%, and deaths due to AEs in 0.3%. In the 10 mg/kg every 2 weeks cohort ($N = 660$), any AEs occurred in 21.5% of patients, grade 3 to 5 AEs in 5.3%, SAEs in 5.0%, discontinuation due to AEs in 3.0%, and no deaths due to AEs were reported. In the 10 mg/kg every 3 weeks pooled cohort ($N = 1,399$), any AEs occurred in 21.7%, grade 3 to 5 AEs in 5.7%, SAEs in 5.9%, and discontinuation due to AEs in 3.4%.

The study concluded that established ER evidence indicates that efficacy and safety were expected to be comparable to the 200 mg and 2 mg/kg every 3 weeks regimens across tumour types.

Tremelimumab

Two studies reported on this ICI.

Fujiwara⁴² was a phase I, open-label trial with 65 participants. For the fixed-versus-weight-based comparison in part 2, 3 cohorts were included: Cohort 1 (weight-based) — 6 doses of tremelimumab 10 mg/kg every 4 weeks then 3 doses every 12 weeks plus 13 doses of durvalumab 15 mg/kg every 4 weeks; cohort 2 (weight-based) — 4 doses of tremelimumab 1 mg/kg every 4 weeks plus 4 doses of durvalumab 20 mg/kg every 4 weeks then 10 mg/kg every 2 weeks (up to 22 doses); and cohort 3 (fixed-dose) — 4 doses of tremelimumab 75 mg every 4 weeks plus 13 doses of durvalumab 1,500 mg every 4 weeks. The study is at serious risk of bias, driven mainly by confounding, because the cohorts were nonrandomized, sequential, very small, and unadjusted for baseline prognostic differences. Moreover, this is not a pure tremelimumab fixed-versus-weight-based comparison because the accompanying durvalumab regimens also differed across cohorts. Pooling the 2 weight-based cohorts, the fixed-dose arm showed lower objective response than the weight-based arms (0 of 6, 0% versus 2 of 10, 20.0%), while disease control was numerically 33.3% in the fixed-dose arm versus 20.0% in the pooled weight-based arms (2 of 6 versus 2 of 10). Toxicity was substantial in both approaches, with any AE reported in 100% versus 90.0%, grade 3 or higher AEs in 50.0% versus 50.0%, and serious AEs in 50.0% versus 50.0% of fixed-dose and pooled weight-based patients, respectively.

The data reported in the study suggest that both weight-based and fixed-dose tremelimumab plus durvalumab regimens were safe and tolerable.

Juergens et al.⁴⁸ was a phase Ib, multicentre, multicohort dose-escalation trial (Rolling Six design) including 136 participants. The study evaluated both weight-based and fixed-dose regimens of durvalumab and tremelimumab across sequential dose levels. Durvalumab dosing included weight-based regimens (15 mg/kg every 3 weeks) and fixed dosing (1,125 mg and 1,500 mg every 3 weeks), while tremelimumab was administered using both weight-based dosing (1 mg/kg and 3 mg/kg) and fixed dosing (56 mg and 75 mg every 3 weeks). The study is at serious risk of bias overall, primarily due to confounding, given that dosing strategies were evaluated in sequential, nonrandomized cohorts without adjustment for baseline or clinical differences. Efficacy and safety outcomes were reported for durvalumab monotherapy (N = 24) and durvalumab plus tremelimumab (N = 112), but not stratified by tremelimumab dosing strategy (fixed versus weight-based). Durvalumab monotherapy achieved an ORR of 29% (CR 4%, PR 25%), while combination therapy demonstrated a higher ORR of 42% (CR 2%, PR 40%). Immune-related AEs were more frequent with combination therapy (77% versus 46%; grade ≥ 3 : 24% versus 4%). However, because outcomes were pooled across multiple tremelimumab dose levels and regimens, no direct comparison between fixed-dose and weight-based tremelimumab could be made.

PK/PD Outcomes

These outcomes are summarized by publication in [Table 14 Appendix 4](#).

Atezolizumab

Ter Heine et al.⁵⁹ was a PK modelling and simulation study that included 500 virtual patients and compared reference dosing regimens with alternative, weight-banded fixed-dosing regimens across multiple ICIs. An alternative weight-banded fixed-dosing atezolizumab regimen (< 70 kg: 840 mg; ≥ 70 kg: 1,200 mg) was compared with the reference fixed dose of 1,200 mg every 3 weeks. The alternative regimen yielded consistently lower modelled exposure, with ratios of 0.82 for cycle 1 trough concentration, steady-state trough concentration, cycle 1 AUC, and AUC_{ss}, suggesting an approximately 18% reduction in exposure relative to the fixed-dose regimen.

The study concluded alternative dosing schedules could reduce drug waste and costs while keeping exposure, effectiveness, and safety similar, based on strong clinical pharmacology data. These regimens may be practical to use in routine care without needing another clinical trial.

Avelumab

Herrera²⁹ was a phase Ib randomized, open-label, parallel-arm PK/PD clinical trial including 31 patients. It evaluated IV avelumab (1-hour infusion) across 4 fixed-dose regimens (70 mg every 2 weeks, 350 mg every 2 weeks, 500 mg every 2 weeks, and 500 mg every 3 weeks) and 1 weight-based dosing regimen (10 mg/kg every 2 weeks). The overall methodological quality of the trial was judged to have some concerns due to deviations from intended interventions (i.e., inclusion of dosing schedules that are a lower intensity than those used in clinical practice), including inconsistent appropriate analyses across outcomes, and potential bias in outcome measurement arising from the unblinded open-label design. Fixed-dose avelumab regimens

generally produced lower systemic exposure than the weight-based regimen of 10 mg/kg every 2 weeks, but the PK profiles were broadly comparable. The most relevant fixed-dose comparison, 500 mg every 2 weeks, showed lower AUC over the dosing interval than 10 mg/kg every 2 weeks at both cycle 1 day 1 (15,436 h × mcg/mL versus 23,780 h × mcg/mL) and cycle 2 day 1 (21,053 h × mcg/mL versus 27,196 h × mcg/mL), and lower $C_{\max}$ at both time points (143 versus 271 mcg/mL at cycle 1; 195 versus 273 mcg/mL at cycle 2). However, trough concentrations at cycle 2 day 1 were more similar between regimens (12.1 mcg/mL for 500 mg every 2 weeks versus 14.4 mcg/mL for 10 mg/kg every 2 weeks), suggesting that fixed dosing may still maintain comparable sustained exposure over the dosing interval. Terminal half-life was also similar across regimens, with values around 105.1 to 110.2 hours for 500 mg every 2 weeks and 93.1 to 101.5 hours for 10 mg/kg every 2 weeks.

Overall, this study suggests that although fixed-dose avelumab, particularly 500 mg every 2 weeks, yields lower overall and peak exposure than weight-based dosing, it may provide broadly similar trough concentrations and elimination characteristics. Also, the target occupancy exceeded 90% across all treatment arms throughout the dosing interval.

Masters⁵¹ was a model-informed drug development study involving PopPK modelling, modelling and simulation, and ER (logistic regression) analyses using trial datasets, with 2,315 patients in the pooled PopPK dataset. PopPK and ER modelling demonstrated that fixed-dose avelumab (800 mg every 2 weeks) produced exposure metrics (AUC, $C_{\max}$, trough concentration [C_{trough}]) that overlapped with those of weight-based dosing (10 mg/kg every 2 weeks), with no meaningful differences across body weight ranges.

Overall, this study suggests similar results for weight-based and fixed dosing for PK outcomes.

Novakovic et al.⁵² was a pharmacometric study using PopPK modelling and simulation based on pooled data from 3 clinical trials (1,827 patients enrolled). The study compared weight-based avelumab (10 mg/kg IV every 2 weeks) with fixed dosing (800 mg IV every 2 weeks). Across 1,663 patients, systemic exposure during the first dosing interval (AUC from time 0 to 336 hours) was comparable between regimens, with median values of 23,160 mg × h/L (range 7,438 to 51,742) for the weight-based dose and 25,913 mg × h/L (range 5,689 to 54,763) for the fixed dose. Variability in exposure was also similar (the coefficient of variation [CV] was 29.0% versus 27.1%, respectively). Exposure varied across body weight strata with fixed dosing, showing relatively higher exposure in lower-weight patients and lower exposure in higher-weight patients, whereas weight-based dosing resulted in more consistent exposure across weight groups.

Overall, this study suggests similar systemic exposure, yet higher exposure may occur in lower-weight patients.

Cemiplimab

Yang⁶⁰ was a PopPK modelling and simulation study using pooled clinical trial PK data, focusing on 548 patients. The weight-based dosing regimens considered in this study were 1 mg/kg IV every 2 weeks, 3 mg/kg IV every 2 weeks, and 3 mg/kg every 3 weeks. The fixed dosing regimens considered were 200 mg IV every 2 weeks and 350 mg every 3 weeks. The study reported that the weight-based and fixed dosing regimens of cemiplimab demonstrated comparable exposure profiles at a steady state. Specifically, when

comparing the commonly used regimens of 3 mg/kg every 2 weeks (weight-based) and 350 mg every 3 weeks (fixed dose), the reported steady-state exposure across body weight quartiles was similar. For 3 mg/kg every 2 weeks, the AUC over 6 weeks at steady state ranged from 3,280 day × mg/L to 4,200 day × mg/L and the trough concentration at steady state ranged from 58.4 mg/L to 74.0 mg/L, whereas for 350 mg every 3 weeks, the AUC over 6 weeks at steady state ranged from 3,190 day × mg/L to 4,510 day × mg/L and the trough concentration at steady state ranged from 49.0 mg/L to 70.3 mg/L. These overlapping exposure ranges across weight quartiles suggest that fixed dosing achieves pharmacokinetic exposures comparable to weight-based dosing, with no substantial impact of body weight on drug exposure. The elimination half-life at steady state was also consistent across patient groups, reported as approximately 544.8 hours in responders and 448.8 hours in patients whose disease did not respond to treatment, further supporting stable PK across dosing strategies. The findings suggest that fixed-dose cemiplimab 350 mg every 3 weeks provides pharmacokinetic exposure comparable to weight-based 3 mg/kg every 2 weeks, with body weight having only a modest, not clinically meaningful, effect on exposure.

Rischin et al. (2024)³⁹ was an open-label, nonrandomized phase II sequential cohort study that compared pooled earlier cohorts (groups 1 to 3, including weight-based cemiplimab 3 mg/kg every 2 weeks and fixed 350 mg every 3 weeks; n = 193) with fixed-dose cemiplimab 600 mg every 4 weeks (group 4; n = 63) in advanced cutaneous squamous cell carcinoma. Methodological quality was at serious risk of bias for fixed-versus-weight-based inference because the comparison involved nonrandomized sequential cohorts and a mixed pooled comparator rather than a pure weight-based arm and acknowledged baseline imbalances without adjusted head-to-head analyses. Based on observed steady-state concentrations at weeks 17 to 19, $C_{\text{trough}}/C_{\text{min}}$ was similar between regimens, with mean concentrations of 68.4 mg/L for the weight-based group and 62.7 mg/L for the fixed-dose group. C_{max} was also very similar, with mean concentrations of 150 mg/L and 151 mg/L, respectively. Half-life and AUC were not reported for this direct fixed-versus-weight-based comparison. Overall, these data suggest broadly comparable steady-state exposure between the weight-based and fixed-dose regimens.

Paccaly et al.⁶¹ was a pooled PopPK modelling and simulation analysis with 505 patients. The study found that fixed-dose cemiplimab 350 mg IV every 3 weeks produced PK exposure broadly similar to weight-based cemiplimab 3 mg/kg IV every 2 weeks. After the first dose, the fixed-dose regimen had higher C_{max} , slightly higher C_{trough} , and slightly higher AUC over 6 weeks. At steady state, the fixed-dose regimen still had a higher C_{max} , but C_{trough} was slightly lower than with weight-based dosing, while overall AUC remained very similar. Half-life was reported overall rather than by arm, increasing from 12.5 days after the first dose to 19.2 days at steady state.

Overall, the modelling reported in this study supports that fixed dosing provides comparable overall exposure to weight-based dosing.

Dostarlimab

Patnaik et al.⁴⁶ was an open-label, first-in-human phase I cohort study. Patnaik et al. compared weight-based dostarlimab regimens of 1 mg/kg, 3 mg/kg, and 10 mg/kg every 2 weeks with fixed-dose regimens of 500 mg every 3 weeks and 1,000 mg every 6 weeks. Across these cohorts, fixed dosing produced PK

profiles broadly comparable to the higher weight-based regimens. In the weight-based groups, terminal half-life ranged from 10.2 to 20.5 days, while in the fixed-dose groups it was 14.5 days for 500 mg every 3 weeks and 19.6 days for 1,000 mg every 6 weeks. The 500 mg every 3 weeks fixed regimen showed PK values close to the 10 mg/kg every 2 weeks regimen, with AUC over the dosing interval of 35,730 versus 36,480 mcg × h/mL to 63,670 mcg × h/mL, C_{max} of 171.1 versus 228.4 mcg/mL to 251.1 mcg/mL, and C_{trough} of 39.17 versus 53.15 mcg/mL to 60.63 mcg/mL. The 1,000 mg every 6 weeks fixed regimen produced the highest overall exposure, with AUC over the dosing interval 95,820 mcg × h/mL and C_{max} 309.4 mcg/mL, while maintaining a C_{trough} of 40.20 mcg/mL, still within the general range observed with higher weight-based dosing. Clearance (CL) was also similar across regimens, ranging from 0.160 L/day to 0.302 L/day for weight-based dosing and 0.212 L/day to 0.216 L/day for fixed dosing, with broadly comparable volume of distribution during terminal phase (V_z) and volume of distribution at steady state (V_{ss}) values.

Overall, these findings suggest that fixed dosing achieved predictable and sustained exposure comparable to weight-based dosing, supporting the PK feasibility of 500 mg every 3 weeks and 1,000 mg every 6 weeks as alternatives to weight-based regimens. Regarding PD outcomes, PD-1 receptor occupancy was essentially complete across both weight-based and fixed-dose dostarlimab regimens, except for 1 patient in the 1 mg/kg cohort.

Durvalumab

Fujiwara⁴² was a phase I, open-label trial with 65 participants that included both weight-based and fixed-dose regimens, but the comparison should be interpreted cautiously because the cohorts did not use equivalent durvalumab doses and also differed in the accompanying tremelimumab regimen. The weight-based cohorts received durvalumab 15 mg/kg every 4 weeks (cohort 1) or 4 doses of 20 mg/kg every 4 weeks then 10 mg/kg every 2 weeks (cohort 2), whereas the fixed-dose cohort received durvalumab 1,500 mg every 4 weeks (cohort 3). In the single-dose PK analysis, exposure was numerically highest in the fixed-dose cohort: AUC from time 0 to last measurable time point (AUC_{0-t}) 4,680 day mcg/mL, C_{max} 439 mcg/mL, and C_{min} 77.7 mcg/mL for 1,500 mg every 4 weeks, compared with AUC_{0-t} 3,390, C_{max} 353, C_{min} 55.4 for 20 mg/kg every 4 weeks and AUC_{0-t} 2,980, C_{max} 278, C_{min} 40.9 for 15 mg/kg every 4 weeks. After multiple doses, the fixed-dose cohort also showed higher steady-state exposures than the weight-based 20 mg/kg cohort, with C_{maxss} 847 versus 404 mcg/mL and C_{minss} 200 versus 94.6 mcg/mL. Overall, this study suggests that fixed-dose durvalumab 1,500 mg every 4 weeks produced higher PK exposure than the tested weight-based regimens, but because this was not a head-to-head comparison of equivalent fixed versus weight-based dosing, the findings are best considered descriptive rather than definitive evidence of superiority of 1 dosing strategy over the other.

Juergens et al.⁴⁸ represents a phase Ib, multicentre, multicohort dose-escalation trial (Rolling Six design) with 136 participants. Durvalumab PK was evaluated across both weight-based (15 mg/kg every 3 weeks) and fixed-dose regimens (1,125 mg and 1,500 mg every 3 weeks), administered either as monotherapy or in combination with tremelimumab. Overall, exposure metrics were broadly comparable across dosing strategies. Mean peak concentrations (C_{max}) ranged from 320 mcg/mL for 15 mg/kg monotherapy to 378 mcg/mL to 474 mcg/mL for fixed-dose regimens, while trough concentrations (C_{trough}) were within a similar

range across regimens (approximately 54.6 mcg/mL to 84.5 mcg/mL). Notably, fixed dosing (1,125 mg and 1,500 mg) produced C_{trough} values (54.6 mcg/mL to 78.5 mcg/mL) that overlapped with those observed for weight-based dosing (59.7 mcg/mL to 84.5 mcg/mL), despite variability across dose levels and combination arms. Although AUC was not reported, the comparable C_{max} and C_{trough} profiles suggest that fixed dosing achieves similar systemic exposure to weight-based dosing, supporting PK comparability across these dosing approaches.

Ter Heine et al.⁵⁹ was a PK modelling and simulation study that included 500 virtual patients and compared reference dosing regimens with alternative, weight-banded fixed-dosing regimens across multiple ICIs. The reference dosing regimen for this ICI was every 4 weeks: 20 mg/kg; whereas the alternative dosing regimens were durvalumab (every 2 weeks): less than 60 kg: 480 mg; 60 kg to 80 kg: 600 mg; more than 80 kg: 720 mg; and durvalumab (every 4 weeks): less than 60 kg: 960 mg; 60 kg to 80 kg: 1,200 mg; more than 80 kg: 1,440 mg. According to the findings, durvalumab every 2 weeks versus every 4 weeks produced very similar exposure, with the geometric mean ratios for C_{trough} and AUC being 0.87 at both the end of cycle 1 and at steady state.

Ipilimumab

Ter Heine et al.⁵⁹ was a PK modelling and simulation study that included 500 virtual patients. Ipilimumab exposure was evaluated by comparing a reference weight-based regimen (1 mg/kg every 6 weeks) with an alternative weight-banded fixed-dose strategy (< 60 kg: 50 mg; 60 kg to 90 kg: 75 mg; > 90 kg: 100 mg). PK modelling demonstrated equivalent exposure between dosing approaches, with geometric mean ratios of 1.0 for C_{trough} (both at end of first cycle and steady state) and 1.0 for AUC (both early and steady state). These findings indicate that the alternative weight-banded fixed dosing strategy achieves virtually identical systemic exposure to standard weight-based dosing, suggesting no meaningful PK differences between the regimens.

Nivolumab

Albiges et al.,²⁸ the largest trial in our included studies for this ICI, was a phase III, open-label, randomized, noninferiority trial (CheckMate 67T; NCT04810078) with 495 patients. There is some concern of bias, mostly due to lack of analysis plans in the protocol. It evaluated SC nivolumab 1,200 mg plus rHuPH20 20,000 units every 4 weeks versus IV nivolumab 3 mg/kg every 2 weeks. Overall, the fixed-dose SC regimen produced substantially higher exposure than the weight-based IV regimen. In the SC arm, geometric mean exposures were an average concentration over 28 days (C_{avgd28}) of 77.343 mcg/mL, minimum (trough) concentration at steady state (C_{minss}) of 122.227 mcg/mL, maximum concentration after first dose or first cycle (C_{max1}) of 108 mcg/mL, minimum concentration over 28 days (study-defined) ($C_{\text{min-d28}}$) of 50.8 mcg/mL, maximum concentration at steady state (C_{maxss}) of 230 mcg/mL, average concentration at steady state (C_{avgss}) of 182 mcg/mL, and week-17 C_{trough} 123 mcg/mL. In the IV weight-based arm, corresponding values were C_{avgd28} 36.875 mcg/mL, C_{minss} 68.901 mcg/mL, C_{max1} 91 mcg/mL, $C_{\text{min-d28}}$ 31.9 mcg/mL, C_{maxss} 160 mcg/mL, C_{avgss} 92.5 mcg/mL, and week-17 C_{trough} 66.3 mcg/mL. The reported geometric mean ratios confirmed higher exposure with fixed SC dosing, with C_{avgd28} ratio 2.098 (90%, CI 2.001 to 2.200) and C_{minss} ratio 1.774 (90% CI 1.633 to 1.927) versus the weight-based IV regimen. SC nivolumab (1,200 mg every 4 weeks) was noninferior to IV weight-based nivolumab (3 mg/kg every 2 weeks) in terms of pharmacokinetics and ORR, with comparable

safety and no new safety signals identified. Additionally, with respect to pharmacodynamics, at day 29, fixed-dose SC nivolumab and weight-based IV nivolumab showed similarly high PD-1 receptor occupancy on circulating CD3+, CD4+, and CD8+ T cells, with slightly higher median occupancy in the fixed-dose SC group for CD3+ (97.0% versus 94.7%) and CD4+ (98.3% versus 93.1%) cells and nearly identical occupancy for CD8+ cells (96.8% versus 96.3%). These results indicated broadly comparable pharmacodynamic target engagement between dosing strategies.

Kato⁴⁹ was a retrospective cohort study with 19 patients. This study is at serious risk of bias, driven primarily by confounding. Notably, serum albumin was significantly greater in the fixed-dose group compared to the weight-based group. Serum albumin is an indicator of the level of cachexia, with low serum albumin suggesting a worsened disease severity. Thus, the difference in serum albumin observed in this study suggests a source of residual confounding associated with prognosis and clinical status. The study compared 3 mg/kg every 2 weeks with 240 mg every 2 weeks and found consistently higher trough concentrations with flat dosing across cycles 2 to 5. Mean (standard deviation [SD]) $C_{\min}$ values for 3 mg/kg every 2 weeks were 14.2 (1.9), 21.5 (2.4), 33.0 (4.6), and 31.4 (4.1) before cycles 2, 3, 4, and 5, respectively, whereas corresponding values for 240 mg every 2 weeks were 27.5 (2.4), 43.3 (4.2), 57.9 (7.0), and 58.6 (8.8).

Between-group differences were statistically significant at all measured time points ($P < 0.01$, $P < 0.01$, $P = 0.01$, and $P = 0.02$, respectively), suggesting that fixed 240 mg every 2 weeks produced substantially higher trough exposure than weight-based 3 mg/kg every 2 weeks.

Gandhi⁵³ represents a prospective, PK study with 25 patients. The study compared a weight-based conventional regimen (3 mg/kg IV every 2 weeks or every 3 weeks) with a fixed low-dose regimen (40 mg flat IV every 2 weeks or every 3 weeks) in a PK analysis. The terminal half-life was broadly similar between groups (264 hours for 3 mg/kg versus 283 hours for 40 mg), but systemic exposure was substantially lower with fixed low-dose nivolumab: $C_{\max}$ was 47.3 mcg/mL with 3 mg/kg versus 9.06 mcg/mL with 40 mg, and AUC_{0-t} was 238 mcg $\times$ day/mL versus 44.3 mcg $\times$ day/mL, respectively. Dose-normalized AUC_{0-t} was relatively close (0.0014 versus 0.0011 day/mL/mg), suggesting broadly comparable exposure per mg administered, but the absolute exposure achieved with the 40 mg fixed dose remained markedly lower than with the 3 mg/kg weight-based regimen.

Zhao et al. (2024)⁶² was a model-based PopPK analysis using phase I or II CheckMate 8KX trial SC nivolumab data pooled with 19 historical IV nivolumab studies, with 3,540 total in the PopPK dataset; 82 patients received SC nivolumab in the CheckMate 8KX trial and 3,458 came from 19 historical IV studies, comparing weight-based nivolumab 3 mg/kg IV every 2 weeks, with 10 mg/kg IV every 2 weeks as an upper safe-exposure reference, versus fixed-dose nivolumab 720 mg SC every 4 weeks, 960 mg SC every 4 weeks, and 1,200 mg SC every 4 weeks (with rHuPH20) in model-based simulations. PK results showed that 720 mg SC every 4 weeks gave exposure similar to 3 mg/kg IV every 2 weeks, while 960 mg and 1,200 mg SC every 4 weeks gave higher trough and average exposure, but all SC regimens remained below the 10 mg/kg IV every 2 weeks benchmark; SC dosing also had a lower, delayed peak concentration than IV dosing.

Ter Heine et al.⁵⁹ was a PK modelling and simulation study that included 500 virtual patients. The study compared standard reference regimens with alternative weight-banded fixed-dose strategies. The reference regimens were 3 mg/kg every 2 weeks and 360 mg every 3 weeks. The alternative regimens were every 2 weeks: less than 50 kg = 120 mg; 50 kg to 75 kg = 160 mg; 75 kg to 100 kg = 200 mg; more than 100 kg = 240 mg; and every 3 weeks: less than 60 kg = 280 mg; 60 kg to 90 kg = 320 mg; more than 90 kg = 360 mg. Compared with the reference regimens, the alternative dosing produced slightly lower exposures. For every 2 weeks, ratios of alternative to reference dosing were 0.90 for geometric mean trough concentration at the end of cycle 1, 0.91 at steady state, 0.87 for AUC at the end of cycle 1, and 0.90 for steady-state AUC. For every 3 weeks, the corresponding ratios were 0.82, 0.81, 0.83, and 0.82, respectively.

Overall, this suggests that the alternative weight-banded nivolumab regimens yielded exposures modestly less than the standard weight-based or flat reference regimens, with the alternative of every 2 weeks remaining closer to the reference than the every 3 weeks alternative.

Sanghavi et al.⁵⁶ was a model-based ER and benefit-risk analysis with 448 patients in the adjuvant melanoma efficacy dataset from the CheckMate 238 trial and 3,008 patients in the pooled safety dataset across 14 studies. It compared weight-based nivolumab 3 mg/kg every 2 weeks with fixed dosing of 240 mg every 2 weeks and 480 mg every 4 weeks. For PK, 240 mg every 2 weeks produced nearly identical exposure to 3 mg/kg every 2 weeks, with very similar minimum concentration after first dose or first cycle (C_{min1} 25.0 mcg/mL versus 24.7 mcg/mL), C_{minss} (96.8 mcg/mL versus 95.6 mcg/mL), C_{max1} (70.6 mcg/mL versus 69.5 mcg/mL), C_{maxss} (171 mcg/mL versus 169 mcg/mL), and C_{avgss} (119 mcg/mL versus 118 mcg/mL). The 480 mg every 4 weeks regimen showed a different concentration profile, with higher peak concentrations (C_{max1} 141 mcg/mL; C_{maxss} 227 mcg/mL) and lower trough concentrations at steady state (C_{minss} 81.8 mcg/mL), but a similar average steady-state exposure (C_{avgss} 119 mcg/mL).

Overall, these findings suggest that fixed-dose nivolumab provides comparable overall PK exposure to weight-based dosing, with 240 mg every 2 weeks most closely matching the standard 3 mg/kg every 2 weeks regimen.

In **Sheng et al.**⁵⁴, 240 mg every 2 weeks (fixed dose) was evaluated against 3 mg/kg every 2 weeks and 10 mg/kg every 2 weeks. Compared with the standard weight-based 3 mg/kg every 2 weeks, the fixed 240 mg every 2 weeks regimen resulted in consistently higher exposure, with geometric mean increases of approximately 26% to 27% across all PK metrics (C_{min} , C_{max} , and C_{avg} at both cycle 1 and steady state). In contrast, when compared with the higher weight-based 10 mg/kg every 2 weeks regimen, the fixed dose produced substantially lower exposure, with reductions of approximately 60% to 62% across all PK parameters. Absolute exposure values supported these findings, with higher concentrations observed in the 240 mg group relative to 3 mg/kg, but markedly lower than 10 mg/kg.

Overall, these results indicate that fixed 240 mg every 2 weeks provides modestly higher exposure than standard weight-based dosing (3 mg/kg), while remaining substantially less than high-dose weight-based exposure (10 mg/kg), suggesting comparable exposure within the clinically relevant dosing range.

Zhao (2020)⁵⁵ compared weight-based nivolumab 3 mg/kg IV every 2 weeks with fixed-dose nivolumab 240 mg IV every 2 weeks and 480 mg IV every 4 weeks. At steady state, 240 mg every 2 weeks produced PK exposure metrics very similar to 3 mg/kg every 2 weeks, with slightly higher concentrations overall: $C_{\min ss}$ 70.6 mcg/mL versus 67.2 mcg/mL, $C_{\max ss}$ 136.0 mcg/mL versus 129.1 mcg/mL, and C_{avgss} 91.2 mcg/mL versus 86.7 mcg/mL, corresponding to differences of about 5% across these measures. In contrast, 480 mg every 4 weeks maintained the same average steady-state concentration as 240 mg every 2 weeks (C_{avgss} 91.2 mcg/mL), but showed a different exposure pattern, with a lower trough concentration ($C_{\min ss}$ 56.3 mcg/mL) and a higher peak concentration ($C_{\max ss}$ 185.1 mcg/mL). AUC was not reported, so this comparison is based on $C_{\min ss}$, $C_{\max ss}$, and C_{avgss} only.

Overall, this modelling study suggests that fixed-dose 240 mg every 2 weeks provides PK exposure closely comparable to weight-based 3 mg/kg every 2 weeks, whereas fixed-dose 480 mg every 4 weeks maintains similar average exposure but produces greater peak-to-trough fluctuation.

Bei (2020)⁵⁷ compared weight-based nivolumab 3 mg/kg IV every 2 weeks with fixed-dose nivolumab 240 mg IV every 2 weeks. Based on the reported PK modelling results, the fixed 240 mg every 2 weeks regimen produced higher modelled exposure than the 3 mg/kg every 2 weeks regimen across all reported parameters. Specifically, geometric mean C_{avgd28} was 44.6 mcg/mL versus 32.5 mcg/mL, $C_{\min -d28}$ was 38.4 mcg/mL versus 27.9 mcg/mL, and $C_{\max 1}$ was 76.1 mcg/mL versus 55.3 mcg/mL. Variability was broadly similar between regimens, with CVs of 21.4% versus 20.6% for C_{avgd28} , 27.7% versus 25.8% for $C_{\min -d28}$, and 21.0% versus 18.3% for $C_{\max 1}$. These results correspond to approximately 37% higher exposure with 240 mg every 2 weeks than with 3 mg/kg every 2 weeks across all 3 PK parameters.

Overall, this study suggests that fixed dosing at 240 mg every 2 weeks results in modestly higher early nivolumab exposure than weight-based 3 mg/kg every 2 weeks, while maintaining similar variability.

Pembrolizumab

Cohen⁶³ was an open-label, phase I, single-arm multicohort clinical trial (cohort B) with 101 patients. ROBINS-I was not applicable because this was a single-arm, nonrandomized study without a concurrent comparator group; although observed outcomes were compared with model-predicted exposures from other regimens, these were indirect external modelling benchmarks rather than a true nonrandomized intervention comparison. Pembrolizumab 400 mg every 6 weeks (fixed dosing) was evaluated and compared indirectly with model-predicted and historical exposures from both fixed (200 mg every 3 weeks) and weight-based regimens (2 mg/kg every 3 weeks and 10 mg/kg every 2 weeks). The geometric mean $C_{\max}$ with 400 mg every 6 weeks was substantially lower than the high-dose weight-based regimen (10 mg/kg every 2 weeks), being approximately 42% lower at cycle 1 and 65% lower at steady state. In contrast, trough concentrations (C_{trough}) were broadly comparable to standard regimens: compared with fixed 200 mg every 3 weeks, C_{trough} was modestly lower (17% at cycle 1 and 22% at steady state), while compared with weight-based 2 mg/kg every 3 weeks, C_{trough} was slightly higher (12% at cycle 1 and 4% at steady state).

Overall, these findings suggest that fixed dosing (400 mg every 6 weeks) achieves exposure levels comparable to standard weight-based and fixed regimens at clinically relevant trough levels, despite lower peak concentrations relative to higher-dose weight-based schedules.

Lala (2025)⁶⁴ was a population PK model-based simulation using data from 3,607 patients. Simulated pembrolizumab regimens included fixed dosing (200 mg every 3 weeks, 400 mg every 6 weeks) and weight-based dosing (2 mg/kg every 3 weeks and an alternative 4 mg/kg regimen as reported). The 2 fixed regimens produced nearly identical geometric mean AUC values overall (1,744 mcg × mL for 200 mg every 3 weeks and 1,756 mcg × mL for 400 mg every 6 weeks), indicating similar total exposure between these fixed schedules. However, trough concentrations differed, with higher overall C_{trough} for 200 mg every 3 weeks (28.3 mcg/mL) than for 400 mg every 6 weeks (17.9 mcg/mL). Compared with 2 mg/kg every 3 weeks, fixed dosing was associated with higher overall exposure, both for AUC (1,744 mcg × mL and 1,756 mcg × mL versus 1,293 mcg × mL) and C_{trough} (28.3 mcg × mL and 17.9 mcg × mL versus 21.0 mcg/mL, depending on schedule). Across body weight strata, fixed dosing resulted in higher exposure in lower-weight patients and lower exposure in higher-weight patients, whereas weight-based dosing showed more consistent exposure across body weights. Despite these differences, the exposure distributions overlapped substantially across regimens. PD activity appears to be comparable across 400 mg every 6 weeks, 200 mg every 3 weeks, and 2 mg/kg every 3 weeks, based on similar exposure within the established flat ER range.

Ter Heine et al.⁵⁹ was a PK modelling and simulation study that included 500 virtual patients. The study evaluated pembrolizumab 2 mg/kg every 3 weeks as the reference weight-based regimen versus an alternative weight-banded fixed-dose regimen of 100 mg every 3 weeks for patients less than 60 kg and 150 mg every 3 weeks for patients more than 60 kg. PK/PD modelling showed that the alternative regimen yielded equivalent predicted exposure to the reference regimen, with ratios of 1.0 for geometric mean C_{trough} at the end of cycle 1, C_{trough} at steady state, AUC at the end of cycle 1, and AUC at steady state. Overall, these findings suggest no meaningful difference in modelled pembrolizumab exposure between the fixed weight-banded and weight-based dosing strategies.

Lala (2020)⁵⁸ is a PK modelling and simulation study (population PK + simulations) with 2,799 patients. The study evaluated fixed-dosing regimens of pembrolizumab (200 mg every 3 weeks and 400 mg every 6 weeks) against weight-based regimens (2 mg/kg every 3 weeks and 10 mg/kg every 2 weeks). Compared with the standard fixed regimen of 200 mg every 3 weeks, the 400 mg every 6 weeks regimen produced similar average exposure (C_{avgss} + 0.7%) but lower trough concentrations (C_{minss} -34%) and higher peak concentrations (C_{maxss} + 59%). When compared with the weight-based 2 mg/kg every 3 weeks regimen, 400 mg every 6 weeks resulted in higher average exposure (C_{avgss} + 35%), modestly lower trough levels (C_{minss} -12%), and substantially higher peak concentrations (C_{maxss} + 113%). In contrast, compared with the higher weight-based dose of 10 mg/kg every 2 weeks, 400 mg every 6 weeks yielded markedly lower overall exposure (C_{avgss} -81.8%) and peak concentrations (C_{maxss} -65.6%), supporting its positioning within the established ER safety range. Overall, these findings suggest that fixed-dosing regimens provide comparable or clinically acceptable exposure relative to weight-based dosing, despite differences in peak and trough variability.

Tremelimumab

Fujiwara⁴² was a phase I, open-label trial with 65 participants and 3 cohorts: cohort 1 (weight-based) — 6 doses of tremelimumab 10 mg/kg every 4 weeks then 3 doses every 12 weeks plus 13 doses of durvalumab

15 mg/kg every 4 weeks; cohort 2 (weight-based) — 4 doses of tremelimumab 1 mg/kg every 4 weeks plus 4 doses of durvalumab 20 mg/kg every 4 weeks then 10 mg/kg every 2 weeks (up to 22 doses); and cohort 3 (fixed-dose) — 4 doses of tremelimumab 75 mg every 4 weeks plus 13 doses of durvalumab 1,500 mg every 4 weeks. Overall, systemic exposure was substantially higher with the higher weight-based dose (10 mg/kg) compared with both the lower weight-based (1 mg/kg) and fixed-dose (75 mg) regimens. Specifically, single-dose tremelimumab exposure (AUC_{0-t}) was 2,010 day $\times$ mcg/mL for 10 mg/kg, compared with 153 mg/day for 1 mg/kg and 239 mg/day for the 75 mg fixed dose, with corresponding increases in C_{max} and C_{min} . Importantly, the fixed-dose (75 mg) produced slightly higher exposure than the low weight-based dose (1 mg/kg) (AUC 239 versus 153; C_{min} 3.35 mcg/mL versus 2.71 mcg/mL), suggesting comparable or modestly greater exposure at lower dosing levels. At steady state, accumulation was also greater in the fixed-dose regimen than in the low weight-based regimen, with higher accumulation ratio values (e.g., C_{min} : 2.03 versus 1.44) and higher steady-state concentrations (C_{minss} : 9.20 mcg/mL versus 4.14 mcg/mL), indicating greater drug accumulation and sustained exposure with fixed dosing. Similar patterns were observed for durvalumab, for which the fixed-dose combination (1,500 mg) yielded the highest exposure (AUC_{0-t} 4,680 versus 3,390 and 2,980 in weight-based cohorts). Overall, these findings suggest that fixed dosing (75 mg) achieves exposure comparable to or higher than lower weight-based dosing (1 mg/kg), with greater accumulation over time, while higher weight-based dosing (10 mg/kg) predictably results in the greatest exposure. This supports the PK feasibility of fixed dosing, particularly at lower dose ranges, although no direct exposure-matching equivalence analysis was reported.

Juergens et al.⁴⁸ was a phase Ib, multicentre, multicohort dose-escalation trial using a Rolling Six design (N = 136). The study evaluated tremelimumab PK across weight-based and fixed-dose regimens within durvalumab combination cohorts: 1 mg/kg every 3 weeks (dose level [DL] 1, DL2a), 3 mg/kg every 3 weeks (DL2b), 56 mg every 3 weeks (DL3), and 75 mg every 3 weeks (DL4). Based on the reported PK results, exposure with fixed-dose tremelimumab 75 mg every 3 weeks was broadly comparable to that observed with 1 mg/kg every 3 weeks, whereas 3 mg/kg every 3 weeks produced clearly higher concentrations. Specifically, the mean C_{max} and C_{trough} were 24.6 mcg/mL and 4.66 mcg/mL in DL1 and 25.6 mcg/mL and 4.34 mcg/mL in DL2a for 1 mg/kg, compared with 26.6 mcg/mL and 5.55 mcg/mL for the fixed 75 mg regimen. In contrast, the fixed 56 mg every 3 weeks regimen showed somewhat lower exposure (18.56 mcg/mL and 3.65 mcg/mL), while 3 mg/kg every 3 weeks yielded substantially higher values (73.2 mcg/mL and 13.5 mcg/mL). AUC was not reported, so comparisons are limited to peak and trough concentrations.

Overall, these findings suggest that fixed-dose tremelimumab 75 mg every 3 weeks achieves PK exposure similar to 1 mg/kg every 3 weeks, whereas 56 mg every 3 weeks may result in somewhat lower exposure and 3 mg/kg every 3 weeks in markedly higher exposure.

Hwang et al.⁶⁵ conducted a PopPK modelling study using a pooled nonlinear mixed-effect modelling methodology (NONMEM) analysis, with external validation based on additional pooled studies, including 956 participants. The interventions and comparators included tremelimumab administered intravenously, both as monotherapy and in combination with durvalumab, across multiple phase I to III solid-tumour studies. Dosing regimens comprised weight-based dosing (e.g., 1 mg/kg, 3 mg/kg, and 10 mg/kg every 4 weeks) and flat dosing (e.g., 750 mg every 4 weeks for monotherapy; 75 mg every 4 weeks in combination). Tremelimumab

had an estimated half-life of approximately 18 days (about 432 hours). The study did not provide a direct observed head-to-head comparison with summary AUC, $C_{\max}$, or $C_{\min}$ estimates presented uniformly for fixed versus weight-based dosing; instead, it used model-based simulations. Reported exposure metrics included cycle 1 $C_{\min}$ and $C_{\max}$ by dose group and average exposure over the first 16 weeks for the comparison of 75 mg fixed dosing versus 1 mg/kg weight-based dosing. Simulation results suggested broadly comparable exposure, with overlap proportions of approximately 86.3% in patients more than 90 kg, 73.7% in those more than 110 kg, 72.0% in those less than 50 kg, and 63.6% in those less than 40 kg.

Overall, this study supports that fixed-dose tremelimumab 75 mg provides comparable model-predicted exposure to 1 mg/kg weight-based dosing, but the evidence comes from population PK modelling rather than a direct comparative PK/PD trial.

System- and Implementation-Related Outcomes

The studies included in our review did not contain any results pertaining to system- and implementation-related outcomes (e.g., preparation time, risk of repetitive strain injuries for staff, resource use, staff workflow, or satisfaction).

Limitations

Main Take-Aways

This report suggests that the available evidence is not consistent enough to support a single “best” dosing approach in every setting or for specific ICIs. We did not pool results in a meta-analysis or formally rate certainty of evidence using GRADE; our findings are presented descriptively and do not include formal estimates of effect or certainty.

This review is reported according to the PRISMA checklist ([Appendix 7](#)), but it has several important limitations that should be considered when interpreting the findings.

First, we did not conduct a quantitative meta-analysis. Because the included evidence was heterogeneous in terms of study designs (e.g., clinical trials, nonrandomized studies, PK/PD models), dosing, and intervention components, we summarized results descriptively rather than pooling effect estimates. As a result, we could not generate an overall quantitative estimate of effect, formally evaluate statistical heterogeneity, or explore modifiers (e.g., cancer type, line of therapy, dosing frequency) using meta-regression or subgroup meta-analyses.

Second, we did not apply the GRADE framework to assess confidence in the body of evidence.⁶⁶ Without a structured certainty assessment, our ability to scientifically and clinically interpret the overall strength of the evidence is limited. In particular, it is more difficult to judge how methodological or analytical issues such as imprecision, inconsistency, indirectness, and publication bias affect the credibility and applicability of the conclusions.

Third, risk-of-bias assessment was challenging for PK/PD modelling studies. Although reporting guidance and checklists exist for pharmacometric and PK/PD model studies, there is no widely accepted, validated risk-of-bias tool tailored to these designs. Consequently, we could not apply a standardized approach to evaluate internal validity for this important subset of evidence.

Conclusions and Implications for Decision- or Policy-Making

Main Take-Aways

The evidence on different ICI dosing regimens is inconsistent; therefore, firm comparative clinical conclusions are often not possible. Policy decisions may need to weigh this uncertainty alongside feasibility, patient burden, and patient preferences.

Conclusions

Efficacy, Effectiveness, and Safety Outcomes

Overall, there was limited direct head-to-head clinical evidence comparing fixed versus weight-based dosing. Most comparative evidence involved pembrolizumab and nivolumab, with less evidence available for the other ICIs. Across studies evaluating fixed dosing versus weight-based dosing, patients often had comparable survival, progression, treatment response, and rate of serious side effects. However, the evidence was not rigorous for all ICIs. Many studies also had important methodological flaws in their design, conduct, and analysis, such as small sample sizes, nonrandomized designs, and differences between patient groups.

Pharmacokinetic and Pharmacodynamics Outcomes

The evidence suggests that fixed-dose and weight-based dosing often give patients a similar average drug exposure, whereas extended-interval regimens — such as dosing every 4 or 6 weeks — may produce higher peak drug concentrations and lower trough concentrations. Some studies also showed that fixed dosing may lead to higher exposure in lower-weight patients and lower exposure in higher-weight patients; however, these differences appeared minimal and were not explicitly linked to meaningful differences in clinical outcomes.

Overall Conclusion

Overall, the evidence suggests that fixed-dose and weight-based regimens often produce comparable clinical outcomes, particularly for nivolumab and pembrolizumab, which had the largest body of evidence. Evidence describing pharmacokinetics and pharmacodynamics suggested that fixed dosing results in a similar average drug exposure compared with weight-based dosing, though extended-interval regimens may produce higher peak and lower trough concentrations.

However, many of the included studies had weaknesses that make the results less reliable, and we could not draw firm conclusions for all drugs and cancer types. Decisions regarding ICI dosing policy should weigh the

conclusions together with this uncertainty, while also considering patient burden, patient preferences, and health system resource impacts.

Comparison With the Previous INESSS Report: Key Differences and Similarities

INESSS Report (2022)

The INESSS report⁷ published in 2022 focused on 7 ICIs (atezolizumab, avelumab, cemiplimab, dostarlimab, durvalumab, nivolumab, pembrolizumab). The review examined scientific efficacy, safety and PK data from systematic reviews of primary studies, pharmacoeconomic data, and recommendations from clinical practice guidelines to examine different dosing strategies of different ICI drugs. These data were enriched with information specific to the Quebec context and with experiential knowledge provided by clinicians with different expertise and specialties. The results of this systematic review were presented in the form of a narrative synthesis. For each efficacy and safety end point, a summary statement of scientific evidence is provided, to which an overall level of scientific evidence was assigned. The recommendations were developed in collaboration with an advisory committee. The information on contextual and experiential data is presented in narrative form and is summarized in tables. Lastly, the overall quality of the initiative, its acceptability and applicability were evaluated using external reviewers who specialize in the field of interest and who did not take part in the work.

The methodological quality was assessed using R-AMSTAR (Revised Assessment of Multiple Systematic Reviews)⁶⁷ to assess the quality of systematic reviews; the Public Health Agency of Canada Critical Appraisal of Analytical Studies tool or the Critical Appraisal Skills Programme tool for RCTs or non-RCTs, quasi-experimental studies, and nonrandomized (cohort) studies.⁶⁸

The assessment of the scientific evidence of the statements answering the assessment questions is based on the examination of the body of scientific evidence according to the following 4 criteria: the methodological quality of the studies, coherence, clinical impact, and generalizability. The overall level of scientific evidence reflects the integration of the results of the 4 criteria for assessing scientific evidence to report confidence in the results of the scientific evidence. The quality of the scientific evidence was assessed by the assessors who conducted the systematic review to answer the assessment questions.

CDA-AMC Update (2026)

The current review included the 7 ICIs reported in the prior review and added 2 additional ICIs, ipilimumab and tremelimumab. Consistent with the INESSS report, our eligibility criteria encompassed different primary study designs, including RCTs, nonrandomized studies, and PK/PD modelling studies. We included systematic reviews to scan their references for additional records, assess their methodological quality, and compare their findings with our report (the overlap between selected flagged systematic reviews and the primary studies included in this review is provided in [Appendix 8](#)). We did not include clinical practice guidelines in this review. In contrast to the INESSS report that investigated a broad dosing regimen, this review targeted studies that evaluated a fixed-dosing regimen versus weight-based dosing for the ICI. Similarly, we performed a descriptive synthesis of the included studies to report on the evidence. Nevertheless, in descriptive systematic reviews, particularly when there are many included studies, synthesis

statements are often limited to reporting the number of relevant studies and the direction and magnitude of effect estimates. There is no quantitative pooling of data in this synthesis strategy.

The largest difference between our review and the INESSS report⁷ is that the INESSS report⁷ involved clinical judgments to move from evidence to recommendations, which was beyond the scope of this report. To do this would require a systematic and evidence-based approach, including pooling data quantitatively when possible through meta-analyses, assessing the certainty of evidence using grading frameworks such as GRADE,⁶⁶ and then moving from evidence to recommendations and guidelines using an evidence-to-decision framework.⁶⁹ This framework would consider not only the pooled evidence, but also additional contextual factors such as patient values and preferences, feasibility, costs, and equity. We addressed this as a limitation in the report.

Lastly, this review appraised the quality (internal validity) of both primary and secondary included studies. In the INESSS report,⁷ quality appraisal was conducted using generic design tools such as those from the Public Health Agency of Canada and the Critical Appraisal Skills Programme.⁶⁸ These tools are not study design-specific and may miss important and specific methodological issues linked to each design. We used Cochrane RoB 2 for RCTs,¹⁴ ROBINS-I for nonrandomized studies,¹⁵ and AMSTAR 2 for reviews.¹⁶ These tools are intended to assess internal validity only and may not be useful for informing aspects such as applicability (generalizability) and external validity. Assessing external validity would require additional clinical judgment beyond the scope of this review.

ICI-Specific Conclusions and Synthesis With Findings From the INESSS Report

We summarized and compared the findings from the INESSS report and this review in [Table 5](#).

Atezolizumab

Safety and Efficacy Outcomes

Our included study (Patel, 2024)³⁸ did not provide atezolizumab-specific comparisons between fixed and weight-based dosing because outcomes were reported only at the pooled ICI level and included very few patients receiving atezolizumab. At the overall group level, ORRs were 72.2% with fixed dosing, 60.9% with per-body-weight dosing, and 75.7% with low-dose treatment; however, OS was not reported by arm, and safety outcomes were not reported, so no conclusions can be drawn regarding comparative efficacy or safety for atezolizumab specifically. The external validity of this study to the context in Canada is limited because this was a single-centre study from India conducted in a resource-limited setting with multiple tumour types, various clinical settings, and mixed concurrent treatments, which the authors noted makes generalization difficult.

These findings are consistent with those of the INESSS report,⁷ which also found a lack of robust comparative data. The report concluded that the evidence is insufficient to assess differences in efficacy between fixed and weight-based dosing and that the available safety data are limited and of low certainty. Although some differences in AE rates were observed at higher weight-based doses (e.g., 20 mg/kg versus fixed 1,200 mg), these findings do not establish a clear or consistent advantage for either dosing strategy.

Systematic review evidence also aligns with this interpretation. The network meta-analysis by Hong et al.²¹ evaluated different fixed-dose regimens of atezolizumab and identified some variation in AE risk across doses; however, it did not include weight-based comparisons, limiting its applicability to the question of interest. Similarly, Wesevich et al.²³ reported no direct clinical comparative data for atezolizumab dosing strategies, relying instead on PK simulations suggesting adequate exposure across alternative dosing approaches.

Taken together, the available evidence from the included study and external sources consistently demonstrates a lack of reliable, direct comparative evidence. Our findings do not support a clear conclusion regarding differences in efficacy or safety between fixed and weight-based dosing of atezolizumab.

PK/PD Modelling Outcomes

Our included PK/PD modelling study (Ter Heine)⁵⁹ found that the alternative weight-banded fixed dosing regimen, compared with the reference fixed-dose regimen of atezolizumab 1,200 mg every 3 weeks, produced consistently lower modelled exposure across all reported PK parameters, with ratios of 0.82 for cycle 1 trough concentration, steady-state trough concentration, cycle 1 AUC, and steady-state AUC. These findings indicate an approximately 18% reduction in exposure with the weight-banded fixed dosing regimen relative to fixed dosing. External validity may be limited because the simulations were based on a representative population living in Europe, and the authors noted that populations with higher average body weight may receive higher doses. In addition, the study relied on modelled PK outcomes rather than real-world clinical data.

These findings are partially consistent with the INESSS report.⁷ INESSS similarly identified PK variation across atezolizumab dosing strategies but, overall, interpreted the exposure differences as modest and unlikely to be clinically important. In particular, the report noted that predicted AUC values were similar across regimens such as 840 mg every 2 weeks, 1,200 mg every 3 weeks, and 1,680 mg every 4 weeks, whereas C_{min} and C_{max} varied somewhat depending on schedule and body weight. Thus, both sources suggest that alternative atezolizumab dosing can alter exposure, but the included study found a more consistent reduction across trough and AUC measures than the broader equivalence suggested by INESSS.

The findings are more closely aligned with the narrative reviews by Wesevich et al.²³ and Sehgal.²⁶ Wesevich et al.²³ summarized evidence indicating that alternative atezolizumab dosing maintained trough concentrations higher than the proposed PD target of 6 mcg/mL. Similarly, Sehgal²⁶ reported that for atezolizumab 1,680 mg every 4 weeks versus 1,200 mg every 3 weeks, predicted C_{min} was only modestly lower, AUC was slightly higher, and exposure remained above the target concentration considered sufficient for receptor saturation. Taken together, these reviews support the interpretation that, although alternative regimens may reduce exposure relative to standard fixed dosing, the reduction may still remain within a clinically acceptable and pharmacodynamically adequate range.

Overall, the included study suggests that weight-banded fixed dosing results in consistently lower systemic exposure than fixed dosing, whereas external evidence indicates that such reductions may still preserve pharmacodynamic sufficiency. Therefore, the direction of effect is broadly consistent with prior evidence

showing some exposure differences between regimens, although the magnitude of reduction observed in the included study appears greater than that reported in the INESSS report.⁷

Avelumab

Safety and Efficacy Outcomes

Our included studies suggest that fixed-dose and weight-based avelumab have broadly similar efficacy and safety. In the small clinical trial by Herrera,²⁹ response outcomes for the 10 mg/kg weight-based arm were generally within the range observed across the fixed-dose arms, without showing a clear advantage for 1 strategy overall. Applicability of this study is limited because the trial was very small, included a highly selected group of heavily pretreated patients, and evaluated several experimental dosing regimens, including doses that are not standard in routine practice. The 2 model-based studies, Masters⁵¹ and Novakovic,⁵² likewise found no meaningful ER differences between 800 mg fixed dosing and 10 mg/kg weight-based dosing for either efficacy or safety. Although Novakovic⁵² reported a slightly higher predicted rate of irAEs with fixed dosing, the difference was small, and overall both studies supported comparable safety profiles. For the Masters⁵¹ study, applicability is somewhat limited because the findings are based on pharmacokinetic modelling and simulations rather than direct clinical comparisons of outcomes, and the analysis relies on selected clinical trial populations with strict eligibility criteria. Although Novakovic⁵² used a large, pooled dataset, generalizability is likewise limited because the study relies on PK modelling and simulations rather than direct comparative clinical outcomes.

Overall, these findings are consistent with the INESSS report,⁷ which also concluded that efficacy and irAEs appear similar between fixed-dose (800 mg) and weight-based (10 mg/kg) avelumab, while noting that the certainty of evidence is limited. No additional literature reviews were identified for this ICI.

PK/PD Modelling Outcomes

Our included studies suggest that fixed-dose and weight-based avelumab produce broadly comparable PK profiles. In the small clinical PK/PD trial (Herrera),²⁹ fixed dosing — particularly 500 mg every 2 weeks — resulted in lower overall exposure (AUC) and peak concentrations ($C_{\max}$) compared with weight-based dosing (10 mg/kg every 2 weeks), although trough concentrations (C_{trough}) and terminal half-life were similar, indicating comparable sustained exposure and elimination. In contrast, larger model-based studies (Masters;⁵¹ Novakovic⁵²) showed that fixed dosing (800 mg every 2 weeks) and weight-based dosing (10 mg/kg every 2 weeks) produced overlapping exposure metrics (AUC, $C_{\max}$, C_{trough}) with no meaningful overall differences. These studies also found that fixed dosing leads to weight-dependent variability in exposure, whereas weight-based dosing results in more consistent exposure across body weight groups.

These findings are consistent with the INESSS report,⁷ which similarly concluded that PK parameters — including AUC, $C_{\max}$, and $C_{\min}$ — are almost similar between 10 mg/kg and 800 mg every 2 weeks, with substantial overlap in exposure across body weight categories. INESSS⁷ also reported similar half-life across dosing regimens and noted weight-related variability in exposure with fixed dosing, while emphasizing that these differences are modest and unlikely to be clinically meaningful. No additional literature reviews were identified for this ICI.

Cemiplimab

Safety and Efficacy Outcomes

Across our included studies, fixed-dose and weight-based cemiplimab appeared broadly similar for efficacy and safety in advanced or metastatic cutaneous squamous cell carcinoma. Hughes et al.³² provided the clearest direct comparison, although generalizability was somewhat limited due to the nonrandomized design. Rischin et al. (2020)⁵⁰ and Rischin et al. (2024)³⁹ provided supportive but less direct evidence, but their generalizability was impacted by selected trial populations, and for Rischin et al. (2024),³⁹ also by the small sample size and single-arm design. Overall, confidence in this conclusion remains limited by serious risk of bias, lack of adjusted head-to-head analyses, and some concerns about external validity.

These findings are consistent with both the INESSS report⁷ and the narrative review by Lee et al.²⁵ The INESSS report⁷ concluded that overall response, disease control, time to response, duration of response, and AE rates were similar between cemiplimab 3 mg/kg every 2 weeks and 350 mg every 3 weeks in metastatic cutaneous squamous cell carcinoma, and our included studies support that same overall interpretation. Similarly, Lee et al.²⁵ reported broadly similar ORRs, durable responses, and comparable rates of grade 3 or higher TRAEs across cemiplimab dosing strategies, which is consistent with the pattern observed in Hughes et al.³² and Rischin et al. (2020).⁵⁰

PK/PD Modelling Outcomes

Across our included studies, fixed-dose and weight-based cemiplimab produced broadly similar PK exposure. Both the PopPK analyses (Yang,⁶⁰ which included a large, diverse pooled clinical trial population across multiple tumour types and body weight ranges, although limited by reliance on modelling and trial populations, and Paccaly,⁶¹ which similarly incorporated a wide weight range and multiple malignancies but was also based on modelled and trial data) and the observed phase II data from Rischin et al. (2024)³⁹ demonstrated comparable steady-state exposure between 350 mg every 3 weeks and 3 mg/kg every 2 weeks, with overlapping or very similar AUC, C_{trough} or C_{min} , and C_{max} values. Although minor early differences and some variation across body weight groups were reported, these findings did not indicate a clear or clinically meaningful exposure advantage for either dosing strategy.

These findings are consistent with both the INESSS report⁷ and the narrative review by Lee et al.²⁵ The INESSS report⁷ similarly concluded, based on Paccaly⁶¹ and Yang,⁶⁰ that simulated AUC was comparable between 350 mg every 3 weeks and 3 mg/kg every 2 weeks and that although minimum and maximum concentrations may differ after the first dose, steady-state concentrations were similar across dosing strategies. INESSS⁷ also noted opposing exposure trends by body weight depending on dosing strategy but emphasized that overall AUC remained similar across a wide range of body weights. Likewise, Lee et al.²⁵ reported comparable steady-state exposure between regimens, with AUC_{ss} values of 3.710 day × mg/L for 3 mg/kg every 2 weeks and 3.800 day × mg/L for 350 mg every 3 weeks, as well as a terminal half-life of approximately 19 days. Together, these external sources support the same overall conclusion as our included studies: fixed-dose cemiplimab provides PK exposure similar to weight-based dosing.

Dostarlimab

Safety and Efficacy Outcomes

Early-phase evidence from Patnaik et al.⁴⁶ did not show a clear safety or efficacy advantage for either fixed or weight-based dostarlimab dosing, but interpretation is limited by small events, small cohorts, and serious methodological limitations. External validity is limited, because this early-phase, small, highly selected trial population (advanced solid tumours, trial-eligible patients, mainly US-based multicentre settings) may not fully reflect real-world oncology populations. Similarly, the INESSS report⁷ found no statistically significant differences across fixed-dose regimens and judged the evidence insufficient to determine whether fixed and weight-based dosing differ in efficacy or safety. No additional literature reviews were identified for this ICI.

PK/PD Modelling Outcomes

Our included study (Patnaik et al.)⁴⁶ suggests that fixed-dose dostarlimab provides PK exposure broadly comparable to higher weight-based regimens, with 1,000 mg every 6 weeks producing higher overall exposure than 500 mg every 3 weeks.

This was consistent with the INESSS report,⁷ which also found increased exposure with higher fixed doses, although the evidence was interpreted more cautiously in the report because of very small sample sizes and reliance on modelling. No additional literature reviews were identified for this ICI.

Durvalumab

Safety and Efficacy Outcomes

Across the included studies, direct comparisons of fixed versus weight-based dosing were limited and at serious risk of bias. Patel³⁸ and Fujiwara⁴² showed no consistent efficacy or safety advantage for either approach, Juergens⁴⁸ did not report outcomes in a way that allowed a valid comparison by dosing strategy, and Hijmering-Kappelle⁴³ found broadly similar safety and efficacy between fixed and weight-based durvalumab. Overall, the evidence does not suggest a clear clinical advantage of 1 dosing approach over the other. In terms of external validity, Patel was a resource-constrained single-centre study in India. By contrast, Juergens was a Canadian multicentre trial, whereas Hijmering-Kappelle's real-world Dutch NSCLC study may also be reasonably transferable to practice in Canada, although its COVID-era dose-escalation design still limits generalizability.

These findings are broadly consistent with the INESSS report.⁷ INESSS⁷ concluded that there was insufficient evidence comparing fixed-dose with weight-based durvalumab, and our findings support that conclusion, given that the available direct comparative studies were few and methodologically limited. Although Hijmering-Kappelle⁴³ provided a more direct comparison and suggested similar safety and efficacy between approaches, the serious risk of bias means this evidence is still not strong enough to establish superiority of either dosing strategy. No additional literature reviews were identified for this ICI.

PK/PD Modelling Outcomes

Included studies suggest broadly similar PK exposure between fixed and weight-based durvalumab, with 1 exception. Juergens et al.⁴⁸ and Ter Heine et al.⁵⁹ supported PK comparability across dosing strategies, whereas Fujiwara et al.⁴² found higher exposure with fixed dosing; however, that study used nonequivalent

regimens, so its findings should be interpreted cautiously. In terms of external validity, Juergens et al.⁴⁸ is particularly relevant to the context in Canada because it was a Canadian multicentre trial conducted across major oncology centres and under Health Canada oversight. By contrast, Fujiwara et al.⁴² was conducted only in patients living in Japan, and Ter Heine et al.⁵⁹ was a European modelling study in virtual patients, so both may not be directly generalizable to routine practice in Canada.

Overall, this is consistent with the INESSS report,⁷ which also found that fixed and weight-based durvalumab produce similar exposure in modelling studies, with no clear evidence of clinically important over- or under-exposure. Fujiwara⁴² is the main partial inconsistency, but it has weak comparative evidence and does not materially change the overall conclusion of broad PK similarity. No additional literature reviews were identified for this ICI.

Ipilimumab

Safety and Efficacy Outcomes

We did not find any study reporting on this ICI regarding the safety and efficacy outcomes of interest, and the INESSS report⁷ did not include this ICI either. No additional literature reviews were identified for this ICI.

PK/PD Modelling Outcomes

Ter Heine et al.⁵⁹ found that weight-banded fixed dosing of ipilimumab produced equivalent PK exposure to standard weight-based dosing. Compared with 1 mg/kg every 6 weeks, the alternative regimen (< 60 kg: 50 mg; 60 kg to 90 kg: 75 mg; > 90 kg: 100 mg) demonstrated similar C_{trough} and AUC, with geometric mean ratios of 1.0 at both early and steady state, indicating no clinically meaningful PK/PD differences. External validity is limited, given that the model was based on a representative population living in Europe with similar clinical and regulatory contexts, but is limited by reliance on simulated rather than real-world data. The INESSS report⁷ did not contain this ICI either. No additional literature reviews were identified for this ICI.

Nivolumab

Safety and Efficacy Outcomes

Overall, our included studies are largely consistent with the INESSS summary.⁷ Across the randomized trial, several real-world comparative cohorts, and multiple model-informed analyses, the most common finding was that fixed-dose nivolumab and weight-based nivolumab produced broadly similar safety and efficacy outcomes, especially for ORR, PFS, OS, and immune-related toxicity. This aligns well with the INESSS⁷ conclusions that fixed dosing at 240 mg every 2 weeks or 480 mg every 4 weeks appears to have similar efficacy and similar adverse-effect rates compared with 3 mg/kg every 2 weeks, and that evidence for cross-dose comparisons more generally suggests little meaningful difference in response or toxicity.

For safety, the agreement is particularly strong. Most of our included comparative studies found no statistically significant difference in irAEs, grade 3 or higher toxicity, TRAEs, or discontinuation between fixed and weight-based dosing. This is very much in line with the INESSS statements⁷ that adverse-effect rates are similar between nivolumab dosing strategies. The model-based studies also supported this pattern, generally predicting negligible differences in safety outcomes across regimens.

External validity is somewhat limited: most evidence comes from retrospective, single-country or single-centre studies (e.g., Europe, India, Japan), which may not fully reflect broader oncology populations or practice in Canada. However, inclusion of some multicentre and international trial data (e.g., from the CheckMate 67T trial) improves generalizability, indicating findings are likely applicable to high-income settings like Canada, yet it is still constrained by selection bias and real-world heterogeneity.

For efficacy, our review also mostly supports the INESSS⁷ conclusions, though with a bit more nuance. Several studies found similar ORR, PFS, and OS between dosing strategies, and the modelling studies consistently predicted near-identical outcomes. However, a few nonrandomized studies showed numerically better survival or response with fixed dosing, such as Campo le Brun³⁰ and Leroy.³⁷ These findings do not clearly contradict INESSS,⁷ because they come from studies at serious risk of bias, where calendar-time effects, treatment selection, and residual confounding are likely explanations. As such, the apparent differences are better interpreted as uncertain signals from weaker real-world evidence rather than firm inconsistency.

There are also a few studies that are only partly informative for the fixed-versus-weight-based question. Horisaki³¹ did not report a direct fixed-versus-weight-based comparison; Gandhi⁵³ compared weight-based dosing with a low fixed dose rather than the standard, approved fixed regimens; and Sheng,⁵⁴ Zhao,⁵⁵ Bei⁵⁷, and Sanghavi⁵⁶ were model-informed rather than direct clinical comparisons. Even so, their overall direction still supports the same general conclusion as INESSS:⁷ no major clinically meaningful difference between fixed and weight-based nivolumab dosing.

PK/PD Modelling Outcomes

Across the included PK/PD modelling and PK-focused studies of nivolumab, fixed dosing generally produced exposures that were either very similar to or modestly higher than standard weight-based dosing, although findings varied by regimen. Several modelling studies found that 240 mg every 2 weeks closely approximated 3 mg/kg every 2 weeks, with only small differences in steady-state exposure metrics such as C_{min} , C_{max} , and C_{avg} (e.g., Sanghavi,⁵⁶ Zhao⁵⁵). Other studies suggested somewhat higher exposure with fixed dosing: Bei (2020)⁵⁷ reported an approximately 37% higher modelled early exposure with 240 mg every 2 weeks, Sheng et al.⁵⁴ found approximately a 26% to 27% higher exposure versus 3 mg/kg every 2 weeks, and Kato⁴⁹ observed significantly higher trough concentrations with 240 mg every 2 weeks in a small retrospective cohort. In contrast, Gandhi⁵³ showed that a low fixed dose of 40 mg resulted in markedly lower absolute exposure than 3 mg/kg, indicating that equivalence does not hold for substantially reduced flat doses.

For alternative schedules and formulations, the exposure profile differed but remained broadly within a clinically relevant range. Zhao (2020)⁵⁵ found that 480 mg every 4 weeks had similar average exposure to 240 mg every 2 weeks or 3 mg/kg every 2 weeks, but with lower troughs and higher peaks, while Albiges²⁸ and Zhao (2024)⁶² showed that SC fixed-dose nivolumab regimens produced similar or higher overall exposure than IV weight-based dosing, with delayed and lower peak concentrations than IV administration. Ter Heine's⁵⁹ simulation study suggested that weight-banded fixed dosing regimens yielded slightly lower

exposure than standard reference regimens, especially for dosing every 3 weeks, but the reductions were modest.

Overall, our findings are largely consistent with the INESSS report.⁷ Both our review and INESSS⁷ suggest that a fixed dosage of 240 mg every 2 weeks provides PK exposure broadly comparable to 3 mg/kg every 2 weeks, whereas 480 mg every 4 weeks maintains similar average exposure but with lower troughs and higher peaks. The main point of inconsistency is that some of our included studies, especially Kato,⁴⁹ Bei,⁵⁷ and Sheng,⁵⁴ suggest fixed dosing may produce modestly higher exposure than weight-based dosing rather than near-equivalent exposure. This likely reflects differences in study design, populations, and whether evidence came from nonrandomized study data, trial-based PK analyses, or model-based simulations.

Our findings are also consistent with the Sehgal systematic review.²⁶ Consistent with Sehgal,²⁶ we found that extended-interval nivolumab dosing (480 mg every 4 weeks) leads to lower troughs, higher peaks, and similar time-averaged exposure compared with 3 mg/kg every 2 weeks. More broadly, both syntheses support the conclusion that approved fixed-dose and extended-interval nivolumab regimens achieve exposure within the range considered clinically acceptable, despite some shifts in peak-to-trough fluctuation.

Pembrolizumab

Safety and Efficacy Outcomes

Across our included studies, which were mostly retrospective cohort studies at serious risk of bias largely because of confounding, fixed and weight-based dosing strategies generally appeared to result in similar safety and efficacy outcomes, particularly for pembrolizumab. Larger real-world studies such as Chaitesipaseut et al.³⁵ and Berard et al.⁴⁰ found no meaningful differences in OS, PFS, or toxicity between fixed and weight-based approaches. Likewise, Staender et al.³⁴ reported no statistically significant differences in survival or irAEs. Some studies suggested possible numerical differences between strategies: Smeenk et al.³³ and Grit et al.³⁶ observed longer survival with hybrid or weight-banded fixed dosing, whereas To et al.⁴⁷ reported higher response rates and PFS with fixed dosing as well as a higher incidence of any-grade irAEs. However, these apparent differences were inconsistent across studies and should be interpreted cautiously given the high potential for residual confounding, nonrandom treatment allocation, and limited adjustment for baseline differences. In terms of external validity, these studies were conducted in routine-care settings across several health systems, including Canada (Quebec), Germany, India, the Netherlands, Taiwan, and the US, which supports some real-world generalizability. However, applicability to the context in Canada is still somewhat limited because most evidence came from retrospective cohorts from outside of Canada, although the Quebec study offers the most directly relevant Canadian data.

These findings are largely consistent with the INESSS report.⁷ Similar to INESSS,⁷ our review found that OS, PFS, response outcomes, and AE rates were generally comparable across fixed and weight-based pembrolizumab dosing strategies. Although a few of our included real-world studies suggested numerical advantages for either weight-banded fixed dosing or fixed dosing, these results were not consistent and were likely influenced by confounding and other design limitations. As a result, our synthesis supports the same overall conclusion as INESSS:⁷ current evidence does not show a clear efficacy or safety advantage

for 1 dosing approach over another, and the available comparative evidence remains limited in certainty. No additional literature reviews were identified for this ICI.

PK/PD Modelling Outcomes

Across the included studies, fixed pembrolizumab dosing (e.g., 200 mg every 3 weeks or 400 mg every 6 weeks) generally produced comparable overall exposure (AUC and C_{avg}) to weight-based dosing (2 mg/kg every 3 weeks), despite differences in peak and trough concentrations. Extended-interval fixed dosing (400 mg every 6 weeks) tended to result in lower trough concentrations (C_{min} or C_{trough}) and higher peak concentrations (C_{max}) compared with more frequent dosing schedules, while maintaining similar average exposure. Compared with weight-based regimens, fixed dosing often led to slightly higher exposure overall — particularly in lower-weight patients — whereas weight-based dosing produced more consistent exposure across body weights. Importantly, exposure distributions overlapped substantially across regimens; and modelling studies, including weight-banded fixed dosing approaches, consistently demonstrated no meaningful differences in predicted exposure. Overall, these findings suggest that fixed dosing provides clinically comparable and acceptable PK/PD profiles, with variability in peak and trough levels but no evidence of clinically meaningful differences in exposure. External validity is moderate: the evidence includes large multitumour population PK datasets, which supports generalizability, but much of it comes from modelling or simulation studies and selected trial populations rather than routine real-world practice. In addition, direct applicability to the context in Canada is reasonable but somewhat limited, because most studies were multinational or model-based rather than conducted specifically in oncology settings in Canada.

These findings are highly consistent with the INESSS report,⁷ which similarly shows that pembrolizumab exhibits linear PK, with dose-proportional increases in exposure. INESSS⁷ also reports that fixed dosing (200 mg every 3 weeks or 400 mg every 6 weeks) yields similar average exposure to standard regimens, but with lower trough and higher peak concentrations for extended-interval dosing. Additionally, both sources indicate that fixed dosing can result in higher exposure compared with 2 mg/kg in some cases (approximately 35%), while still maintaining adequate PD-1 receptor saturation. The influence of body weight on exposure under fixed dosing — higher exposure in lower-weight patients and lower exposure in higher-weight patients — is also consistent across both the included studies and INESSS⁷ findings. Overall, both sources suggest that fixed and weight-based dosing produce broadly comparable exposure within acceptable therapeutic ranges.

Similarly, the findings align with the systematic review by Sehgal et al. (2020),²⁶ which reported comparable AUCs across fixed and weight-based regimens, alongside lower trough and higher peak concentrations with extended-interval fixed dosing. The review also noted that only a very small proportion of patients were predicted to fall below exposure thresholds, and only for a short duration, with overall exposure remaining within clinically effective and safe ranges. Taken together, the evidence consistently indicates that differences between dosing strategies are primarily quantitative (i.e., variability in PK parameters) rather than clinically meaningful, supporting the equivalence of fixed and weight-based dosing approaches.

Tremelimumab

Safety and Efficacy Outcomes

Across the included studies, there was no clear evidence that fixed dosing was meaningfully better or worse than weight-based dosing for safety or efficacy. In Fujiwara et al.,⁴² response appeared numerically lower with fixed dosing, whereas AEs were broadly similar across groups; however, the comparison was heavily limited by very small, nonrandomized cohorts and differences in the accompanying durvalumab regimens. In Juergens et al.,⁴⁸ outcomes were not reported separately by tremelimumab dosing strategy, so no direct fixed-versus-weight-based comparison could be made. External validity to the context in Canada is moderate to high because this was a Canadian multicentre trial conducted in routine oncology centres in Canada using clinically relevant platinum-doublet backbones, although generalizability is still limited by its early-phase, nonrandomized design and heterogeneous mixed-tumour population. Overall, the evidence is sparse and at serious risk of bias. The INESSS report⁷ did not contain this ICI either. No additional literature reviews were identified for this ICI.

PK/PD Modelling Outcomes

Across studies, fixed-dose tremelimumab 75 mg produced PK exposure broadly similar to low weight-based dosing (1 mg/kg), whereas higher weight-based dosing (e.g., 3 mg/kg or 10 mg/kg) predictably resulted in greater exposure. Fujiwara⁴² and Juergens⁴⁸ showed that 75 mg fixed dosing yielded comparable, and in some cases slightly higher, trough levels and accumulation than 1 mg/kg, whereas Hwang's⁶⁵ PopPK analysis demonstrated substantial exposure overlap across body weight groups. The Hwang study⁶⁵ could be informative for the context in Canada, given its large, multinational population that included a centre in Canada (Princess Margaret Cancer Centre) and similar oncology practice settings, although generalizability remains limited by reliance on clinical trial populations and PK modelling. Overall, these findings support the PK feasibility of fixed dosing at standard lower dose levels, though the evidence is primarily based on early-phase studies and modelling rather than direct exposure-equivalence trials. The INESSS report⁷ did not contain this ICI either. No additional literature reviews were identified for this ICI.

Table 5: Comparison of INESSS Recommendations and CDA-AMC Findings on ICI Dosing Strategies

ICI	Doses and regimens described in INESSS report (2022)	INESSS report recommendations	Doses and regimens described in CDA-AMC update (2026)	Alignment of reports	Areas of consistency or divergence
Atezolizumab	Fixed dosing: 850 mg q.2.w. 1,200 mg q.3.w. 1,680 mg q.4.w. Weight-based dosing: 10 mg/kg q.3.w.	After analyzing all the information collected, the following dosages should be used for atezolizumab (in all approved indications): 840 mg IV every	Fixed dosing: 1,200 mg q.3.w. Weight-banded fixed dosing: < 70 kg: 840 mg q.3.w. ≥ 70 kg: 1,200 mg q.3.w.	Safety and efficacy outcomes: Consistent PK/PD modelling outcomes: Somewhat consistent	Safety and efficacy outcomes: Both sources reported on limited available data to compare fixed dosing vs. weight-based dosing

ICI	Doses and regimens described in INESSS report (2022)	INESSS report recommendations	Doses and regimens described in CDA-AMC update (2026)	Alignment of reports	Areas of consistency or divergence
	15 mg/kg q.3.w. 20 mg/kg q.3.w.	2 weeks or 1,200 mg IV every 3 weeks or 1,680 mg IV every 4 weeks.			PK/PD modelling outcomes: Current review suggested lower exposure with weight-banded fixed dosing than the INESSS report.
Avelumab	Fixed dosing: 800 mg q.2.w. Weight-based dosing: 1 mg/kg q.2.w. 3 mg/kg q.2.w. 10 mg/kg q.2.w. 20 mg/kg q.2.w.	After analyzing all the information collected, the following avelumab dosage should be used (in all approved indications): 10 mg/kg IV every 2 weeks (maximum 800 mg per dose)	Fixed dosing: 70 mg q.2.w. 350 mg q.2.w. 500 mg q.2.w. 500 mg q.3.w. 800 mg IV q.2.w. Weight-based dosing: 10 mg/kg q.2.w.	Safety and efficacy outcomes: Consistent PK/PD modelling outcomes: Consistent	Safety and efficacy outcomes: Both reports found similar efficacy and immune-related safety between fixed-dose and weight-based avelumab PK/PD modelling outcomes: Both reports found broadly similar PK exposure between fixed-dose and weight-based avelumab, with modest weight-related variability.
Cemiplimab	Fixed dosing: 350 mg q.3.w. Weight-based dosing: 3 mg/kg q.2.w.	After analyzing all the information collected, the following cemiplimab dosage should be used (in all approved indications): 350 mg IV every 3 weeks	Fixed dosing: 200 mg q.2.w. 350 mg q.3.w. 600 mg q.4.w. Weight-based dosing: 1 mg/kg 3 mg/kg q.2.w. 10 mg/kg q.2.w.	Safety and efficacy outcomes: Consistent PK/PD modelling outcomes: Consistent	Safety and efficacy outcomes: Both reports found similar efficacy and immune-related safety between fixed-dose and weight-based cemiplimab. PK/PD modelling outcomes: Both reports consistently found comparable PK exposure between fixed-dose and

ICI	Doses and regimens described in INESSS report (2022)	INESSS report recommendations	Doses and regimens described in CDA-AMC update (2026)	Alignment of reports	Areas of consistency or divergence
					weight-based cemiplimab.
Dostarlimab	Fixed dosing: • 500 mg q.3.w. • 1,000 mg q.6.w. Weight-based dosing: • 1 mg/kg q.2.w. • 3 mg/kg q.2.w. • 10 mg/kg q.2.w.	Not reported	Fixed dosing: • 500 mg q.3.w. • 1,000 mg q.6.w. Weight-based dosing: • 1 mg/kg q.2.w. • 3 mg/kg q.2.w. • 10 mg/kg q.2.w.	Safety and efficacy outcomes: Consistent PK/PD modelling outcomes: Consistent	Safety and efficacy outcomes: Both reports found insufficient evidence to determine whether fixed- and weight-based dostarlimab differ in efficacy or safety. PK/PD modelling outcomes: Both reports found increased dostarlimab exposure with higher fixed-dose regimens.
Durvalumab	Fixed dosing: • 750 mg q.2.w. • 1,500 mg q.2.w. Weight-based dosing: • 1 mg/kg q.2.w. • 3 mg/kg q.2.w. • 10 mg/kg q.2.w. • 15 mg/kg q.2.w. • 20 mg/kg q.2.w.	After analyzing all the information collected, the following durvalumab dosages should be used (for all approved indications): • 10 mg/kg IV every 2 weeks (maximum 750 mg) or • 15 mg/kg IV every 3 weeks (maximum 1,125 mg) or • 20 mg/kg IV every 4 weeks (maximum 1,500 mg)	Fixed dosing: • 1,125 mg q.3.w. • 1,500 mg q.3.w. • 1,500 mg q.4.w. Weight-based dosing: • 15 mg/kg q.3.w. (during chemotherapy, then 20 mg/kg q.4.w.) • 10 mg/kg q.2.w. Weight-banded fixed dosing: Durvalumab (q.2.w.): • < 60 kg: 480 mg • 60 kg to 80 kg: 600 mg • > 80 kg: 720 mg Durvalumab (q.4.w.): • < 60 kg: 960 mg	Safety and efficacy outcomes: Consistent PK/PD modelling outcomes: Consistent	Safety and efficacy outcomes: Both reports found insufficient comparative evidence for durvalumab, with no clear safety or efficacy advantage for either dosing strategy. PK/PD modelling outcomes: Both reports found broadly similar durvalumab PK exposure across dosing strategies, with no clear clinically important exposure differences.

ICI	Doses and regimens described in INESSS report (2022)	INESSS report recommendations	Doses and regimens described in CDA-AMC update (2026)	Alignment of reports	Areas of consistency or divergence
			60 kg to 80 kg: 1,200 mg > 80 kg: 1,440 mg		
Ipilimumab	Not reported	Not reported	Weight-based dosing: - q.6.w.: 1 mg/kg Weight-banded fixed dosing: < 60 kg: 50 mg 60 kg to 90 kg: 75 mg > 90 kg: 100 mg	Not applicable	Not applicable
Nivolumab	Fixed dosing: 240 mg q.2.w. 360 mg q.3.w. 480 q.4.w. Weight-based dosing: 0.1 mg/kg q.2.w. 0.3 mg/kg q.3.w. 1 mg/kg q.2.w. 2 mg/kg q.3.w. 3 mg/kg q.2.w. 10 mg/kg q.2.w. 20 mg/kg q.2.w.	After analyzing all the information collected, the following dosages should be used for nivolumab monotherapy (for all approved indications): 3 mg/kg IV every 2 weeks (maximum 240 mg) or 4.5 mg/kg IV every 3 weeks (maximum 360 mg) or 6 mg/kg IV every 4 weeks (maximum 480 mg) After analyzing all the information collected, the following dosages should be used for nivolumab in combination with ipilimumab:	Fixed dosing: 40 mg q.2.w. 40 mg q.3.w. 240 mg q.2.w. 240 mg q.4.w. 480 mg q.4.w. 720 mg q.4.w. 960 mg q.4.w. 1,200 mg q.4.w. Weight-based dosing: 2 mg/kg q.3.w. 3 mg/kg q.2.w. 3 mg/kg q.3.w. 10 mg/kg q.2.w.	Safety and efficacy outcomes: Largely consistent PK/PD modelling outcomes: Somewhat consistent	Safety and efficacy outcomes: Both reports found broadly similar nivolumab safety and efficacy between fixed- and weight-based dosing, although the CDA-AMC review included more real-world and model-informed evidence, with some uncertain numerical differences, and in favour of the fixed-dose in a few nonrandomized studies. PK/PD modelling outcomes: The CDA-AMC report identified some studies suggesting modestly higher exposure with fixed dosing

ICI	Doses and regimens described in INESSS report (2022)	INESSS report recommendations	Doses and regimens described in CDA-AMC update (2026)	Alignment of reports	Areas of consistency or divergence
		1 mg/kg IV every 3 weeks (for metastatic melanoma) 3 mg/kg IV (maximum 240 mg) every 3 weeks for metastatic renal adenocarcinoma and colorectal cancer			
Pembrolizumab	Fixed dosing: 200 mg q.3.w. 400 mg q.6.w. Weight-based dosing: 1 mg/kg q.2.w. 2mg/kg q.3.w. 3 mg/kg q.2.w. 10 mg/kg q.2.w. 10 mg/kg q.3.w.	After analyzing all the information collected, the following dosages should be used for pembrolizumab (in all approved indications): 2 mg/kg IV every 3 weeks (maximum 200 mg) or 4 mg/kg IV every 6 weeks (maximum 400 mg)	Fixed dosing: 200 mg q.3.w. 400 mg q.6.w. Weight-banded fixed dosing: 100 mg/150 mg/200 mg q.3.w. (by weight: < 65 kg/ 65 kg to 90 kg/> 90 kg) or - double q.6.w. (200 mg/300 mg/400 mg). Weight-based: 2 mg/kg q.3.w. 10 mg/kg q.2.w. (plus 10 mg/kg q.3.w. in pooled safety) 4 mg/kg q.6.w.	Safety and efficacy outcomes: Consistent PK/PD modelling outcomes: Consistent	Safety and efficacy outcomes: Both reports found comparable efficacy and safety across dosing strategies, with no clear advantage for either approach. PK/PD modelling outcomes: Both reports found broadly comparable PK exposure across dosing strategies, with expected peak and trough and body weight-related variability.
Tremelimumab	Not reported	Not reported	Fixed-dosing: 75 mg q.4.w. × 4 + durvalumab 1,500 mg q.4.w. × 13 750 mg q.4.w. monotherapy Weight-based dosing: 1 mg/kg q.4.w. 3 mg/kg q.4.w. x	Not applicable	Not applicable

ICI	Doses and regimens described in INESSS report (2022)	INESSS report recommendations	Doses and regimens described in CDA-AMC update (2026)	Alignment of reports	Areas of consistency or divergence
			6 then q.12.w. • 10 mg/kg x 6 then q.12.w. x 3 + durvalumab 15 mg/kg q.4.w. x 1 • 1 mg/kg q.4.w. x 4 + durvalumab 20 mg/kg q.4.w. x 4 then 10 mg/kg q.2.w. up to 22 doses		

CDA-AMC = Canada's Drug Agency; ICI = immune checkpoint inhibitor; INESSS = Institut national d'excellence en santé et en services sociaux; PK = pharmacokinetic; PK/PD = pharmacokinetics and pharmacodynamics; q.2.w. = every 2 weeks; q.3.w. = every 3 weeks; q.4.w. = every 4 weeks; q.6.w. = every 6 weeks; q.12.w. = every 12 weeks; vs. = versus.

Authors and Contributors

Authors

Shahab Sayfi contributed to conceptualization and methods; screening, data extraction, formal analysis, and critical appraisal; project administration and visualization; and drafting and revising the report.

Quenby Mahood designed and executed literature searches, drafted and edited the methods and results sections, and completed referencing.

Yonda Lai contributed to piloting, screening (title and abstract, and full-text), data extraction, and drafting and revising the report.

Jasmeen Dourka screened citations and grey literature at the title and abstract and full-text level; and reviewed and provided feedback on the draft report.

Rodrigue Ndabashinze contributed to the design of the systematic review and acquisition of data; performed study screening and selection, and data extraction from included studies; participated in analysis and interpretation of the study results and reviewed the draft report for important intellectual content, including the results, their interpretation, and the key messages and conclusions; and reviewed and approved the final version of the report.

Rebecca Raj contributed to the abstract and full-text article screening for eligible studies, and to the review and revision of the report.

Dipika Neupane contributed to the risk-of-bias assessment of included studies, and reviewed the draft and final report.

Kelvin Chan contributed to the design of the study, screening of citations, interpretation of results, and reviewing of the manuscript.

Andrea C. Tricco obtained funding, contributed to conceptualization and methods, interpreted results, and revised the report critically.

Contributors

Clinical Expert

This individual kindly provided comments on this report:

Scott Walker, MScPhm

Professor

Leslie Dan Faculty of Pharmacy, University of Toronto

Conflicts of Interest

Funding Declarations

Funding award declarations: Dr. Andrea Tricco holds a Tier 1 Canada Research Chair in Knowledge Synthesis for Knowledge Users and the Keenan Chair in Health Services Research Leadership. Dr. Rodrigue Ndabashinze was supported by the Irish Health Research Board and the HSC Public Health Agency (Grant number ESI-2021-001) in association with Evidence Synthesis Ireland/Cochrane Ireland.

No conflicts of interest were declared.

References

1. Brenner DR, Gillis J, Demers AA, et al. Projected estimates of cancer in Canada in 2024. *CMAJ*. 2024;196(18):E615-e623. [PubMed](#)
2. Cavalcanti IDL, Soares JCS. *Advances in cancer treatment: from systemic chemotherapy to targeted therapy*. Springer International Publishing; 2021: <https://doi.org/10.1007/978-3-030-68334-4>. Accessed 2026 Feb 20.
3. Shiravand Y, Khodadadi F, Kashani SMA, et al. Immune checkpoint inhibitors in cancer therapy. *Curr Oncol*. 2022;29(5):3044-3060. [PubMed](#)
4. Parvez A, Choudhary F, Mudgal P, et al. PD-1 and PD-L1: architects of immune symphony and immunotherapy breakthroughs in cancer treatment. *Front Immunol*. 2023;14:1296341. [PubMed](#)
5. Yin Q, Wu L, Han L, et al. Immune-related adverse events of immune checkpoint inhibitors: a review. *Front Immunol*. 2023;14:1167975. [PubMed](#)
6. Walker S, de Léséleuc L, Butcher R. Dosing and timing of immuno-oncology drugs (CADTH Technology Review: Optimal Use 360 Report) Ottawa: Canadian Agency for Drugs and Technology in Health; 2019: <https://www.cda-amc.ca/sites/default/files/ou-tr/ho0008-dosing-timing-immuno-oncology-drugs.pdf>. Accessed 2025 Jun 10.
7. Institut national d'excellence en santé et en services sociaux (INESSS). *Update of the tool for choosing the dosage of monoclonal antibodies targeting PD-1 or PD-L1: supporting report developed by Catherine Awad and Geneviève Duplain Cyr*. Québec City (QC): INESSS; 2023.
8. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. [PubMed](#)
9. Tricco A, Sayfi S, Mahood Q, Lai Y, Ndabashinze R. Comparative effectiveness and pharmacokinetics of weight-based vs. fixed-dose immuno-oncology therapy: a systematic review of anti-PD-1/PD-L1 monoclonal antibodies across approved and emerging indications. PROSPERO CRD420251071290. Centre for Reviews and Dissemination, University of York. 2026; <https://www.crd.york.ac.uk/PROSPERO/view/CRD420251071290>. Accessed 2026 Mar 18.
10. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol*. 2016;75:40-46. [PubMed](#)
11. Grey Matters: a tool for searching health-related grey literature. Ottawa (ON): Canada's Drug Agency (CDA). 2025; <https://greymatters.cda-amc.ca/>.
12. Tricco A, Sayfi S, Conline M-C, Mahood Q, Rai Y, Ndabashinze R. Dosing of immune checkpoint inhibitors (Health Technology Review). 2026; <https://www.cda-amc.ca/dosing-immune-checkpoint-inhibitors>. Accessed 2026 Aug 05.
13. DistillerSR. Version 2.35. DistillerSR Inc. 2023; <https://www.distillersr.com/>. Accessed 2026 Feb 19.
14. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. [PubMed](#)
15. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. [PubMed](#)
16. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008. [PubMed](#)
17. McGuinness L, Higgins JPT. Risk-of-Bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. *Res Syn Meth*. 2020;1-7. <https://doi.org/10.1002/jrsm.1411>. Accessed 2026 Feb 23.
18. Hoyek C, Zheng-Lin B, Bauernfeind JJ, et al. Overcoming financial and access barriers in global cancer care with low-dose immunotherapy: a systematic review. *JCO Glob Oncol*. 2025;11:e2400409. [PubMed](#)
19. Tan Z, Voller S, Sancho-Araiz A, Knibbe CAJ, Moes D. A systematic evaluation of the dosing regimens for approved targeted therapies and immune checkpoint inhibitors in metastatic renal cell carcinoma from a project optimus perspective. *J Clin Pharmacol*. 2025;02:02.

20. Mao YT, Wang Y, Chen XX, Liu CJ, Bao Q. Comparative severe dermatologic toxicities of immune checkpoint inhibitors in malignant melanoma: a systematic review and network meta-analysis. *J Cosmet Dermatol*. 2024;23(4):1165-1177. [PubMed](#)
21. Hong B, Zheng J, Chen R, et al. Pulmonary toxicity associated with immune checkpoint inhibitors-based therapy: current perspectives and future directions. *Drug Saf*. 2023;46(12):1313-1322. [PubMed](#)
22. Li Y, Liang X, Li H, Chen X. Comparative efficacy and safety of immune checkpoint inhibitors for unresectable advanced melanoma: a systematic review and network meta-analysis. *Int Immunopharmacol*. 2023;115:109657. [PubMed](#)
23. Wesevich A, Goldstein DA, Paydary K, Peer CJ, Figg WD, Ratain MJ. Interventional pharmacoeconomics for immune checkpoint inhibitors through alternative dosing strategies. *Br J Cancer*. 2023;129(9):1389-1396. [PubMed](#)
24. Jiang M, Hu Y, Lin G, Chen C. Dosing regimens of immune checkpoint inhibitors: attempts at lower dose, less frequency, shorter course. *Front Oncol*. 2022;12:906251. [PubMed](#)
25. Lee A, Duggan S, Deeks ED. Cemiplimab: a review in advanced cutaneous squamous cell carcinoma. *Drugs*. 2020;80(8):813-819. [PubMed](#)
26. Sehgal K, Costa DB, Rangachari D. Extended-interval dosing strategy of immune checkpoint inhibitors in lung cancer: will it outlast the COVID-19 pandemic? *Front Oncol*. 2020;10:1193. [PubMed](#)
27. World Bank Group. World Bank country and lending groups. 2026; <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>. Accessed 2026 June 11.
28. Albiges L, Bourlon MT, Chacon M, et al. Subcutaneous versus intravenous nivolumab for renal cell carcinoma. *Ann Oncol*. 2025;36(1):99-107. [PubMed](#)
29. Herrera AF, Burton C, Radford J, et al. Avelumab in relapsed/refractory classical Hodgkin lymphoma: phase 1b results from the JAVELIN Hodgkins trial. *Blood Adv*. 2021;5(17):3387-3396. [PubMed](#)
30. Le Brun IC, Dalle S, Mortier L, et al. Methods of nivolumab administration in advanced melanoma: a comparison of patients' clinical outcomes treated with flat dose or weight-adjusted dose, a multicenter observational study. *Cancer*. 2025;131(1):e35679. [PubMed](#)
31. Horisaki K, Yoshikawa S, Omata W, Tsutsumida A, Kiyohara Y. The real-world efficacy and side effects of different nivolumab regimens in Japanese patients with advanced melanoma: a single-center retrospective study. *Cancers (Basel)*. 2025;17(14):10. [PubMed](#)
32. Hughes BGM, Guminski A, Bowyer S, et al. A phase 2 open-label study of cemiplimab in patients with advanced cutaneous squamous cell carcinoma (EMPOWER-CSCC-1): final long-term analysis of groups 1, 2, and 3, and primary analysis of fixed-dose treatment group 6. *J Am Acad Dermatol*. 2025;92(1):68-77. [PubMed](#)
33. Smeenk MM, van der Noort V, Hendriks JMA, Abedian Kalkhoran H, Smit EF, Theelen W. Pembrolizumab hybrid dosing is non-inferior to flat dosing in advanced non-small cell lung cancer: a real-world, retrospective bicenter cohort study. *J Immunother Cancer*. 2025;13(2):06.
34. Staender HF, Langan EA. Fixed-dose versus weight-adapted immune checkpoint inhibitor therapy in melanoma: a retrospective monocentric analysis of efficacy and immune-related adverse events. *Cancers (Basel)*. 2025;17(7):28. [PubMed](#)
35. Chaitesipaseut L, Shah N, Truong TG, et al. Outcomes of weight-based vs. fixed dose of Pembrolizumab among patients with non-small cell lung cancer. *J Oncol Pharm Pract*. 2024;30(8):1352-1357. [PubMed](#)
36. Grit GF, van Geffen E, Malmberg R, et al. Real-world overall survival after alternative dosing for pembrolizumab in the treatment of non-small cell lung cancer: a nationwide retrospective cohort study with a non-inferiority primary objective. *Lung Cancer*. 2024;196:107950. [PubMed](#)
37. Leroy M, Desmedt E, Deramoudt L, et al. Retrospective comparison of a weight-based dose every 2 weeks with a fixed dose every month: a real-life analysis of nivolumab in the treatment of advanced melanoma. *Melanoma Res*. 2024;34(3):258-264. [PubMed](#)
38. Patel A, Hande V, Mr K, et al. Effectiveness of immune checkpoint inhibitors in various tumor types treated by low, per-weight, and conventional doses at a tertiary care center in Mumbai. *JCO Glob Oncol*. 2024;10:e2300312. [PubMed](#)

39. Rischin D, Hughes BGM, Basset-Seguín N, et al. High response rate with extended dosing of cemiplimab in advanced cutaneous squamous cell carcinoma. *J Immunother Cancer*. 2024;12(3):11. [PubMed](#)
40. Bérard G, Guevremont C, Marcotte N, Schroeder C, Bouchard N, Rajan R. Descriptive analysis of first-line non-small cell lung cancer treatment with pembrolizumab in tumors expressing PD-L1 $\geq$ 50% in patients treated in Quebec's university teaching hospitals (DALP-First Study). *Curr Oncol*. 2023;30(3):3251-3262. [PubMed](#)
41. Samlowski W, Robert NJ, Chen L, et al. Real-World nivolumab dosing patterns and safety outcomes in patients receiving adjuvant therapy for melanoma. *Cancer Med*. 2023;12(3):2378-2388. [PubMed](#)
42. Fujiwara Y, Takahashi Y, Okada M, et al. Phase I study of tremelimumab monotherapy or in combination with durvalumab in Japanese patients with advanced solid tumors or malignant mesothelioma. *Oncologist*. 2022;27(9):e703-e722. [PubMed](#)
43. Hijmering-Kappelle LBM, Hiltermann TJN, Bensch F. Safety and efficacy of extended interval dosing for immune checkpoint inhibitors in non-small cell lung cancer during the covid-19 pandemic. *Clin Lung Cancer*. 2022;23(2):143-150. [PubMed](#)
44. Ikura Y, Aoyama T, Hiraide M, et al. Safety evaluation of fixed-dose nivolumab in patients with gastric cancer. *Health Sci Rep*. 2022;5(4):e673. [PubMed](#)
45. Okada T, Fushimi C, Matsuki T, et al. Comparison of dosage of nivolumab in efficacy and safety for recurrent metastatic squamous cell carcinoma. *Anticancer Res*. 2022;42(3):1607-1613. [PubMed](#)
46. Patnaik A, Weiss GJ, Rasco DW, et al. Safety, antitumor activity, and pharmacokinetics of dostarlimab, an anti-PD-1, in patients with advanced solid tumors: a dose-escalation phase 1 trial. *Cancer Chemother Pharmacol*. 2022;89(1):93-103. [PubMed](#)
47. To SY, Kao LT, Shih JH, et al. Modified-dose pembrolizumab and prognostic outcomes among non-small cell lung cancer patients: A chart review study. *Int J Environ Res Public Health*. 2022;19(10):15. [PubMed](#)
48. Juergens RA, Hao D, Ellis PM, et al. A phase IB study of durvalumab with or without tremelimumab and platinum-doublet chemotherapy in advanced solid tumours: Canadian Cancer Trials Group Study IND226. *Lung Cancer*. 2020;143:1-11. [PubMed](#)
49. Kato R, Ikarashi D, Matsuura T, et al. Analyses of nivolumab exposure and clinical safety between 3-mg/kg dosing and 240-mg flat dosing in asian patients with advanced renal cell carcinoma in the real-world clinical setting. *Transl Oncol*. 2020;13(6):100771. [PubMed](#)
50. Rischin D, Migden MR, Lim AM, et al. Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing. *J Immunother Cancer*. 2020;8(1):06.
51. Masters JC, Khandelwal A, di Pietro A, Dai H, Brar S. Model-informed drug development supporting the approval of the avelumab flat-dose regimen in patients with advanced renal cell carcinoma. *CPT Pharmacometrics Syst Pharmacol*. 2022;11(4):458-468. [PubMed](#)
52. Novakovic AM, Wilkins JJ, Dai H, et al. Changing body weight-based dosing to a flat dose for avelumab in metastatic merkel cell and advanced urothelial carcinoma. *Clin Pharmacol Ther*. 2020;107(3):588-596. [PubMed](#)
53. Gandhi KA, Shirsat A, Hj SK, et al. Pharmacokinetics and clinical outcomes of low-dose nivolumab relative to conventional dose in patients with advanced cancer. *Cancer Chemother Pharmacol*. 2024;94(5):659-668. [PubMed](#)
54. Sheng J, Zhang J, Baudelet C, Roy A. Clinical benefit-risk assessment of nivolumab 240 mg every 2 weeks in Chinese patients with advanced and metastatic solid tumors. *J Clin Pharmacol*. 2021;61(8):1045-1053. [PubMed](#)
55. Zhao X, Shen J, Ivaturi V, et al. Model-based evaluation of the efficacy and safety of nivolumab once every 4 weeks across multiple tumor types. *Ann Oncol*. 2020;31(2):302-309. [PubMed](#)
56. Sanghavi K, Vuppala P, Ivaturi V, Hamuro L, Roy A, Suryawanshi S. Nivolumab exposure-response analysis for adjuvant treatment of melanoma supporting a change in posology. *CPT Pharmacometrics Syst Pharmacol*. 2021;10(7):748-759. [PubMed](#)
57. Bei D, Osawa M, Uemura S, et al. Benefit-risk assessment of nivolumab 240 mg flat dose relative to 3 mg/kg Q2W regimen in Japanese patients with advanced cancers. *Cancer Sci*. 2020;111(2):528-535. [PubMed](#)
58. Lala M, Li TR, de Alwis DP, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. *Eur J Cancer*. 2020;131:68-75. [PubMed](#)

59. Ter Heine R, van den Heuvel MM, Piet B, et al. A systematic evaluation of cost-saving dosing regimens for therapeutic antibodies and antibody-drug conjugates for the treatment of lung cancer. *Target Oncol.* 2023;18(3):441-450. [PubMed](#)
60. Yang F, Paccaly AJ, Rippley RK, Davis JD, DiCioccio AT. Population pharmacokinetic characteristics of cemiplimab in patients with advanced malignancies. *J Pharmacokinet Pharmacodyn.* 2021;48(4):479-494. [PubMed](#)
61. Paccaly AJ, Migden MR, Papadopoulos KP, et al. Fixed dose of cemiplimab in patients with advanced malignancies based on population pharmacokinetic analysis. *Adv Ther.* 2021;38(5):2365-2378. [PubMed](#)
62. Zhao Y, Sanghavi K, Roy A, et al. Model-based dose selection of subcutaneous nivolumab in patients with advanced solid tumors. *Clin Pharmacol Ther.* 2024;115(3):488-497. [PubMed](#)
63. Cohen G, Rapoport B, Chan SW, et al. Pembrolizumab 400 mg every 6 weeks as first-line therapy for advanced melanoma (KEYNOTE-555): results from cohort B of an open-label, phase 1 study. *PLoS ONE.* 2024;19(11):e0309778. [PubMed](#)
64. Lala M, Bardia A, Calles A, et al. Weight-based pembrolizumab dosing at 4 mg/kg every 6 weeks leads to exposures below approved doses with unestablished efficacy: a pharmacokinetic model-based simulation analysis. *Target Oncol.* 2025;20(6):955-965. [PubMed](#)
65. Hwang M, Chia YL, Zheng Y, et al. Population pharmacokinetic modelling of tremelimumab in patients with advanced solid tumours and the impact of disease status on time-varying clearance. *Br J Clin Pharmacol.* 2023;89(5):1601-1616. [PubMed](#)
66. Guyatt G, Agoritsas T, Brignardello-Petersen R, et al. Core GRADE 1: overview of the Core GRADE approach. *BMJ.* 2025;389:e081903. [PubMed](#)
67. Kung J, Chiappelli F, Cajulis OO, et al. From systematic reviews to clinical recommendations for evidence-based health care: Validation of Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) for grading of clinical relevance. *Open Dent J.* 2010;4:84-91. [PubMed](#)
68. Critical Appraisal Skills Programme: CASP checklists. 2026; <https://casp-uk.net/casp-tools-checklists/>. Accessed 2026 Mar 26.
69. Alonso-Coello P, Schunemann HJ, Moher J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ.* 2016;353:i2016. [PubMed](#)
70. Public Health Agency of Canada. Infection prevention and control guidelines: critical appraisal tool kit. Ottawa (ON): PHAC; 2014: https://publications.gc.ca/collections/collection_2014/aspc-phac/HP40-119-2014-eng.pdf. Accessed 2026 Mar 26.

Appendix 1: Literature Search Methods

Please note that this appendix has not been copy-edited.

Table 6: Search Strategy Yield Summary

Database(s) searched	Date of search	Number of results
Ovid MEDLINE(R) ALL 1946 to July 29, 2025 (OVID)	July 30, 2025	2,911
Embase Classic+Embase 1947 to 2025 July 25 (OVID)	July 30, 2025	4,929
Cochrane Database of Systematic Reviews 2005 to July 23, 2025 (OVID)	July 30, 2025	0
Cochrane Central Register of Controlled Trials June 2025 (OVID)	July 30, 2025	616

Note: The total of the database search results was 8,456 references. A total of 1,992 references were identified as duplicates and removed, leaving 6,464 references. A total of 1,558 references were removed because they had publication dates before 2020. These were retrieved because the field codes used for date limits in MEDLINE and Embase were broader than publication date and included the date the records were added to the database. This is a common practice when updating literature searches in these databases. The final number of references from the database searches was 4,906. Grey literature searches identified 517 references.

Table 7: Search Strategy — Ovid MEDLINE(R) ALL — 1946 to July 29, 2025

#	Searches	Results
1	Nivolumab/	6,410
2	Pembrolizumab.nm.	5,079
3	(BMS936558 or BMS-936558 or CMAB819 or CMAB-819 or keytruda* or lambrolizumab* or MDX1106 or MDX-1106 or MK3475 or MK-3475 or nivolumab* or ONO4538 or ONO-4538 or opdivo* or pembrolizumab* or SCH900475 or SCH-900475).ti,ab,kf,ot.	19,552
4	Durvalumab.nm.	923
5	(durvalumab* or imfinzi* or medi4736 or medi-4736).ti,ab,kf,ot.	2,342
6	Avelumab.nm.	494
7	(avelumab* or bavencio* or "msb 0010682" or msb 0010718c or msb 10682 or msb 10718c or msb0010682 or msb0010718c or msb10682 or msb10718c or "pf 06834635" or pf 6834635 or pf06834635 or pf6834635).ti,ab,kf,ot.	1,237
8	Atezolizumab.nm.	1,725
9	(anti-PDL1 or atezolizumab* or mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or tecentriq* or tecntriq*).ti,ab,kf,ot.	4,544
10	Cemiplimab.nm.	191
11	(cemiplimab* or libtayo* or regn 2810 or regn2810 or sar 439684 or sar439684).ti,ab,kf,ot.	604
12	dostarlimab.nm.	79
13	("anb 011" or anb011 or dostarlimab* or gsk 4057190 or gsk4057190 or jemperi* or "tsr 042" or tsr042 or wbp 285 or wbp285).ti,ab,kf,ot.	210
14	Ipilimumab/	3,415
15	(ipilimumab* or strentarga* or yervoy* or bms 734016 or bms734016 or cs 1002 or cs1002 or eb 1003 or eb1003 or hlx 13 or hlx13 or ibi 310 or ibi310 or "mdx 010" or mdx 101 or mdx010 or mdx101 or pbp 1701 or pbp1701).ti,ab,kf,ot.	6,006
16	tremelimumab.nm.	308

#	Searches	Results
17	(tremelimumab* or Imjudo* or ticilimumab* or cp 675 206 or cp 675,206 or cp 675206 or cp675 206 or cp675,206 or cp675206 or medi 1123 or medi1123).ti,ab,kf,ot.	686
18	or/1-17	28,833
19	Dose-Response Relationship, Drug/	429,022
20	Drug Administration Schedule/	104,132
21	Drug Dosage Calculations/	2,820
22	(dosing* or dose* or dosage*).ti.	251,776
23	(fixed dosage* or fixed dose* or fixed dosing* or flat dosage* or flat dose* or flat dosing* or Q2W or Q3W or Q4W or Q6W or posolog* or administration schedule*).ti,ab,kf.	17,674
24	((dose* or dosage* or dosing*) adj3 (model* or weight* or weight-based* or schedule* or regimen* or frequenc* or amount* or duration* or response* or calculation*)).ti,ab,kf.	206,026
25	(administration strategies or administration strategy or administration time* or daily dosage* or daily dose* or daily dosing* or different dosage* or different dose* or different dosing* or dosage* response relationship* or dose* response relationship* or dosing* response relationship* or dosage* design* or dose* design* or dosing* design* or dosage* interval* or dose* interval* or dosing* interval* or high* dosage* or high* dose* or high* dosing* or low* dosage* or low* dose* or low* dosing* or small* dosage* or small* dose* or small* dosing* or various dosage* or various dose* or various dosing* or recommended dose* or recommended dosing* or recommended dosage* or optimal dose* or optimal dosage* or optimal dosing* or dose* strategies or dose* strategy or dosage* strategies or dosage* strategy or dosing* strategies or dosing strategy).ti,ab,kf.	497,574
26	(Exposure adj4 response).ti,ab,kf.	22,984
27	exp Pharmacokinetics/	348,970
28	(pharmacokinetic* or pharmaco-kinetic* or kinetic* or elimination half-life or washout or wash-out).ti,ab,kf.	716,681
29	(time adj3 "peak concentration").ti,ab,kf.	1,132
30	Area Under Curve/	47523
31	("area* under the curve*" or "area* under curve*").ti,ab,kf.	120,457
32	Nivolumab/ad, pk [Administration & Dosage, Pharmacokinetics]	1,045
33	Ipilimumab/ad, pk [Administration & Dosage, Pharmacokinetics]	560
34	(pharmacodynamic* or pharmaco-dynamic*).ti,ab,kf.	58,769
35	Immune Checkpoint Inhibitors/ad, pk [Administration & Dosage, Pharmacokinetics]	1,110
36	or/19-35	2,155,287
37	18 and 36	3,906
38	(2020* or 2021* or 2022* or 2023* or 2024* or 2025*).dt,ez,da.	9,444,130
39	37 and 38	2,948
40	limit 39 to (english or french)	2,911

Table 8: Search Strategy — Embase Classic+Embase — 1947 to July 25, 2025

#	Searches	Results
1	*Nivolumab/ or *Pembrolizumab/	28,462
2	(BMS936558 or BMS-936558 or CMAB819 or CMAB-819 or keytruda* or lambrolizumab* or MDX1106 or MDX-1106 or MK3475 or MK-3475 or nivolumab* or ONO4538 or ONO-4538 or opdivo* or pembrolizumab* or SCH900475 or SCH-900475).ti,ab,kf.	47,602
3	*Durvalumab/	4,037
4	(durvalumab* or imfinzi* or medi4736 or medi-4736 or L01XC28).ti,ab,kf.	6,680
5	*Avelumab/	1,719
6	(avelumab* or bavencio* or "msb 0010682" or msb 0010718c or msb 10,682 or msb 10718c or msb0010682 or msb0010718c or msb10682 or msb10718c or "pf 06834635" or pf 6834635 or pf06834635 or pf6834635).ti,ab,kf.	3,032
7	*Atezolizumab/	5,662
8	(anti-PDL1 or atezolizumab* or mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or tecentriq* or tecntriq*).ti,ab,kf.	11,246
9	*Cemiplimab/	885
10	(cemiplimab* or libtayo* or regn 2810 or regn2810 or sar 439684 or sar439684).ti,ab,kf.	1,426
11	*dostarlimab/	397
12	("anb 011" or anb011 or dostarlimab* or gsk 4057190 or gsk4057190 or jemperi* or "tsr 042" or tsr042 or wbp 285 or wbp285).ti,ab,kf.	569
13	*ipilimumab/	7,166
14	(ipilimumab* or strentarga* or yervoy* or bms 734016 or bms734016 or cs 1002 or cs1002 or eb 1003 or eb1003 or hlx 13 or hlx13 or ibi 310 or ibi310 or "mdx 010" or mdx 101 or mdx010 or mdx101 or pbp 1701 or pbp1701).ti,ab,kf.	14,373
15	*ticilimumab/	1,140
16	(tremelimumab* or Imjudo* or ticilimumab* or cp 675 206 or cp 675,206 or cp 675206 or cp675 206 or cp675,206 or cp675206 or medi 1123 or medi1123).ti,ab,kf.	1,818
17	or/1-16 [ICI Drug Terms]	70,296
18	dose response/	413,851
19	drug administration/	96,150
20	dose calculation/	26,172
21	(dosing* or dose* or dosage*).ti.	408,354
22	(fixed dosage* or fixed dose* or fixed dosing* or flat dosage* or flat dose* or flat dosing* or Q2W or Q3W or Q4W or Q6W or posolog* or administration schedule*).ti,ab,kf.	47,348
23	((dose* or dosage* or dosing*) adj3 (model* or weight* or weight-based* or schedule* or regimen* or frequenc* or amount* or duration* or response* or calculation*)).ti,ab,kf.	318,452
24	(Exposure adj4 response).ti,ab,kf.	30,791
25	(administration strategies or administration strategy or administration time* or daily dosage* or daily dose* or daily dosing* or different dosage* or different dose* or different dosing* or dosage* response relationship* or dose* response relationship* or dosing* response relationship* or dosage* design* or dose* design* or dosing* design* or dosage* interval* or dose* interval* or dosing* interval* or high* dosage* or high* dose*	787,724

#	Searches	Results
	or high* dosing* or low* dosage* or low* dose* or low* dosing* or small* dosage* or small* dose* or small* dosing* or various dosage* or various dose* or various dosing* or recommended dose* or recommended dosing* or recommended dosage* or optimal dose* or optimal dosage* or optimal dosing* or dose* strategies or dose* strategy or dosage* strategies or dosage* strategy or dosing* strategies or dosing strategy).ti,ab,kf.	
26	exp pharmacokinetics/	968,297
27	(pharmacokinetic* or pharmaco-kinetic* or kinetic* or elimination half-life or washout or wash-out).ti,ab,kf.	940,002
28	(time adj3 "peak concentration").ti,ab,kf.	1,448
29	exp area under the curve/	243,503
30	("area* under the curve*" or "area* under curve").ti,ab,kf.	166,736
31	nivolumab/do, pk [Drug Dose, Pharmacokinetics]	441
32	pembrolizumab/do, pk [Drug Dose, Pharmacokinetics]	421
33	durvalumab/do, pk [Drug Dose, Pharmacokinetics]	116
34	avelumab/do, pk [Drug Dose, Pharmacokinetics]	81
35	atezolizumab/do, pk [Drug Dose, Pharmacokinetics]	166
36	cemiplimab/do, pk [Drug Dose, Pharmacokinetics]	40
37	dostarlimab/do, pk [Drug Dose, Pharmacokinetics]	12
38	ipilimumab/do, pk [Drug Dose, Pharmacokinetics]	386
39	ticilimumab/do, pk [Drug Dose, Pharmacokinetics]	100
40	(pharmacodynamic* or pharmaco-dynamic*).ti,ab,kf.	101,002
41	immune checkpoint inhibitor/do, pk [Drug Dose, Pharmacokinetics]	132
42	or/18-41 [Dosage or Pharmacokinetic Terms]	3,243,250
43	17 and 42 [Combining ICI Drugs + Dosage or Pharmacokinetic Terms]	16,858
44	limit 43 to dc = 20200101-20251231	11,520
45	limit 44 to (english or french)	11,451
46	(conference review or conference abstract).pt.	5,566,774
47	45 not 46	4,929

Table 9: Search Strategy — Cochrane Database of Systematic Reviews — 2005 to July 23, 2025

#	Searches	Results
1	(BMS936558 or BMS-936558 or CMAB819 or CMAB-819 or keytruda* or lambrolizumab* or MDX1106 or MDX-1106 or MK3475 or MK-3475 or nivolumab* or ONO4538 or ONO-4538 or opdivo* or pembrolizumab* or SCH900475 or SCH-900475).ti,ab,kw.	8
2	(durvalumab* or imfinzi* or medi4736 or medi-4736).ti,ab,kw.	0
3	(avelumab* or bavencio* or "msb 0010682" or msb 0010718c or msb 10682 or msb 10718c or msb0010682 or msb0010718c or msb10682 or msb10718c or "pf 06834635" or pf 6834635 or pf06834635 or pf6834635).ti,ab,kw.	2

#	Searches	Results
4	(anti-PDL1 or atezolizumab* or mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or tecentriq* or tecntriq*).ti,ab,kw.	1
5	(cemiplimab* or libtayo* or regn 2810 or regn2810 or sar 439684 or sar439684).ti,ab,kw.	0
6	("anb 011" or anb011 or dostarlimab* or gsk 4057190 or gsk4057190 or jemperi or "tsr 042" or tsr042 or wbp 285 or wbp285).ti,ab,kw.	0
7	(ipilimumab* or strentarga* or yervoy* or bms 734016 or bms734016 or cs 1002 or cs1002 or eb 1003 or eb1003 or hlx 13 or hlx13 or ibi 310 or ibi310 or "mdx 010" or mdx 101 or mdx010 or mdx101 or pbp 1701 or pbp1701).ti,ab,kw.	4
8	(tremelimumab* or Imjudo* or ticilimumab ticarcillin* or cp 675 206 or cp 675,206 or cp 675206 or cp675 206 or cp675,206 or cp675206 or medi 1123 or medi1123).ti,ab,kw.	0
9	(immune checkpoint* blockade* or immune* checkpoint blocker* or immune checkpoint* inhibition* or immune checkpoint* inhibitor* or PD-1 inhibitor* or PD-1-PD-L1 blockade* or PD-L1 inhibitor* or PD-L1 blockade* or programmed cell death protein 1 inhibitor* or programmed death-ligand 1 inhibitor*).ti,ab,kw.	22
10	or/1-9	26
11	(dosing* or dose* or dosage*).ti.	173
12	(fixed dosage* or fixed dose* or fixed dosing* or flat dosage* or flat dose* or flat dosing* or Q2W or Q3W or Q4W or Q6W or posolog* or administration schedule*).ti,ab,kw.	172
13	((dose* or dosage* or dosing*) adj3 (model* or weight* or weight-based* or schedule* or regimen* or frequenc* or amount* or duration* or response* or calculation*)).ti,ab,kw.	505
14	(Exposure adj4 response).ti,ab,kw.	2
15	(administration strategies or administration strategy or administration time* or daily dosage* or daily dose* or daily dosing* or different dosage* or different dose* or different dosing* or dosage* response relationship* or dose* response relationship* or dosing* response relationship* or dosage* design* or dose* design* or dosing* design* or dosage* interval* or dose* interval* or dosing* interval* or high* dosage* or high* dose* or high* dosing* or low* dosage* or low* dose* or low* dosing* or small* dosage* or small* dose* or small* dosing* or various dosage* or various dose* or various dosing* or recommended dose* or recommended dosing* or recommended dosage* or optimal dose* or optimal dosage* or optimal dosing* or dose* strategies or dose* strategy or dosage* strategies or dosage* strategy or dosing* strategies or dosing strategy).ti,ab,kw.	841
16	(pharmacokinetic* or pharmaco-kinetic* or kinetic* or elimination half-life or washout or wash-out).ti,ab,kw.	66
17	(time adj3 "peak concentration").ti,ab,kw.	0
18	("area* under the curve*" or "area* under curve*").ti,ab,kw.	6
19	(pharmacodynamic* or pharmaco-dynamic*).ti,ab,kw.	5
20	or/11-19	1,338
21	10 and 20	1
22	limit 21 to yr = "2020-current"	0

Table 10: Search Strategy — Cochrane Central Register of Controlled Trials — June 2025

#	Searches	Results
1	Nivolumab/	1,050
2	Pembrolizumab.sh.	349
3	(BMS936558 or BMS-936558 or CMAB819 or CMAB-819 or keytruda* or lambrolizumab* or MDX1106 or MDX-1106 or MK3475 or MK-3475 or nivolumab* or ONO4538 or ONO-4538 or opdivo* or pembrolizumab* or SCH900475 or SCH-900475).ti,ab,kf,ot.	7,014
4	Durvalumab.sh.	141
5	(durvalumab* or imfinzi* or medi4736 or medi-4736).ti,ab,kf,ot.	1,512
6	Avelumab.sh.	22
7	(avelumab* or bavencio* or "msb 0010682" or msb 0010718c or msb 10682 or msb 10718c or msb0010682 or msb0010718c or msb10682 or msb10718c or "pf 06834635" or pf 6834635 or pf06834635 or pf6834635).ti,ab,kf,ot.	475
8	Atezolizumab.sh.	144
9	(anti-PDL1 or atezolizumab* or mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or tecentriq* or tecntriq*).ti,ab,kf,ot.	1,758
10	Cemiplimab.sh.	28
11	(cemiplimab* or libtayo* or regn 2810 or regn2810 or sar 439684 or sar439684).ti,ab,kf,ot.	219
12	dostarlimab.sh.	18
13	("anb 011" or anb011 or dostarlimab* or gsk 4057190 or gsk4057190 or jemperi* or "tsr 042" or tsr042 or wbp 285 or wbp285).ti,ab,kf,ot.	168
14	Ipilimumab/	615
15	(ipilimumab* or strentarga* or yervoy* or bms 734016 or bms734016 or cs 1002 or cs1002 or eb 1003 or eb1003 or hlx 13 or hlx13 or ibi 310 or ibi310 or "mdx 010" or mdx 101 or mdx010 or mdx101 or pbp 1701 or pbp1701).ti,ab,kf,ot.	2,054
16	tremelimumab.sh.	38
17	(tremelimumab* or Imjudo* or ticilimumab* or cp 675 206 or cp 675,206 or cp 675206 or cp675 206 or cp675,206 or cp675206 or medi 1123 or medi1123).ti,ab,kf,ot.	524
18	or/1-17	11,099
19	dose-response relationship, drug/	36,470
20	Drug Administration Schedule/	27,469
21	Drug Dosage Calculations/	317
22	(dosing* or dose* or dosage*).ti.	92,078
23	(fixed dosage* or fixed dose* or fixed dosing* or flat dosage* or flat dose* or flat dosing* or Q2W or Q3W or Q4W or Q6W or posolog* or administration schedule*).ti,ab,kf.	17,459
24	((dose* or dosage* or dosing*) adj3 (model* or weight* or weight-based* or schedule* or regimen* or frequenc* or amount* or duration* or response* or calculation*)).ti,ab,kf.	44,058
25	(administration strategies or administration strategy or administration time* or daily dosage* or daily dose* or daily dosing* or different dosage* or different dose* or different dosing* or dosage* response relationship* or dose* response relationship* or dosing* response relationship* or dosage* design* or dose* design* or dosing* design* or dosage* interval* or dose* interval* or dosing* interval* or high* dosage* or high* dose*	112,214

#	Searches	Results
	or high* dosing* or low* dosage* or low* dose* or low* dosing* or small* dosage* or small* dose* or small* dosing* or various dosage* or various dose* or various dosing* or recommended dose* or recommended dosing* or recommended dosage* or optimal dose* or optimal dosage* or optimal dosing* or dose* strategies or dose* strategy or dosage* strategies or dosage* strategy or dosing* strategies or dosing strategy).ti,ab,kf.	
26	(Exposure adj4 response).ti,ab,kf.	2,365
27	exp Pharmacokinetics/	20,456
28	(pharmacokinetic* or pharmaco-kinetic* or kinetic* or elimination half-life or washout or wash-out).ti,ab,kf.	94,909
29	(time adj3 "peak concentration").ti,ab,kf.	654
30	Area Under Curve/	8,948
31	("area* under the curve*" or "area* under curve").ti,ab,kf.	15,775
32	(pharmacodynamic* or pharmaco-dynamic*).ti,ab,kf.	20,149
33	or/19-32	309,582
34	18 and 33	3,549
35	limit 34 to yr = "2020 -Current"	2,055
36	limit 35 to (english or french)	2,047
37	limit 36 to conference proceeding	1,431
38	36 not 37	616

Table 11: Legends Within the Search Strategies Across the Databases

Syntax	Description
/	Subject Heading (MeSH or EmTree)
exp	means that the narrower MeSH or EmTree headings underneath are included
*	truncation (e.g., child* finds child or children or childhood etc.)
.tw.	textword (word/phrase appears in title or abstract)
.ti.	textword (word/phrase appears in the title field)
.ab.	textword (word/phrase appears in the abstract field)
.kf.	keyword field (author assigned keywords)
.ot.	original title (word/phrase appears in the original title, which includes any non-English title in the original language)
.sh.	subject heading (work/phrase appears in the subject heading field)
adj#	adjacency operator (words are # adjacent to each other, in both directions)

Appendix 2: Study Characteristics

Please note that this appendix has not been copy-edited.

Table 12: Study Characteristics

Author and Publication Year	Country	Study Design	Intervention and Comparator(s)	Sample Size	Cancer Type
RCTs (n = 2)					
Albiges, 2025²⁸	Multinational (17 countries; enrolled across 73 sites)	Phase III, open-label, randomized, noninferiority trial	• SC nivolumab 1,200 mg q.4.w. (fixed) + Recombinant human hyaluronidase (rHuPH20) • IV nivolumab 3 mg/kg q.2.w. (weight-based)	495	Advanced (not amenable to curative surgery or radiation therapy) or metastatic, histologically confirmed ccRCC with or without sarcomatoid features
Herrera, 2021²⁹	US and western Europe	Phase Ib randomized, open-label, parallel-arm pharmacokinetic/ pharmacodynamic clinical trial	• Avelumab fixed-dose (70 mg q.2.w.; 350 mg q.2.w.; 500 mg q.2.w.; 500 mg q.3.w.) • Avelumab weight-based dosing; different fixed doses and dosing intervals (q.2.w. vs. q.3.w.)	31	Classical Hodgkin lymphoma (cHL)
Nonrandomized studies (n = 22)					
Campo Le Brun, 2025³⁰	France	Prospective cohort	• Nivolumab fixed dose (240 mg q.2.w. or 480 mg q.4.w.) • Nivolumab weight-adjusted dose (3 mg/kg q.2.w.)	348	Advanced melanoma (unresectable stage III to IV)
Horisaki, 2025³¹	Japan	Retrospective cohort	• Nivolumab fixed dose (Arm 1: 240 mg q.2.w./ Arm 2: 480 mg q.4.w.) • Nivolumab weight-based dose (Arm 3: 2 mg/kg q.3.w./ Arm 4: 3 mg/kg q.2.w.)	153	Advanced melanoma (Stage IV)

Author and Publication Year	Country	Study Design	Intervention and Comparator(s)	Sample Size	Cancer Type
Hughes, 2025 ³²	Australia, Germany, US (groups 1 to 3); Australia, Brazil, France, Germany, Greece, Italy, Spain (group 6)	Phase II, open-label, nonrandomized, multicohort study	• Cemiplimab Weight-based: 3 mg/kg IV q.2.w. (groups 1 to 2) • Cemiplimab fixed-dose: 350 mg IV q.3.w. (groups 3 and 6)	• Enrolled: 360 total; • Treated/analyzed (≥ 1 dose): 358	Advanced CSCC, metastatic cutaneous squamous cell cancer (mCSCC), and Locally Advanced (laCSCC)
Smeenk, 2025 ³³	The Netherlands	Real-world, retrospective bicentre cohort study	• Pembrolizumab hybrid (weight-based) dosing • Pembrolizumab standard-of-care fixed dosing (200 mg q.3.w. or 400 mg q.6.w.)	766	Advanced NSCLC
Staender, 2025 ³⁴	Germany	Retrospective cohort study	Nivolumab and Pembrolizumab • FDT • WAT	47	Melanoma
Chaitesipaseut, 2024 ³⁵	US	Retrospective cohort study	• Pembrolizumab WBD • Pembrolizumab fixed dosing	1,413	NSCLC
Cohen, 2024 ⁶³	South Africa, Australia, Sweden, and Spain	Open-label, phase I, single-arm multicohort clinical trial (cohort B)	• Pembrolizumab fixed dose 400 q6 for the entire cohort • Pemrolizumab model prediction of 2 mg/kg q3, or 200 mg q3, or 10 mg/kg q3	101	Advanced melanoma
Grit, 2024 ³⁶	Netherlands	Retrospective cohort	Pembrolizumab • Arm 1 (Alternative, weight-based): ◦ q.3.w.: < 65 kg 100 mg, 65 kg to 90 kg 150 mg, ≥ 90 kg 200 mg; ◦ q.6.w.: < 65 kg 200 mg, 65 kg to 90 kg 300 mg, ≥ 90 kg 400 mg.	1,966	NSCLC (Stage IIIB/IV)

Author and Publication Year	Country	Study Design	Intervention and Comparator(s)	Sample Size	Cancer Type
			• Arm 2 (Standard, fixed): ◦ q.3.w. 200 mg; ◦ q.6.w. 400 mg.		
Leroy, 2024³⁷	France	Retrospective cohort	• Nivolumab 3 mg/kg IV q.2.w. (WBD) • Nivolumab 480 mg IV q.4.w. (FD)	337	Advanced melanoma
Patel, 2024³⁸	India	Retrospective study (cohort)	Pembrolizumab, nivolumab, atezolizumab, Durvalumab • conventional fixed dosing • per-body-weight dosing • low-dose dosing	100	mNSCLC, extensive-stage small cell lung cancer, and biliary tract cancer
Rischin, 2024³⁹	International multicenter study	Open-label, nonrandomized phase II cohort comparison using sequential study groups	• Fixed dose: cemiplimab 350 mg IV q.3.w. (Group 3) • Weight-based: cemiplimab 3 mg/kg IV q.2.w. (Groups 1, 2). • The paper also reports a separate fixed-dose 600 mg q.4.w. cohort, but that is not helpful with fixed-vs.-weight-based comparison.	• PK comparison: Groups 1& 2 (n = 96) vs. group 3 (n = 34). • AE comparison across earlier cohorts combined: Groups 1 to 3 (n = 193) vs. group 4 (n = 63)	CSCC
Berard, 2023⁴⁰	Canada	Retrospective cohort	• Pembrolizumab fixed dose 200 mg q.3.w. • Pembrolizumab weight-based capped dose 2 mg/kg (max 200 mg) q.3.w.	279	NSCLC
Samlowski, 2023⁴¹	US	Retrospective study (cohort)	• Nivolumab 480 mg q.4.w. (de novo or switched) • nivolumab 240 mg q.2.w. • nivolumab 3 mg/kg q.2.w.	191	Melanoma

Author and Publication Year	Country	Study Design	Intervention and Comparator(s)	Sample Size	Cancer Type
Fujiwara, 2022⁴²	Japan	Phase I, open-label trial (cohort)	• Cohort 3 (fixed): tremelimumab 75 mg + durvalumab 1,500 mg • Cohort 1 to 2 (weight-based): tremelimumab + durvalumab in mg/kg regimens	65	Advanced solid tumours (part 2); study overall also includes malignant mesothelioma (part 1 expansion)
Hijmering-Kappelle et al., 2022⁴³	The Netherlands	Retrospective single-centre cohort study	• Durvalumab adjuvant: standard-dose 10 mg/kg every 2 weeks • Durvalumab extended-interval fixed dose 1,500 mg every 4 weeks	66	NSCLC
Iikura, 2022⁴⁴	Japan	Retrospective cohort	• Nivolumab Weight-based: 3 mg/kg q.2.w.; • Fixed-dose: 240 mg q.2.w.	113	Advanced gastric cancer
Okada, 2022⁴⁵	Japan	Retrospective cohort	• Nivolumab 3 mg/kg q.2.w. • Nivolumab 240 mg fixed dose q.2.w.	199	Recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN)
Patnaik, 2022⁴⁶	US	Open-label, first-in human, phase I study (cohort)	• Part 1: dostarlimab 1mg/kg q.2.w. with subsequent dose escalation to levels of 3 and 10 mg/kg • Part 2a: dostarlimab fixed dose of 500 mg (q.3.w.) and 1,000 mg q.6.w.	34	Advanced (unresectable) or metastatic solid tumours with disease progression after treatment with available standard-of-care treatments or treatment intolerance
To, 2022⁴⁷	Taiwan	Retrospective chart review study (cohort)	• Pembrolizumab modified-dose (2 mg/kg q.3.w.) • Pembrolizumab 100 mg q.3.w. • Pembrolizumab standard-dose (200 mg q.3.w.)	64	Advanced NSCLC

Author and Publication Year	Country	Study Design	Intervention and Comparator(s)	Sample Size	Cancer Type
Juergens, 2020 ⁴⁸	Canada	Phase Ib, multicenter, multicohort dose-escalation trial (Rolling Six design)	• DL0 = durvalumab alone • DL1, DL2a, DL2b = weight-based dosing • DL3, DL4 = fixed dosing (Arm 1: Durvalumab + chemotherapy (DL0; no tremelimumab); arm 2: Durvalumab + Tremelimumab + chemotherapy (DL1; WBD, lower tremelimumab dose); arm 3: Durvalumab + Tremelimumab + chemotherapy (DL2a/2b; WBD, higher tremelimumab exposure); arm 4: Durvalumab + Tremelimumab + chemotherapy (DL3; fixed-ratio dosing); arm 5: Durvalumab + Tremelimumab + chemotherapy (DL4; fixed-ratio dosing, highest tested cohort / RP2D))	136	Advanced/metastatic solid tumours (majority lung cancer; NSCLC subgroup reported)
Kato, 2020 ⁴⁹	Japan	Retrospective cohort study	• Nivolumab weight-based dosing of 3 mg/kg • Nivolumab flat dosing of 240 mg	19	RCC
Rischin, 2020 ⁵⁰	International, multicenter	Phase II, open-label, nonrandomized, multicenter, international study	• Cemiplimab 350 mg IV q.3.w. (Group 3) • cemiplimab 3 mg/kg IV q.2.w. (Group 1)	115	mCSCC
PK/PD modelling or simulation studies (n = 14)					
Lala, 2025 ⁵⁴	NA (modelling and Simulation)	PK modelling (population model-based simulation)	• Pembrolizumab 4 mg/kg q.6.w. • Pembrolizumab 400 mg	Dataset of 3,607 patients	PK model was based on patient data from studies

Author and Publication Year	Country	Study Design	Intervention and Comparator(s)	Sample Size	Cancer Type
			q.6.w. • Pembrolizumab 200 mg q.3.w. • Pembrolizumab 2 mg/kg q.3.w. (all IV)		that examined melanoma, (NSCLC) and RCC patients
Gandhi, 2024⁵³	India	Prospective PK study	• Nivolumab 40 mg flat (q.2.w./q.3.w.) • Nivolumab weight-based 3 mg/kg (q.2.w./q.3.w.)	25	Advanced solid tumours
Zhao, 2024⁶²	NA	Model-based PopPK analysis	• Weight-based comparator: nivolumab 3 mg/kg IV q.2.w. (also benchmarked against 10 mg/kg IV q.2.w. as an upper safe-exposure reference). • Fixed-dose regimens: nivolumab 720 mg SC q.4.w., 960 mg SC q.4.w., and 1,200 mg SC q.4.w. (with rHuPH20) in model-based simulations	3,540 total in PopPK dataset	Advanced solid tumours; SC cohort included metastatic melanoma, RCC, NSCL, hepatocellular carcinoma, colorectal cancer, and urothelial carcinoma; pooled historical IV dataset also included multiple other tumour types
Ter Heine, 2023⁵⁹	NA	PK modelling and simulation (population PK; Monte Carlo; NONMEM)	Atezolizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab • Reference dosing regimen • Alternative dosing regimen	500 virtual patients	Lung cancer
Hwang, 2023⁶⁵	Multinational (US, Canada, Europe, Asia)	PopPK modelling; pooled-analysis model using NONMEM; external validation using additional pooled studies	Tremelimumab; Durvalumab • Weight-based • Flat-dose conversion scenario (1 mg/kg vs. 75 mg projected); also monotherapy vs. combination with	Model development: 956 patients (pooled from 5 studies). External validation: 554 patients (pooled from 4 studies).	Advanced solid tumours (NSCLC, mesothelioma, SCCHN, urothelial, and so forth)

Author and Publication Year	Country	Study Design	Intervention and Comparator(s)	Sample Size	Cancer Type
			durvalumab (therapy regimen effects on CL)		
Masters, 2022 ⁵¹	NA	Model-informed drug development: PopPK modelling + modelling/simulation; ER (logistic regression) analyses using trial datasets	• Avelumab weight-based clinical regimen: 10 mg/kg IV q.2.w. (with axitinib) • Avelumab fixed-dose regimen: 800 mg IV q.2.w. (predicted/simulated for aRCC)	aRCC combination-treatment analysis population: 488 patients (from 2 trials). Pooled PopPK dataset: 2,315 total (488 aRCC combo + 1,827 monotherapy)	aRCC in the combination dataset; reference monotherapy populations include solid tumours/UC/MCC (used for comparative exposure context)
Paccaly, 2021 ⁶¹	NA	PopPK modelling and simulation analysis	• Fixed-dose cemiplimab 350 mg IV q.3.w. • Weight-based cemiplimab 3 mg/kg IV q.2.w.;	505 total patients pooled	Advanced malignancies overall; includes advanced CSCC
Sanghavi, 2021 ⁵⁶	NA	Model-based ER/benefit-risk analysis	• Weight-based nivolumab 3 mg/kg q.2.w. • Fixed-dose regimens of nivolumab 240 mg q.2.w. and 480 mg q.4.w..	448 patients for adjuvant melanoma efficacy analysis; 3,008 patients for pooled safety analysis.	Melanoma in the adjuvant setting for efficacy; pooled safety dataset also included advanced solid tumours.
Sheng, 2021 ⁵⁴	China + global pooled populations	Model-informed benefit-risk assessment using popPK modelling + comparative safety/efficacy analyses across trial datasets	• Arm 1 (fixed): Nivolumab 240 mg q.2.w.; • Comparator (weight-based): Nivolumab 3 mg/kg q.2.w.; • Reference: Nivolumab 10 mg/kg q.2.w. (included as well-tolerated regimen)	Exposure simulations: Chinese 240 mg q.2.w. n = 314; Chinese 3 mg/kg q.2.w. n = 294. Observed Chinese safety: CheckMate 077 (240 mg n = 20, 3 mg/kg n = 15) and CheckMate 078 (3 mg/kg n = 241). Global pooled safety: 3 mg/kg n = 1375, 10 mg/kg n = 131.	Advanced and metastatic solid tumours, including melanoma, and squamous and nonsquamous cell NSCLC
Yang, 2021 ¹⁶⁰	NA	PopPK modelling + simulations using pooled clinical trial PK data	• Cemiplimab fixed 350 mg q.3.w. IV • Cemiplimab weight-based 3 mg/kg q.2.w. IV (exposure comparison/confirmation)	548 patients pooled (11,178 PK observations); CSCC subset 178 patients (2,266 PK observations)	Advanced malignancies (including advanced CSCC)

Author and Publication Year	Country	Study Design	Intervention and Comparator(s)	Sample Size	Cancer Type
Lala, 2020⁵⁸	NA	PK modelling and simulation (population PK + simulations)	• Pembrolizumab 400 mg q.6.w. fixed • Pembrolizumab 200 mg q.3.w. fixed • Pembrolizumab 2 mg/kg q.3.w. weight-based • Pembrolizumab 10 mg/kg q.2.w. weight-based	2,799	Advanced melanoma and NSCLC
Novakovic, 2020⁵²	Mixed	Pharmacometrics / PopPK modelling + simulation using data from 3 clinical trials	• Flat dose regimen of avelumab of 800 mg q.2.w. • Weight-based dosing of avelumab of 10 mg/kg q.2.w.	The population PK model is developed from data in 1,827 patients enrolled across 3 clinical trials	mMCC; advanced/metastatic UC (plus “various advanced/ metastatic solid tumors” in the pooled PK dataset)
Zhao, 2020⁵⁵	NA	Model-informed drug development: PopPK simulations + ER (safety and efficacy) + intratumoral receptor occupancy modelling	• Nivolumab fixed-dose / extended-interval (480 mg IV q.4.w.) • Nivolumab weight-based standard schedule (nivolumab 3 mg/kg IV q.2.w.) • Nivolumab flat-dose 240 mg IV q.2.w. also included in comparisons	PK simulation dataset: 3,203; Safety E–R dataset: 2,560; Efficacy E–R datasets: OS 1,615 and ORR 1,579	Multiple tumour types (melanoma; NSCLC; RCC; SCCHN; UC; classical Hodgkin lymphoma; plus other tumours in pooled safety)
Bei, 2020⁵⁷	Japan	Model-based quantitative clinical pharmacology (PopPK + ER safety/efficacy; benefit-risk assessment)	• Nivolumab 240 mg q.2.w. (flat) • Nivolumab 3 mg/kg r (weight-based)	Safety E-R dataset: 273 patients living in Japan Efficacy E-R dataset: 134 patients living in Japan PopPK modelling/ simulations: 3,939 total (420 living in Japan)	Multiple advanced cancers/ tumour types (e.g., melanoma, NSCLC, RCC, colorectal cancer, cHL, UC, SCCHN)

aRCC = advanced renal cell carcinoma; ccRCC = clear cell renal cell carcinoma; cHL = classical Hodgkin lymphoma; CL = clearance; CRC = colorectal cancer; CSCC = cutaneous squamous cell cancer; dMMR = deficient mismatch repair; ER = exposure-response; FDT = fixed-dose therapy; FD = fixed dose; HCC = hepatocellular carcinoma; ICI = immune checkpoint inhibitor; laCSCC = locally advanced cutaneous squamous cell cancer; mCRC = metastatic colorectal cancer; mCSCC = metastatic cutaneous squamous cell cancer; mMCC = metastatic Merkel cell carcinoma; mNSCLC = metastatic non-small cell lung cancer; mRCC = metastatic renal cell carcinoma; MGMT = O6-methylguanine-DNA methyltransferase; MSI-H = microsatellite instability-high; MSS = microsatellite stable; NCT = National Clinical Trial (ClinicalTrials.gov identifier); NMA = network meta-analysis; NR = not reported; NSCLC = non-small cell lung cancer; PD = progressive disease; PD-1 = programmed cell death protein 1; PK = pharmacokinetics; PopPK = population pharmacokinetic; q.12.w. = every 12 weeks; q.2.w. = every 2 weeks; q.3.w. = every 3 weeks

every 3 weeks; q.4.w. = every 4 weeks; q.6.w. = every 6 weeks; rHuPH20 = recombinant human hyaluronidase PH20; RCT = randomized controlled trial; RCC = renal cell carcinoma; RP2D = recommended phase 2 dose; SC = subcutaneous; SCCHN = squamous cell carcinoma of the head and neck; SCLC = small cell lung cancer; uHCC = unresectable hepatocellular carcinoma; UC = urothelial carcinoma; vs. = versus; WAT = weight-adapted therapy; WBD = weight-based dosing.

Appendix 3: Summary of Efficacy, Effectiveness, and Safety Outcomes

Please note that this appendix has not been copy-edited.

Table 13: Summary of Efficacy, Effectiveness, and Safety Outcomes

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
RCTs				
Albiges, 2025²⁸	• SC: nivolumab 1,200 mg + rHuPH20 20,000 units q.4.w. • IV: nivolumab 3 mg/kg q.2.w..	Efficacy outcomes • ORR at minimum 8 months • ORR at minimum 15 months • BOR (CR, PR, SD, PD, UTD) • DCR • Median TTR • Median PFS (BICR) + HR • OS rate at 6 months • OS rate at 12 months • Safety outcomes (<i>minimum 15 months follow-up</i>) • Any-grade AEs • Grade 3/4 AEs • TRAEs • Discontinuations due to all-causality AEs • Discontinuations due to TRAEs • Selected immune-mediated AEs • Treatment-related deaths	• Nivolumab + rHuPH20 SC (n = 248) ORR, n, % (95% CI) with minimum 8 months' follow-up: 60, 24.2% (95% CI, 19.0 to 30.0) BOR, n (%) with minimum 8 months' follow-up - CR:5 (2.0); PR: 55 (22.2); SD: 96 (38.7); PD: 62 (25.0); UTD: 30 (12.1) ORR, n, % (95% CI) with minimum 15 months' follow-up: 66, 26.6% (95% CI, 21.2 to 32.6) BOR, n (%) with minimum 15 months' follow-up - CR:5 (2.0); PR: 61 (24.6); SD: 89 (35.9); PD: 63 (25.4); UTD: 30 (12.1) DCR, n (%), 95% CI, 155 (62.5); 56.2 to 68.5 Median time to response, months (range): 3.71 (1.7 to 11.3); 6-month OS rate, % (95% CI): 83.8 (78.5 to 87.9); 12-month OS rate, % (95% CI): 72.4 (66.2 to 77.6); Median PFS, months (95% CI): 6.34 (5.13 to 7.49) Any grade AE, n (%): 230 (93.1); Any Grade 3/4 AE, n (%): 99 (40.1); Any grade TRAE, n(%): 152 (61.5);	• ORR (min 8 months): RR 0.75 (0.54 to 1.06) (converted to IV vs. SC from reported SC vs. IV RR 1.33); P value NR. • ORR (min 15 months): RR 0.78 (0.57 to 1.08) (converted from reported 1.28); P value NR. • DCR (min 15 months): RR 1.00 (0.88 to 1.15) (reported RR was ~1.00; direction essentially unchanged); P value NR. • PFS: HR 1.06 (0.85 to 1.32); P value NR.

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			Any-grade 3/4 TRAE, n(%): 29 (11.7); All-causality AE leading to discontinuation, any grade, n(%): 31 (12.6); All-causality AE leading to discontinuation, grade 3/4, n(%): 31 (12.6); Any grade TRAE leading to discontinuation, n (%): 11 (4.5); Grade 3/4 TRAE leading to discontinuation, n (%): 7 (2.8); All-causality AEs that required immune-modulating medication, any grade, n (%): 94 (38.1); All-causality AEs that required immune-modulating medication, grade 3/4, n (%): 34 (13.8); Hypersensitivity/IRR TRAEs, any grade, n (%): 1 (0.4); Hypersensitivity/IRR TRAEs, grade 3/4, n (%): 1 (0.4); Any grade local site reaction TRAEs, n (%): 5 (2.0); Any grade local site reaction TRAEs, n (%): 18 (7.3); Grade 3/4 local site reaction TRAE, n (%): 0; Death: 3 (1.2) Any grade all-causality endocrine immune-mediated adverse events, n (%): Hypothyroidism/thyroiditis: 24 (9.7); adrenal insufficiency: 6 (2.4); hyperthyroidism: 3 (1.2); hypophysitis: 0 Grade 3/4 all-causality endocrine immune-mediated adverse event, n (%): Hypothyroidism/thyroiditis: 0; adrenal insufficiency: 2 (0.8); hyperthyroidism: 0; hypophysitis: 0 Any grade all-causality nonendocrine immune-mediated	

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			adverse events, n (%): Rash: 18 (7.3); hepatitis: 9 (3.6); diarrhea/colitis: 8 (3.2); pneumonitis: 7 (2.8); nephritis/renal dysfunction: 4 (1.6) Grade 3/4 all-causality nonendocrine immune-mediated adverse events, n (%): Rash: 2 (0.8); hepatitis: 7 (2.8); diarrhea/colitis: 1 (0.4); pneumonitis: 3 (1.2); nephritis/renal dysfunction: 0 • Nivolumab i.v. (n = 247) ORR, n, % (95% CI) with minimum 8 months' follow-up: 45, 18.2% (95% CI, 13.6 to 23.6) BOR, n (%) with minimum 8 months' follow-up - CR:4 (1.6); PR: 41 (16.6); SD: 110 (44.5); PD: 66 (26.7); UTD: 26 (10.5) ORR, n, % (95% CI) with minimum 15 months' follow-up: 51, 20.6% (95% CI, 15.8 to 26.2) BOR, n (%) with minimum 15 months' follow-up - CR:7 (2.8); PR: 44 (17.8); SD: 104 (42.1); PD: 66 (26.7); UTD: 26 (10.5) DCR, n (%), 95% CI, 155 (62.8); 56.4 to 68.8 Median time to response, months (range): 3.68 (1.6 to 13.8); 6-month OS rate, % (95% CI): 86.4 (81.3 to 90.2); 12-month OS rate, % (95% CI): 72.9 (66.7 to 78.2); Median PFS, months (95% CI): 5.65 (5.19 to 7.39) Any grade AE, n (%): 231 (94.3);	

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			Any Grade 3/4 AE, n (%): 114 (46.5); Any grade TRAE, n(%): 161 (65.7); Any Grade 3/4 TRAE, n(%): 42 (17.1); All-causality AE leading to discontinuation, any grade, n(%): 34 (13.9); All-causality AE leading to discontinuation, grade 3/4, n(%): 24 (9.8); Any grade TRAE leading to discontinuation, n (%): 13 (5.3); Grade 3/4 TRAE leading to discontinuation, n (%): 9 (3.7); All-causality AEs that required immune-modulating medication, any grade, n (%): 106 (43.3); All-causality AEs that required immune-modulating medication, grade 3/4, n (%): 39 (15.9); Hypersensitivity/IRR TRAEs, any grade, n (%): 7 (2.9); Hypersensitivity/IRR TRAEs, grade 3/4, n (%): 0; Any grade local site reaction TRAEs, n (%): 5 (2.0); Grade 3/4 local site reaction TRAE, n (%): 0; Death: 2 (0.8) Any grade all-causality endocrine immune-mediated adverse events, n (%): Hypothyroidism/thyroiditis: 27 (11.0); adrenal insufficiency: 3 (1.2); hyperthyroidism: 11 (4.5); hypophysitis: 3 (1.2) Grade 3/4 all-causality endocrine immune-mediated adverse event, n (%): Hypothyroidism/thyroiditis: 1 (0.4); adrenal insufficiency: 0; hyperthyroidism: 0; hypophysitis: 2 (0.8) Any grade all-causality	

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			nonendocrine immune-mediated adverse events, n (%): Rash: 15 (6.1); hepatitis: 18 (7.3); diarrhea/colitis: 7 (2.9); pneumonitis: 7 (2.9); nephritis/renal dysfunction: 2 (0.8) Grade 3/4 all-causality nonendocrine immune-mediated adverse events, n (%): Rash: 3 (1.2); hepatitis: 12 (4.9); diarrhea/colitis: 0; pneumonitis: 2 (0.8); nephritis/renal dysfunction: 0	
Herrera, 2021²⁹	• Avelumab IV (1-hour infusion). Arms: • 70 mg q.2.w.; • 350 mg q.2.w.; • 500 mg q.2.w.; • 500 mg q.3.w.; • 10 mg/kg q.2.w..	Efficacy outcomes • BOR (CR, PR, SD, PD, not evaluable) • ORR • Time to response • DOR • PFS (median) • 1-year PFS rate Safety outcomes • TRAEs (any grade) • TRAEs (grade ≥ 3) • Treatment discontinuation due to AE • Treatment-related death • irAEs (any grade) • irAEs (grade ≥ 3) Follow-up / data cut-off • Data cut-off: April 11, 2019 • Median PFS follow-up: 5.6 months	• Arm 1 = 70 mg q.2.w. (n = 6): CR 1/6 = 16.7%; PR 1/6 = 16.7%; SD 1/6 = 16.7%; PD 2/6 = 33.3%; not evaluable 1/6 = 16.7%; ORR 2/6 = 33.3% • Arm 2 = 350 mg q.2.w. (n = 7 randomized): CR 0/7 = 0%; PR 0/7 = 0%; SD 4/7 = 57.1%; PD 1/7 = 14.3%; not evaluable 2/7 = 28.6%; ORR 0/7 = 0%. • Arm 3 = 500 mg q.2.w. (n = 6): CR 0/6 = 0%; PR 2/6 = 33.3%; SD 2/6 = 33.3%; PD 1/6 = 16.7%; not evaluable 1/6 = 16.7%; ORR 2/6 = 33.3% • Arm 4 = 500 mg q.3.w. (n = 6): CR 4/6 = 66.7%; PR 1/6 = 16.7%; SD 1/6 = 16.7%; PD 0/6 = 0%; not evaluable 0/6 = 0%; ORR 5/6 = 83.3% • Arm 5 = 10 mg/kg q.2.w. (n = 6): CR 1/6 = 16.7%; PR 3/6 = 50.0%; SD 0/6 = 0%; PD 2/6 = 33.3%; not	ORR overall (all randomized): 13/31 = 41.9%; CR 6/31 = 19.4%; PR 7/31 = 22.6%. Median PFS 5.7 months; 1-year PFS rate 18.2%. Any-grade TRAE: 26/30 = 86.7%. Grade ≥ 3 TRAE: 13/30 = 43.3%. Treatment-related death (pneumonitis): 1/30 = 3.3%. Immune-related AEs: 9/30 = 30.0%; grade ≥ 3 irAEs: 5/30 = 16.7%. Discontinuation due to AEs: 6/31 = 19.4% (reported as a main reason for discontinuation).

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			evaluable 0/6 = 0%; ORR 4/6 = 66.7% 16.7%; ORR 3/6 = 55.6%.	
Nonrandomized studies				
Campo Le Brun, 2025³⁰	• Nivolumab at a fixed dose of 240 mg/2W or 480 mg/4W dose • Nivolumab WAD a proportional dose of 3 mg/kg/2W.	Safety: • any-grade irAEs • grade 3 to 4 irAEs • grade 5 toxicities Efficacy: • ORR • DCR • median OS/PFS (after IPTW) + landmark OS/PFS at 6/12/18/24 months (before and after IPTW)	WAD: • Grade 3 to 4 irAEs: 21/160 = 13.1% • Any irAE: 101/160 = 63.1% • No grade 5 • ORR: 64/160 = 40.0% • DCR: 98/160 = 61.2% • Median OS (after IPTW): 24.8 months • Median PFS (after IPTW): 3.1 months • Landmark OS% (after IPTW) at 6/12/18/24 months: 78.8 / 61.0 / 56.7 / 51.5 • Landmark PFS % (after IPTW) at 6/12/18/24 months: 39.4 / 27.4 / 24.0 / 22.2. FD: • Grade 3 to 4 irAEs: 22/188 = 11.7%; Any irAE: 126/188 = 67.0% • No grade 5 • ORR: 91/188 = 48.4% • DCR: 124/188 = 66.0% • Median OS (after IPTW): 37.0 months • Median PFS (after IPTW): 3.7 months • Landmark OS % (after IPTW) at 6/12/18/24 months: 81.5 / 72.8 /	• Severe irAEs (grade 3 to 4): P = 0.8 • Any irAE: P = 0.5 • ORR: P = 0.14 • DCR: P = 0.42 • OS HR (FD vs. WAD, after IPTW): 0.74 (0.54 to 1.01) • PFS HR (FD vs. WAD, after IPTW): 0.84 (0.65 to 1.07)

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			64.5 / 60.2 • Landmark PFS % (after IPTW) at 6/12/18/24 months: 42.5 / 33.9 / 32.8 / 29.9	
Horisaki, 2025 ³¹	Nivolumab • Arm 1: 240 mg q.2.w.; • Arm 2: 480 mg q.4.w.; • Arm 3: 2 mg/kg q.3.w.; • Arm 4: 3 mg/kg q.2.w..	Efficacy outcomes • BOR (CR, PR, SD, PD) • ORR • DCR (best response) • PFS (median; from nivolumab start) • OS (median; from nivolumab start) • 6-month PFS rate • 12-month PFS rate Safety outcomes • Any-grade irAEs • Grade ≥ 3 irAEs • Discontinuation due to irAEs • Reasons for discontinuation	Arm 1 (240 mg q.2.w., n = 40): CR 1/40 (2.5%); PR 10/40 (25.0%); SD 8/40 (20.0%); PD 21/40 (52.5%); ORR 27.5%; DCR 47.5%. Median PFS 3.9 months; median OS 16.5 months. 6-month PFS 17/40 (42.5%); 12-month PFS 11/40 (27.5%). Any-grade irAE 17/40 (42.5%); Grade ≥ 3 irAE 3/40 (7.5%). Stopped due to irAE: 5/37 (13.5%)* Arm 2 (480 mg q.4.w., n = 35): CR 2/35 (5.7%); PR 2/35 (5.7%); SD 11/35 (31.4%); PD 20/35 (57.1%); ORR 11.4%; DCR 42.8%. Median PFS 3.6 months; median OS 9.4 months. 6-month PFS 12/35 (34.3%); 12-month PFS 4/35 (11.4%). Any-grade irAE 16/35 (45.7%); Grade ≥ 3 irAE 1/35 (2.9%). Stopped due to irAE: 2/31 (6.5%)* Arm 3 (2 mg/kg q.3.w., n = 41): CR 0/41 (0.0%); PR 6/41 (14.6%); SD 13/41 (31.7%); PD 22/41 (53.7%); ORR 14.6%; DCR 46.3%. Median PFS 3.1 months; median OS 11.8 months. 6-month PFS 13/41 (31.7%); 12-mo PFS 7/41 (17.1%). Any-grade irAE 19/41 (46.3%); Grade ≥ 3 irAE 8/41 (19.5%). Stopped due to irAE: 8/41 (19.5%)*	Arm 2 vs. 1: ORR: 11.4% vs. 27.5% (P = 0.082). DCR: 42.8% vs. 47.5% (P = 0.687). Log-rank: PFS P = 0.841; OS P = 0.852. Multivariable Cox (vs. 240 mg q.2.w. reference): PFS HR 0.959 (95% CI, 0.561 to 1.642), P = 0.881; OS HR 1.028 (0.572 to 1.847), P = 0.928 Median PFS: 3.6 vs. 3.9 months (log-rank P = 0.841). Median OS: 9.4 vs. 16.5 months (log-rank P = 0.852). 6-month PFS: 12/35 (34.3%) vs. 17/40 (42.5%) (P = 0.487). 12-month PFS: 4/35 (11.4%) vs. 11/40 (27.5%) (P = 0.147). Any-grade irAE: 45.7% vs. 42.5% (P = 0.819) Grade ≥ 3 irAE: 2.9% vs. 7.5% (P = 0.618) Arm 4 vs. arm 3: ORR: 24.3% vs. 14.6% (P = 0.278). DCR: 40.5% vs. 46.3% (P = 0.606). Median PFS: 2.6 vs. 3.1 months (log-rank P = 0.753). Median OS: 18.9 vs. 11.8 months (log-rank P = 0.892). 6-month PFS: 13/37 (35.1%) vs. 13/41 (31.7%) (P = 0.812). 12-month PFS: 8/37 (21.6%) vs. 7/41 (17.1%)

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			Arm 4 (3 mg/kg q.2.w., n = 37): CR 2/37 (5.4%); PR 7/37 (18.9%); SD 6/37 (16.2%); PD 22/37 (59.5%); ORR 24.3%; DCR 40.5%. Median PFS 2.6 months; median OS 18.9 months. 6-month PFS 13/37 (35.1%); 12-mo PFS 8/37 (21.6%). Any-grade irAE 18/37 (48.6%); Grade $\geq$ 3 irAE 4/37 (10.8%). Stopped due to irAE: 4/36 (11.1%)*	(P = 0.775). Arm 3 vs. 1: Multivariable Cox (vs. 240 mg q.2.w. reference): PFS HR 1.460 (95% CI, 0.848 to 2.513), P = 0.172; OS HR 1.316 (0.758 to 2.287), P = 0.329 Any-grade irAE: 46.3% vs. 48.6% (P = 1.000) Grade $\geq$ 3 irAE: 19.5% vs. 10.8% (P = 0.356) Arm 4 vs. 1: Multivariable Cox (vs. 240 mg q.2.w. reference): PFS HR 1.282 (95% CI, 0.761 to 2.160), P = 0.350; OS HR 1.299 (0.759 to 2.222), P = 0.3294
Hughes, 2025 ³²	- Groups 1 to 2: cemiplimab 3 mg/kg IV q.2.w. for $\leq$ 96 weeks (Group 1 for mCSCC patients and Group 2 for laCSCC). - Group 3: 350 mg IV q.3.w. for $\leq$ 54 weeks. - Group 6: 350 mg IV q.3.w. for $\leq$ 108 weeks	Efficacy outcomes • ORR (ICR) • CR • Partial response (PR) • Stable disease (SD) • PD • Nonevaluable • Time to CR • Duration of response (DOR) • 12-month DOR estimate • Median progression-free survival (PFS) • Median OS Safety outcomes • Any treatment-emergent adverse event (TEAE) • Grade $\geq$ 3 TEAE • Serious TEAE	Arm 1 = 3 mg/kg q.2.w. (weight-based; n = 59; mCSCC): CR 12/59 = 20.3%; PR 18/59 = 30.5%; SD 9/59 = 15.3%; PD 10/59 = 16.9%; Non-CR/non-PD 3/59 = 5.1%; Not evaluable 7/59 = 11.9%; ORR 30/59 = 50.8% (95% CI, 37.5 to 64.1). Median time to CR 11.1 months (3.7 to 22.1). Median PFS 18.4 months (95% CI, 7.3 to 53.2). Median OS 57.7 months (95% CI, 29.3 to NE). 48-month OS probability 57.1% (95% CI, 43.0 to 68.9). DOR estimates: 12-month 89.5%; 24-month 70.1%; 36-month 61.8%. Safety: any irTEAE 40/59 = 67.8%; grade $\geq$ 3 irTEAE 8/59 = 13.6%; serious irTEAE 6/59 = 10.2%; irTEAE leading to discontinuation 6/59 = 10.2%;	NR

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
		• Serious grade ≥ 3 TEAE • TEAE leading to discontinuation • TEAE leading to death Follow-up / measurement timing • Median follow-up: 42.5 months for Groups 1 to 3 • Median follow-up: 8.71 months for Group 6 • Data cut-off/lock: October 25, 2021 for Group 6; March 1, 2022 for Groups 1 to 3	irTEAE leading to death 0/59 = 0%; any grade ≥ 3 TEAE 30/59 = 50.8%. Arm 2 = 350 mg q.3.w. (fixed dose; n = 56; mCSCC): CR 11/56 = 19.6%; PR 15/56 = 26.8%; SD 8/56 = 14.3%; PD 14/56 = 25.0%; Non-CR/non-PD 2/56 = 3.6%; Not evaluable 6/56 = 10.7%; ORR 26/56 = 46.4% (95% CI, 33.0 to 60.3). Median time to CR 12.7 months (6.2 to 22.8). Median PFS 21.7 months (95% CI, 3.8 to 43.3). Median OS 48.4 months (95% CI, 29.5 to NE). 48-month OS probability 52.3% (95% CI, 37.9 to 64.9). DOR estimates: 12-month 88.5%; 24-month 84.6%; 36-month 84.6%. Safety: any irTEAE 35/56 = 62.5%; grade ≥ 3 irTEAE 6/56 = 10.7%; serious irTEAE 4/56 = 7.1%; irTEAE leading to discontinuation 2/56 = 3.6%; irTEAE leading to death 0/56 = 0%; any grade ≥ 3 TEAE 24/56 = 42.9%.	
Smeenk, 2025³³	• Arm 1: Pembrolizumab Hybrid: 100/150/200 mg q.3.w. (by weight: < 65 / 65 to 90 / > 90 kg) or double q.6.w. (200/300/400 mg). • Arm 2: Pembrolizumab Flat: 200 mg q.3.w. or 400 mg q.6.w..	Efficacy outcomes • Median OS • 1-year OS • Deaths during overall follow-up • Median progression-free survival (PFS) Safety / treatment-course outcomes (proxies) • Discontinuation due to PD or death (%) • Discontinuation due to toxicity (%)	Arm 1: • Deaths: 256/375. • Median OS: 17.7 months (95% CI, 14.9 to 20.9). • 1-year OS: 61% (95% CI, 56 to 66). • Median PFS: 6.4 months (95% CI 5.7 to 7.7). • Discontinued due to PD/death: 56% (n/N NR) • Discontinued due to toxicity: 21%	• OS HR = 0.76 (95% CI, 0.65 to 0.90), P < 0.0001 (hybrid vs. flat as reported). • PFS HR = 0.82 (95% CI, 0.70 to 0.96), P < 0.0001. (Paper frames this as noninferiority with margin HR 1.15.) • Corticosteroids for irAE, P = 0.48

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
		• Corticosteroid use (%) • Oligoprogression (%)	(n/N NR) • Oligoprogression: 29% (n/N NR) • Corticosteroids: 23% (n/N NR) • Systemic progression: 71% (183/375) Arm 2: • Deaths: 320/391 • Median OS: 11.8 months (95% CI 9.3 to 13.8) • 1-year OS: 50% (95% CI 45 to 55) • Median PFS: 4.6 months (95% CI 3.9 to 5.5) • Discontinued due to PD/death: 60% (n/N NR) • Discontinued due to toxicity: 22% (n/N NR) • Systemic progression: 75% (192/391) • Oligoprogression: 25% (n/N NR) • Corticosteroids: 21% (n/N NR)	
Staender, 2025³⁴	Anti-PD1 monotherapy (nivolumab or pembrolizumab). • WAT: nivolumab 3 mg/kg q.2.w.; pembrolizumab 2 mg/kg q.3.w. • FDT: nivolumab 240 mg q.2.w. or 480 mg monthly; pembrolizumab 200 mg q.3.w. or 400 mg q.6.w..	Efficacy outcomes • PFS • OS Outcome definitions / timing • PFS: measured from treatment initiation to first radiologic progression, based on radiologic evaluation per RECIST v1.1 • OS: measured from treatment initiation to death or last follow-up (31.12.2020)	WAT group • Median PFS: 174 days • Median OS: 980 days • irAEs: authors state no difference vs. FDT FDT group • Median PFS: 208 days • Median OS: undefined (not reached)	• PFS: Log-rank P = 0.595 • OS: Log-rank P = 0.502 (HR/CI not reported.)

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
		Safety outcomes irAEs, classified by type/severity		
Chaitesipaseut, 2024³⁵	- Arm 1: FD pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks - Arm 2: WBD Pembrolizumab 2 mg per kg every 3 weeks or 4 mg per kg every 6 weeks	Efficacy outcomes - OS at end of follow-up Safety outcomes - All-cause ER visits - All-cause hospitalizations - New incidence of selected irAEs (5 organ systems) Follow-up / measurement period - Safety outcomes measured from index date to 6 months after last pembrolizumab administration - Overall follow-up until death, loss of membership, or June 30, 2022	Arm 1 (FD) - OS (rate at end of follow-up: June 30, 2022): 36.6% - All-cause emergency department visits (proportion of patients): 15.6% - All-cause Hospitalizations (Proportion of patients): 19.7% - Composite Incidence of irAEs (Up to 6 months after the last infusion): 21.0% Arm 2 (WD) - OS (Rate at End of Follow-up: 30 June 2022): 37.7% - All-cause emergency department visits (proportion of patients): 14.5% - All-cause Hospitalizations (Proportion of patients): 17.4% - Composite Incidence of irAEs (Up to 6 months after the last infusion): 23.2%	OS (rate at end of follow-up: June 30, 2022) Rate difference (RD): 1% (90% CI, -6%–8%), Noninferiority (NI) P value < 0.01 Kaplan-Meier log-rank test, P = 0.88 Adjusted HR of Mortality (FD vs. WBD): 1.06 (95% CI, 0.84 to 1.32); P value = 0.63 All-cause Emergency department Visits (Proportion of patients): RD: 1.1% (90% CI, -0.05 to 0.07); NI P value < 0.01 All-cause Hospitalizations (Proportion of patients): RD: 2.3% (90% CI, -0.04 to 0.09); NI P value < 0.01 Composite Incidence of irAEs (Up to 6 months after the last infusion) RD: -2.2% (90% CI, -0.09% to 0.05%); NI P value = 0.03.
Grit, 2024³⁶	Pembrolizumab Arm 1: Standard dosing: q.3.w. 200 mg; q.6.w. 400 mg. Arm 2: q.3.w. < 65 kg 100 mg; 65 to 90 kg 150 mg; ≥ 90 kg 200 mg. q.6.w. < 65 kg 200 mg; 65 to 90 kg 300 mg; ≥ 90 kg 400 mg.	Efficacy outcomes - OS (from pembrolizumab initiation to death; censored at last activity or March 31, 2023) - TTNT-D (from treatment initiation to next line of therapy or death) Safety outcomes - No comparative safety outcomes reported	Arm 1: - Median OS: 15.2 months (95% CI, 14.2 to 17.2); deaths after 24 months: 537 events - Median TTNT-D: 11.3 months (95% CI, 10.3 to 12.3) Arm 2: - Median OS: 18.1 months (95% CI, 15.4 to 23.0); deaths after 24	Adjusted HR for OS (alt. dose vs. std dose) = 0.83 (95% CI, 0.69 to 1.003, P = 0.053) – established noninferiority (NI) because 95% CI falls within NI margin of 1.2 Adjusted HR for TTNT-D: 0.87 (95% CI, 0.74 to 1.03)

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			months: 144 events • Median TTNT-D: 12.7 months (95% CI, 10.8 to 15.4)	
Leroy, 2024³⁷	• Arm 1: Nivolumab 3 mg/kg IV q.2.w. (WBD) • Arm 2: Nivolumab 480 mg IV q.4.w. (FD)	Efficacy outcomes • OS at 12 months (Kaplan-Meier; log-rank) Safety outcomes • Grade ≥ 3 irAEs at 12 months (cumulative incidence; cause-specific Cox model) • Any-grade irAEs (time frame NR) • Discontinuation due to irAE (time frame NR)	Arm 1: • Grade ≥ 3 irAEs at 12 months: 4 (6.1%) • Discontinuation due to irAE: 10/70 = 14.3% • OS at 12 months: 52.6% (n/N NR) Arm 2: • Grade ≥ 3 irAEs at 12 months: 16 (6.1%) • Discontinuation due to irAE: 57/267 = 21.3% • OS at 12 months: 88.0% (n/N NR)	• Grade ≥ 3 irAEs at 12 months: HR 0.54 (95% CI, 0.21 to 1.36); P = 0.19 • OS at 12 months: P < 0.001 (log-rank; HR NR) • Low grade irAEs affecting the: ◦ endocrine system: HR = 1.44 (95% CI, 0.79 to 2.65) ◦ skin: HR = 0.72 (95% CI, 0.39 to 1.31) ◦ digestive tract: HR = 1.12 (95% CI, 0.47 to 2.65)
Patel, 2024³⁸	Drugs: Nivolumab (n = 47), Pembrolizumab (n = 36), Durvalumab (n = 9), Atezolizumab (n = 8). • Arm 1 (Conventional dose): Fixed approved dosing. • Arm 2 (per-body-weight dose): E.g., Pembrolizumab 2 mg/kg q.3.w.; Nivolumab 3 mg/kg q.2.w. • Arm 3 (Low dose): E.g., Low-dose Nivolumab 40 mg q.2.w. or 80 mg q.4.w.; Low-dose Pembrolizumab 1 mg/kg q.6.w.; Atezolizumab 1 mg/kg q.3.w.	Efficacy outcomes • ORR / response by PET-CT • Response categories: CR, PR, PD • OS • PFS Response assessment / follow-up • Response assessed every 3 months during year 1, then every 6 months • Data censored on July 31, 2023 • Median follow-up: 10.2 months (conventional/fixed), 9.8 months (per-weight), 3.9 months (low-dose)	Arm 1: • Palliative response (n = 18): • CR 2/18 (11.1%) • PR 11/18 (61.1%) • PD 5/18 (27.8%) • ORR (CR+PR): 13/18 = 72.2% Arm 2: • Palliative response (n = 23): ◦ CR 2/23 (8.7%) ◦ PR 12/23 (52.2%) ◦ PD 9/23 (39.1%) • ORR (CR + PR): 14/23 = 60.9% Arm 3: • Palliative response (n = 37):	• Palliative response counts reported as CR/PR/PD. • Median follow-up (months): 10.2 (conventional/fixed), 9.8 (per-weight), 3.9 (low-dose). • Median OS reported overall: 6.8 months (range: 4.6 to 9.0). • Safety end points (AEs/irAEs): NR

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			◦ CR 0/37 (0%) ◦ PR 28/37 (75.7%) ◦ PD 9/37 (24.3%) • ORR (CR + PR): 28/37 = 75.7%	
Rischin, 2024³⁹	• Weight-based/earlier cohorts: Groups 1 to 3 pooled (included earlier 3 mg/kg q.2.w. and fixed 350 mg q.3.w. cohorts), n = 193 • Fixed: Group 4 cemiplimab 600 mg IV q.4.w., n = 63	Efficacy outcomes • ORR • DOR • Disease control • Durable disease control • 12-month PFS • 12-month OS Safety outcomes • Any TEAE • Grade ≥ 3 TEAE • Any treatment-related AE • Grade ≥ 3 treatment-related AE • TEAEs leading to discontinuation or death • Treatment-related AEs leading to discontinuation or death	Groups 1 to 3 pooled (n = 193): any TEAE 192 (100%); grade ≥ 3 TEAE 95 (49%); any treatment-related AE 148 (77%); grade ≥ 3 treatment-related AE 33 (17%); TEAEs leading to discontinuation 19 (10%); TEAEs leading to death 5 (3%); treatment-related AEs leading to discontinuation 16 (8%); treatment-related AEs leading to death 1 (1%). Earlier groups 1 to 3, contextual efficacy only: integrated analysis ORR 46.1% (95% CI, 38.9 to 53.4); ongoing responses at 12 months 87.8% (95% CI, 78.5 to 93.3). Group 4 fixed 600 mg q.4.w. (n = 63): any TEAE 63 (100%); grade ≥ 3 TEAE 34 (54%); any treatment-related AE 52 (83%); grade ≥ 3 treatment-related AE 10 (16%); TEAEs leading to discontinuation 11 (18%); TEAEs leading to death 6 (10%); treatment-related AEs leading to discontinuation 7 (11%); treatment-related AEs leading to death 1 (2%); ORR 39/63 = 61.9% (95% CI, 48.8 to 73.9); complete response 14/63 (22.2%); partial response 25/63 (39.7%); disease control 49/63 = 77.8% (95% CI,	NR

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			65.5 to 87.3); durable disease control 48/63 = 76.2% (95% CI, 63.8 to 86.0); 12-month PFS 65% (95% CI, 51 to 76); 12-month OS 73% (95% CI, 60 to 83).	
Berard, 2023⁴⁰	• Pembrolizumab fixed dose 200 mg (arm 1 – FD) • Pembrolizumab 2 mg/kg up to a maximum dose of 200 mg (arm 2- weight-based capped dose [WCD]))	Efficacy outcomes • Median PFS • Median OS • Landmark PFS at 6, 12, and 24 months • Landmark OS at 6, 12, and 24 months Safety outcomes • irAEs causing treatment delay/interruption • Grade 3 to 4 irAEs • Discontinuation due to irAEs or other side effects • Median time to first irAE causing delay/interruption	Arm 1: • irAE causing delay/interruption 14/49 = 28.6%; cycles median 5 (range 1 to 36; IQR 2 to 14). Arm 2: • irAE causing delay/interruption 63/230 = 27.4%; cycles median 6 (range 1 to 34; IQR 2.25 to 13)	• OS adjusted HR (FD vs. WCD) HR 0.97 (95% CI, 0.61 to 1.53) [P value: 0.88]. • Overall median PFS 9.4 months (95% CI, 6.6 to 11.2); median OS 17.3 months (95% CI, 12.9–NR); PFS at 6/12/24 months = 57.4%/70.1%, 41.7%; OS at 6/12/24 months = 59.1%/29.4%/42.0%. • Switching: 13/49 switched from fixed to WBC during treatment; none switched from WBC to fixed.
Samlowski, 2023⁴¹	Nivolumab adjuvant monotherapy (melanoma), real-world cohorts by regimen: • C1 de novo (de novo referring to patients receiving this as their first dosing regimen and not having received another other flat dosing regimen before) 480 mg q.4.w.; • C2 switched to 480 mg q.4.w. after 240 mg or 3 mg/kg q.2.w.; • C3 de novo 3 mg/kg q.2.w.; • C4 de novo 240 mg q.2.w..	Efficacy / treatment-course outcomes • Duration of therapy (Kaplan-Meier; median months) Safety outcomes • Incidence of TRAEs • Incidence of “significant” TRAEs (hospitalization, ED visit, dose modification, or discontinuation) • Reasons for treatment discontinuation Safety assessment window • Within 12 months of initiation	C1: de novo nivolumab 480 mg q.4.w. (n = 40) • Duration (median [95% CI],months): 10.2 (5.3 to 10.8) • ≥ 1 TRAE: 24/40 = 60.0% • ≥ 1 “significant” TRAE: 7/40 = 17.5% • Prematurely discontinued: 13/40 = 32.5% (common reasons: progression 4/40 = 10.0%, toxicity 5/40 = 12.5%) C4: de novo nivolumab 240 mg q.2.w. (n = 55)	NR

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
		Up to 30 days after discontinuation (if treatment stopped)	- Duration (median [95% CI], months): 10.7 (9.8 to 11.3) ≥ 1 TRAE: 32/55 = 58.2% ≥ 1 “significant” TRAE: 11/55 = 20.0% - Prematurely discontinued: 23/55 = 41.8% (common reasons: progression 13/55 = 23.6%, toxicity 4/55 = 7.3%) C3: de novo nivolumab 3 mg/kg q.2.w. (n = 22) - Duration (median [95% CI], months): 8.3 (5.2 to 10.6) ≥ 1 TRAE: 12/22 = 54.5% ≥ 1 “significant” TRAE: 6/22 = 27.3% - Prematurely discontinued: 9/22 = 40.9% (common reasons: progression 3/22 = 13.6%, toxicity 2/22 = 9.1%)	
Fujiwara, 2022 ⁴²	Study part 1: - Cohort 1 [n = 4]: tremelimumab 3 mg/kg q.4.w. x6 then q.12.w. - Cohort 2 [n = 4]: tremelimumab 10 mg/kg x6 then q.12.w. Study part 2: - Cohort 1 (weight-based) [n = 4]: tremelimumab 10 mg/kg q.4.w. × 6 then q.12.w. × 3 + durvalumab 15 mg/kg q.4.w. × 13. - Cohort 2 (weight-based) [n = 6]: tremelimumab 1 mg/kg q.4.w. × 4 + durvalumab 20 mg/kg q.4.w. × 4 then 10 mg/kg q.2.w. up to 22	Efficacy outcomes (part 2) - ORR - DCR - Durable DCR - Response breakdown: CR, PR, SD ≥ 12 weeks, PD, nonevaluable - Assessed using RECIST 1.1 Outcome definitions / timing - ORR: confirmed CR or PR, with confirmation after 4 weeks - DCR: CR, PR, or SD lasting ≥ 12 weeks (day 81)	Part 1: Cohort 1 (n = 4): Efficacy: ORR 0/4 = 0%; DCR 0/4 = 0%; durable DCR 0/4 = 0%. Response breakdown: CR 0/4 = 0%; PR 0/4 = 0%; SD ≥ 12w 0/4 = 0%; PD 4/4 = 100%; nonevaluable 0/4 = 0% Safety: Any AE 3/4 = 75%; grade ≥ 3 AE 1/4 = 25%; SAE 1/4 = 25%; AE leading to discontinuation 0/4 = 0%; any AESI 3/4 = 75%; treatment-related AESI 3/4 = 75% Cohort 2 (n = 4): Efficacy: ORR 0/4 = 0%; DCR	NR

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
	doses. Cohort 3 (fixed-dose) [n = 6]: tremelimumab 75 mg q.4.w. × 4 + durvalumab 1,500 mg q.4.w. × 13.	- Durable DCR: CR, PR, or SD lasting ≥ 6 months (day 165) from first dose Safety outcomes (part 2) - Any AE - Grade ≥ 3 AE - SAE - AE leading to discontinuation - AESI - Treatment-related AESI - Common AEs by preferred term (≥ 10%) Treatment exposure - Duration of treatment: 44.0 days Other - PFS and OS not reported Efficacy outcomes (part 2) - ORR - DCR - Durable DCR - Response breakdown: CR, PR, SD ≥ 12 weeks, PD, nonevaluable - Assessed using RECIST 1.1 Outcome definitions / timing - ORR: confirmed CR or PR, with confirmation after 4 weeks - DCR: CR, PR, or SD lasting ≥ 12 weeks (day 81) - Durable DCR: CR, PR, or SD lasting ≥ 6 months (day 165) from first dose Safety outcomes (part 2)	1/4 = 25%; durable DCR 1/4 = 25% Response breakdown: CR 0/4 = 0%; PR 0/4 = 0%; SD ≥ 12w 1/4 = 25%; PD 3/4 = 75%; nonevaluable 0/4 = 0%. Safety: Any AE 4/4 = 100%; grade ≥ 3 AE 3/4 = 75%; SAE 1/4 = 25%; AE leading to discontinuation 0/4 = 0%; any AESI 3/4 = 75%; treatment-related AESI 2/4 = 50% Part 2: Arm 1 = cohort 1 (WBD) n = 4. Efficacy: ORR 0/4 = 0%; DCR 0/4 = 0%; durable DCR 0/4 = 0%. Response breakdown: CR 0/4 = 0%; PR 0/4 = 0%; SD ≥ 12w 0/4 = 0%; PD 3/4 = 75%; nonevaluable 1/4 = 25%. Safety: Any AE 4/4 = 100%; grade ≥ 3 AE 2/4 = 50%; SAE 2/4 = 50%; AE leading to discontinuation 2/4 = 50%; any AESI 3/4 = 75%; treatment-related AESI 3/4 = 75%. DLT: Grade 4 myasthenia gravis (reported as a DLT) in 1/4 Arm 2 = cohort 2 (WBD) n = 6. Efficacy: ORR 2/6 = 33.3% (CR 1/6 = 16.7%; PR 1/6 = 16.7%); DCR 2/6 = 33.3%; durable DCR 2/6 = 33.3%. Response breakdown: CR 1/6 = 16.7%; PR 1/6 = 16.7%; SD ≥ 12w 0/6 = 0%; PD 4/6 = 66.7%; nonevaluable 0/6 = 0% Safety: Any AE 5/6 = 83.3%; grade ≥ 3 AE 3/6 = 50%; SAE 3/6 = 50%; AE leading to discontinuation 2/6 =	

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
		- Any AE - Grade ≥ 3 AE - SAE - AE leading to discontinuation - AESI - Treatment-related AESI - Common AEs by preferred term ($\geq 10\%$) Treatment exposure - Duration of treatment: 44.0 days Other - PFS and OS not reported	33.3%; any AESI 5/6 = 83.3%; treatment-related AESI 3/6 = 50% Arm 3 = cohort 3 (FD) n = 6 Efficacy: ORR 0/6 = 0%; DCR 2/6 = 33.3% (driven by SD ≥ 12 weeks 2/6 = 33.3%); durable DCR 0/6 = 0%. Response breakdown: CR 0/6 = 0%; PR 0/6 = 0%; SD ≥ 12 w 2/6 = 33.3%; PD 3/6 = 50%; nonevaluable 1/6 = 16.7% Safety: Any AE 6/6 = 100%; grade ≥ 3 AE 3/6 = 50%; SAE 3/6 = 50%; AE leading to discontinuation 1/6 = 16.7%; any AESI 3/6 = 50%; treatment-related AESI 3/6 = 50%. DLT: Hyperglycemia (reported as a DLT) in 1/6	
Hijmering-Kappelle et al., 2022 ⁴³	Weight-based standard dose: durvalumab 10 mg/kg IV every 2 weeks; Fixed extended-interval dose: durvalumab 1,500 mg IV every 4 weeks; adjuvant treatment in stage III NSCLC	Efficacy outcomes - PFS (from treatment start) - OS (from treatment start) Safety outcomes - All AEs (overall and during escalation window) - Grade ≥ 3 AEs (overall and during escalation window) - Treatment interruption due to AEs - Treatment discontinuation due to AEs	Weight-based SD (n = 17): 26 total AEs; grade ≥ 3 AEs 3 (11.5%). In escalation window (n = 15): 19 total AEs; grade ≥ 3 AEs 2 (10.5%). Treatment interruption 0. Treatment discontinuation 5. Fixed EI (n = 49): 79 total AEs; grade ≥ 3 AEs 6 (7.6%). In escalation window: 46 total AEs; grade ≥ 3 AEs 5 (10.9%). Treatment interruption 1. Treatment discontinuation 3. PFS/OS: median PFS and median OS not reached in both cohorts.	No formal fixed-vs.-weight-based effect estimate reported for survival or safety outcomes. Reported subgroup p-values for adverse events were: overall any-grade P = 0.75; overall grade ≥ 3 P = 0.58; escalation-window any-grade P = 0.11; escalation-window grade ≥ 3 P = 0.74. No confirmed HR, RR, OR, mean difference, 95% CI, or confirmed survival P value reported in the parsed text available here.
Iikura, 2022 ⁴⁴	- Arm 1: Nivolumab WBD: 3 mg/kg q.2.w.; - Arm 2: Nivolumab FD: 240 mg q.2.w.	Safety outcomes - irAEs (any grade) - Grade ≥ 2 irAEs	Arm 1: Any-grade irAE: 23/77 = 29.9% Grade ≥ 2 irAE: 18/77 = 23.3% Discontinuation due to irAEs:	- Hyperthyroidism (Grade ≥ 2, category): P = 0.428 - Pneumonitis (Grade ≥ 2, category): P = 0.550

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
		- Grade ≥ 2 irAE categories: - Hypothyroidism - Pneumonitis - Diarrhea/colitis - Liver dysfunction - Nephritis/renal dysfunction - Rash - Other - Discontinuation due to irAEs	7/77 = 9.1% (pneumonitis 2; rash 1; liver dysfunction 2; diarrhea/colitis 1; other 1). - Grade ≥ 2 irAE categories (counts): hypothyroidism 6; pneumonitis 3; diarrhea/colitis 5; liver dysfunction 3; nephritis/renal dysfunction 1; rash 3; other 1. Arm 2: Any-grade irAE: 7/36 = 19.4% Grade ≥ 2 irAE: 7/36 = 19.4% - Discontinuation due to irAEs: 1/36 = 2.8% (other 1 [due to "idiopathic thrombocytopenic purpura"]). - Grade ≥ 2 irAE categories (counts): hypothyroidism 1; liver dysfunction 1; nephritis/renal dysfunction 1; rash 6; other 1.	- Diarrhea/colitis (Grade ≥ 2, category): P = 0.176 - Liver dysfunction (Grade ≥ 2, category): P = 1.000 - Nephritis and renal dysfunction (Grade ≥ 2, category): P = 0.538 - Other (Grade ≥ 2, category): P = 0.538 - Rash (Grade ≥ 2, category): P = 0.028 (higher in 240 mg).
Okada, 2022 ⁴⁵	- Nivolumab 3 mg/kg q.2.w. [n = 88] (arm 1) - Nivolumab 240 mg/body [n = 111] (arm 2)	Efficacy outcomes - ORR (CR + PR) - DCR (CR + PR + SD) - Best overall response (RECIST 1.1) - Median OS (months) - Median PFS (months) - OS and PFS with 95% CI and HR (log-rank/Cox) Safety outcomes - Patients with any irAE - Per-event irAE counts - Grade 3 to 4 irAEs - Grade 5 irAEs (treatment-related)	Arm 1: - CR: 3/84 (4%); PR: 10/84 (12%); SD: 26/84 (31%); PD: 45/84 (54%) - ORR: 13/84 = 15% (evaluable n = 84) - DCR: 39/84 = 46% - Median OS: 9.5 months (95% CI 7.9 to 11.8) - Median PFS: 3.7 months (95% CI 2.5 to 5.1) - Any irAE: 25/88 = 28% patients experienced ≥ 1 irAE (any grade) - Grade ≥ 3 irAE (any): NR. - Treatment-related death: 0/88	- OS: HR 0.89 (95% CI, 0.57 to 1.37); P = 0.59 - PFS: HR 1.01 (95% CI, 0.71 to 1.44); P = 0.95 - ORR (arm 1 vs. 2): P = 0.15 (15% vs. 25%); DCR: P = 0.15 (46% vs. 57%) - Any irAE (patients): P = 0.24 (23/111 vs. 25/88)

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
		death) Assessment details - Efficacy assessed during the treatment period - irAEs graded using CTCAE v4.0	(none reported) Arm 2: - CR: 9/108 (8%); PR: 18/108 (17%); SD: 35/108 (32%); PD: 46/108 (43%) - ORR: 27/108 = 25% (evaluable n = 108) - DCR: 62/108 = 57% - Median OS: 10.9 months (95% CI 8.7 to 21.7) - Median PFS: 3.8 months (95% CI 2.7 to 5.7) - Any irAE: 23/111 = 21% of patients experienced ≥ 1 irAE (any grade) - Grade ≥ 3 irAE (any): Not reported - Treatment-related death: 1/111 (0.9%) due to Grade 5 interstitial lung disease	
Patnaik, 2022 ⁴⁶	Part 1 — Weight-Based Dose Escalation Arms - Arm 1: Dostarlimab 1 mg/kg q.2.w. - Arm 2: Dostarlimab 3 mg/kg q.2.w. - Arm 3: Dostarlimab 10 mg/kg q.2.w. Part 2A — Fixed-Dose Arms - Arm 4: Dostarlimab 500 mg q.3.w. - Arm 5: Dostarlimab 1,000 mg q.6.w.	Safety: Treatment-emergent adverse events (TEAEs) during the treatment period, including: - Any AE - Treatment-related AE - Grade ≥ 3 AE - Treatment-related grade ≥ 3 AE - Serious AE - AE leading to withdrawal - Treatment interruption - Immune-related AE Efficacy: - Best overall response by	Arm: 1 mg/kg q.2.w. (n = 6) Efficacy: irPR 0/6 = 0%; SD 2/6 = 33.3% Safety: Any AE 6/6 (100%); Dostarlimab-related AE 6/6 (100.0%); Any grade ≥ 3 AE 3/6 (50.0%); Dostarlimab-related grade ≥ 3 AE 1/6 (16.7%); Any serious AE 2/6 (33.3%); Dostarlimab-related serious AE 0/6 (0%); Any AE → withdrawal 0/6 (0%); Dostarlimab-related AE → withdrawal 0/6 (0%); Any AE → interruption 1/6 (16.7%); Any immune-related AE 0/6 (0%)	Fatigue: 1mg/kg q.2.w. 1(16.7); 3mg/kg q.2.w. 2(66.7); 10mg/kg q.2.w. 4(33.3); Part1 7(33.3); 500mg q.3.w. 2(33.3); 1,000mg q.6.w. 3(42.9); Part2A 5(38.5) Nausea: 1mg/kg q.2.w. 1(16.7); 3mg/kg q.2.w. 1(33.3); 10mg/kg q.2.w. 3(25.0); Part1 5(23.8); 500mg q.3.w. 1(16.7); 1,000mg q.6.w. 0; Part2A 1(7.7) Pruritus: 1mg/kg q.2.w. 2(33.3); 3mg/kg q.2.w. 1(33.3); 10mg/kg q.2.w. 1(8.3); Part1 4(19.0); 500mg q.3.w. 0; 1,000mg q.6.w. 0; Part2A 0

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
		irRECIST: - irPR - SD - Time to response - DOR (among responders)	Arm: 3 mg/kg q.2.w. (n = 3) Efficacy: irPR 1/3 = 33.3%; SD 1/3 = 33.3% Safety: Any AE 3/3 (100%); Dostarlimab-related AE 2/3 (66.7%); Any grade ≥ 3 AE 1/3 (33.3%); Dostarlimab-related grade ≥ 3 AE 0/3 (0%); Any serious AE 0/3 (0%); Dostarlimab-related serious AE 0/3 (0%); Any AE $\rightarrow$ withdrawal 0/3 (0%); Dostarlimab-related AE $\rightarrow$ withdrawal 0/3 (0%); Any AE $\rightarrow$ interruption 2/3 (66.7%); Any immune-related AE 0/3 (0%) Arm: 10 mg/kg q.2.w. (n = 12) Efficacy: irPR 1/12 = 8.3%; SD 2/12 = 16.7% Safety: Any AE 12/12 (100%); Dostarlimab-related AE 9/12 (75.0%); Any grade ≥ 3 AE 6/12 (50.0%); Dostarlimab-related grade ≥ 3 AE 1/12 (8.3%); Any serious AE 6/12 (50.0%); Dostarlimab-related serious AE 1/12 (8.3%); Any AE $\rightarrow$ withdrawal 2/12 (16.7%); Dostarlimab-related AE $\rightarrow$ withdrawal 1/12 (8.3%); Any AE $\rightarrow$ interruption 3/12 (25.0%); Any immune-related AE 1/12 (8.3%) Arm: 500 mg q.3.w. (n = 6) Efficacy: irPR 0/6 = 0%; SD 0/6 = 0% (SD responses in part 2A occurred in 1,000 mg q.6.w. cohort) Safety: Any AE 6/6 (100%); Dostarlimab-related AE 5/6 (83.3%);	Arthralgia: 1mg/kg q.2.w. 1(16.7); 3mg/kg q.2.w. 1(33.3); 10mg/kg q.2.w. 1(8.3); Part1 3(14.3); 500mg q.3.w. 1(16.7); 1,000mg q.6.w. 0; Part2A 1(7.7) Decreased appetite: 1mg/kg q.2.w. 2(33.3); 3mg/kg q.2.w. 1(33.3); 10mg/kg q.2.w. 0; Part1 3(14.3); 500mg q.3.w. 1(16.7); 1,000mg q.6.w. 0; Part2A 1(7.7) Maculopapular rash: 1mg/kg q.2.w. 2(33.3); 3mg/kg q.2.w. 1(33.3); 10mg/kg q.2.w. 0; Part1 3(14.3); 500mg q.3.w. 0; 1,000mg q.6.w. 0; Part2A 0 Alopecia: 1mg/kg q.2.w. 0; 3mg/kg q.2.w. 1(33.3); 10mg/kg q.2.w. 1(8.3); Part1 2(9.5); 500mg q.3.w. 0; 1,000mg q.6.w. 0; Part2A 0 Vomiting: 1mg/kg q.2.w. 0; 3mg/kg q.2.w. 0; 10mg/kg q.2.w. 2(16.7); Part1 2(9.5); 500mg q.3.w. 0; 1,000mg q.6.w. 0; Part2A 0 Anemia: 1mg/kg q.2.w. 0; 3mg/kg q.2.w. 0; 10mg/kg q.2.w. 0; 500mg q.3.w. 1(16.7); 1,000mg q.6.w. 0; Part2A 1(7.7) Amylase increased: 1mg/kg q.2.w. 0; 3mg/kg q.2.w. 0; 10mg/kg q.2.w. 0; Part1 0; 500mg q.3.w. 1(16.7); 1,000mg q.6.w. 1(14.3); Part2A 2(15.4) Hypokalemia: 1mg/kg q.2.w. 1(16.7); 3mg/kg q.2.w. 0; 10mg/kg q.2.w. 0; Part1 1(4.8); 500mg q.3.w.

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			Any grade ≥ 3 AE 1/6 (16.7%); Dostarlimab-related grade ≥ 3 AE 1/6 (16.7%); Any serious AE 1/6 (16.7%); Dostarlimab-related serious AE 0/6 (0%); Any AE $\rightarrow$ withdrawal 0/6 (0%); Dostarlimab-related AE $\rightarrow$ withdrawal 0/6 (0%); Any AE $\rightarrow$ interruption 2/6 (33.3%); Any immune-related AE 0/6 (0%) Arm: 1,000 mg q.6.w. (n = 7) Efficacy: irPR 0/7 = 0%; SD 2/7 = 28.6% Safety: Any AE 7/7 (100%); Dostarlimab-related AE 5/7 (71.4%); Any grade ≥ 3 AE 1/7 (14.3%); Dostarlimab-related grade ≥ 3 AE 1/7 (14.3%); Any serious AE 1/7 (14.3%); Dostarlimab-related serious AE 1/7 (14.3%); Any AE $\rightarrow$ withdrawal 1/7 (14.3%); Dostarlimab-related AE $\rightarrow$ withdrawal 1/7 (14.3%); Any AE $\rightarrow$ interruption 0/7 (0%); Any immune-related AE 1/7 (14.3%)	1(16.7); 1,000mg q.6.w. 1(14.3); Part2A 2(15.4)
To, 2022 ⁴⁷	- Arm1:Pembrolizumab 2 mg/kg or 100 mg fixed dose every 3 weeks (q.3.w.) - Arm 2: Pembrolizumab 200 mg fixed dose every 3 weeks (q.3.w.)	Efficacy: - OS: - Time-to-event - Median OS - PFS: - Median PFS (months) - Best overall response - ORR - Disease control rate (DCR) Safety:	Arm 1: - OS: 22.7 months (95% CI, 1.698 to 43.769) - PFS (median): 4.5 months - CR: 0/36 = 0%; PR: 5/36 (13.9%); SD: 18/36 (50%); PD: 9/36 (25%); not evaluable: 4/36 (11.1%) - ORR: 5/36 = 13.9% - DCR: 23/36 = 63.9% - Any-grade irAEs: 11% (n NR) - Grade 3/4 irAEs: 2.8% (n NR)	- OS: No difference in OS between groups; log-rank P = 0.340 - Adjusted HR for OS (ref: arm 1) = 0.591 (95% CI, 0.059 to 5.954), P = 0.656 - PFS: log-rank P = 0.046 (arm 2 vs. 1) median 6.1 vs. 4.5 months) - Adjusted HR for PFS (ref: arm 1) = 0.642 (95% CI, 0.105 to 3.927), P = 0.631 - ORR: P = 0.001 (arm 2 vs. 1:

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
		- Any-grade immune-related adverse events (irAEs) - Grade 3/4 irAEs - Discontinuation due to toxicities Tumour assessment timing: - CT scans every 3 months as part of routine assessment	- Discontinuation due to toxicity: NR by arm (overall 3/64 = 5%) - Treatment duration (median): 2.3 months Arm 2: - OS: Median OS (not reached) - PFS (median): 6.1 months (95% CI, 2.919 to 6.081) - CR: 1/28 = 3.6%; PR: 14/28 (50%); SD: 7/28 (25%); PD: 4/28 (14.3%); not evaluable: 2/28 (7.1%) - ORR: 15/28 = 53.6% - DCR: 22/28 = 78.6% - Any-grade irAEs: 32% (n NR) - Grade 3/4 irAEs: 7.1% (n NR) - Discontinuation due to toxicity: NR by arm (overall 3/64 = 5%) - Treatment duration (median): 5.0 months	53.6% vs. 13.9%) - DCR: P = 0.202 (arm 2 vs. 1: 78.6% vs. 63.9%) - Any-grade irAEs: P = 0.038 (arm 2 vs. 1: 32% vs. 11%) - Grade 3/4 irAEs: P = 0.577 (arm 2 vs. 1: 7.1% vs. 2.8%) - Median duration of treatment: P = 0.018 (arm 2 vs. 1: 5.0 vs. 2.3)
Juergens, 2020 ⁴⁸	Durvalumab: 15 mg/kg q.3.w. (during chemo then 20 mg/kg q.4.w.) for dose levels DL0, DL1, DL2a, DL2b 1,125 mg q.3.w. (DL3) 1,500 mg q.3.w. (DL4) Tremelimumab: 1 mg/kg x1 dose q.6.w. (DL0; specified in protocol but these patients later in the trial did not receive tremelimumab) 1 mg/kg x2 doses q.3.w. (DL1) 3 mg/kg x2 doses q.3.w. (DL2a)	Efficacy: - Best overall response by RECIST 1.1, including: - Objective response rate (ORR) - CR - Partial response (PR) - Stable disease (SD) - PD - Inevaluable - Time-to-event outcomes: - PFS - OS	Durvalumab only (N = 24; dose level 0): ORR 7/24 = 29%; CR 1/24 = 4%; PR 6/24 = 25%; SD 10/24 = 42%; PD 6/24 = 25%; Inevaluable 1/24 = 4%. irAE any grade: 11/24 = 46% Durvalumab + tremelimumab irAEs from total; total: 97/136) . irAE grade ≥ 3: 1/24 = 4% durvalumab + tremelimumab grade ≥ 3 irAEs from total; total: 28/136) . Durvalumab + tremelimumab (N = 112; dose levels 1 to 4): ORR 47/112 = 42%; CR 2/112 = 2%; PR	NR

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
	3 mg/kg x5 doses q.3.w. (DL2b) 56 mg q.3.w. (DL3) 75 mg q.3.w. (DL4)	- Note: PFS and OS were reported in the main paper, but not separately by Arm 1 vs. Arm 2 Safety: - Chemotherapy-related nonhematologic adverse events: - All grades - Grade 3 to 5 - irAEs: - Any grade - Grade ≥ 3 - Treatment discontinuation due to toxicity or irAEs - Treatment-related deaths Assessment/follow-up details: - Tumour assessments every 6 weeks - Analysis cut-off: January 19, 2018 - Median follow-up: 19.61 months	45/112 = 40%; SD 50/112 = 45%; PD 12/112 = 11%; inevaluable 3/112 = 3%. irAE any grade: 86/112 = 77%. irAE grade ≥ 3: 27/112 = 24%.	
Kato, 2020 ⁴⁹	- Group 1 (n = 11): Nivolumab weight-based dosing of 3 mg/kg q.2.w. - Group 2 (n = 8): Nivolumab flat dosing of 240 mg q.2.w.	Efficacy: - Objective response rate (ORR; PR rate) - Tumour response per RECIST 1.1 - Progression-free survival (PFS) - OS 12-month PFS rate 12-month OS rate - Note: Median PFS and OS were not reached (landmark rates reported instead) Safety:	Arm 1: - Any-grade irAEs: 8/11 = 72.7% - Grade 3 to 4 irAEs: 6/11 = 54.6% - ORR (PR): 5/11 = 45.5% 12-month PFS: 53.0% (95% CI, 25.0 to 79.2) 12-month OS: 80.8% (95% CI, 47.2 to 95.2) Arm 2: - Any-grade irAEs: 4/8 = 50.0% - Grade 3 to 4 irAEs: 1/8 = 12.5% - ORR (PR): 2/8 = 25.0% 12-month PFS: 87.5% (95% CI,	- ORR (PR rate): P = 0.63 (no significant difference) - Any-grade irAEs: P = 0.38 - Grade 3 to 4 irAEs: P = 0.15 - PFS/OS: HRs not reported (descriptive landmark rates)

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
		- Any-grade immune-related adverse events (irAEs) - Grade 3 to 4 irAEs - irAEs graded using CTCAE v5.0	46.3 to 98.3) 12-month OS: 100% (CI not estimable)	
Rischin, 2020⁵⁰	- Fixed: cemiplimab 350 mg IV q.3.w. (Group 3, n = 56) - Weight-based: cemiplimab 3 mg/kg IV q.2.w. (Group 1, n = 59)	Efficacy: - ORR, per independent central review - DCR, per independent central review - Durable disease control rate, per independent central review, defined as response or stable disease lasting at least 105 days - Duration of response (DOR), per independent central review, estimated using Kaplan-Meier methods - Median time to response, per independent central review Safety: - TRAE, any grade - TRAEs, grade ≥ 3 - Immune-related adverse events (irAEs), any grade - Immune-related adverse events (irAEs), grade ≥ 3	Fixed dose (cemiplimab 350 mg IV q.3.w.): ORR 41.1% (95% CI, 28.1 to 55.0); disease control rate 64.3% (95% CI, 50.4 to 76.6); durable disease control rate 57.1% (95% CI, 43.2 to 70.3); 8-month DOR 95.0% (95% CI, 69.5 to 99.3); median time to response 2.1 months (range 2.0 to 8.3); treatment-related adverse events any grade 36/56 (64.3%); treatment-related adverse events grade ≥ 3 7/56 (12.5%); immune-related adverse events any grade 32/56 (57.1%); immune-related adverse events grade ≥ 3 7/56 (12.5%). Weight-based dose (cemiplimab 3 mg/kg IV q.2.w.): ORR 49.2% (95% CI, 35.9 to 62.5); disease control rate 71.2% (95% CI, 57.9 to 82.2); durable disease control rate 61.0% (95% CI, 47.4 to 73.5); 12-month DOR 88.9% (95% CI, 69.3 to 96.3); median time to response 1.9 months (range 1.7 to 9.1); treatment-related adverse events any grade 46/59 (78.0%); treatment-related adverse events grade ≥ 3 9/59 (15.3%); immune-related adverse events any grade 40/59 (67.8%); immune-related	NR

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			adverse events grade ≥ 3 8/59 (13.6%).	
PK/PD modelling or simulation studies				
Gandhi, 2024⁵³	- Arm 1 (conventional): nivolumab 3 mg/kg IV (60-minute infusion) q.2.w. (n = 12) or q.3.w. (n = 2) - Arm 2 (low-dose): nivolumab 40 mg flat IV (60-minute infusion) q.2.w. (n = 9) or q.3.w. (n = 2)	Efficacy - Response at 3 months by RECIST 1.1: - CR - Partial response (PR) - Stable disease (SD) - PD - Objective response rate (ORR) - PFS: - Median PFS (months) - Kaplan-Meier estimates Safety - Assessed over the entire treatment duration - Any adverse event (AE) - Immune-related adverse event (irAE) - Grade ≥ 3 irAE - Discontinuation due to AE - Fatal toxicity	Arm 1: - Response (3 months; response-evaluable n = 11): - CR 1/11 = 9.1% - PR 1/11 = 9.1% - SD 3/11 = 27.3% - PD 6/11 = 54.5% - ORR (CR+PR) 2/11 = 18.2% - PFS: median 4.3 months (95% CI, 1.46 to 7.07), p vs. low-dose 0.31 - Any AE (whole treatment; n = 14): 14/14 = 100% - Immune-related AE (any grade): 9/14 = 64.3% - Grade ≥ 3 irAE: 4/14 = 28.6% - Discontinuation due to AE: 0% (none) - Treatment-related death/fatal toxicity: 0 reported Arm 2: - Response (3 months; response-evaluable n = 9): - CR 0/9 = 0% - PR 1/9 = 11.1% - SD 3/9 = 33.3% - PD 5/9 = 55.6% - ORR (CR+PR) 1/9 = 11.1% - PFS: median 5.8 months (95%	Median PFS: P value = 0.31 ORR: no comparative effect estimate reported (no OR/HR).

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			CI, 3.39 to 8.26) • Any AE (whole treatment; n = 11): 7/11 = 63.6% • Immune-related AE (any grade): 6/11 = 85.7% ◦ Grade ≥ 3 irAE: 0/11 = 0% ◦ Discontinuation due to AE: 0% (none) ◦ Treatment-related death/fatal toxicity: 0 reported	
Masters, 2022⁵¹	• Weight-based: avelumab 10 mg/kg IV q.2.w. • Flat dose: avelumab 800 mg IV q.2.w. (simulated/reference flat-dose exposures)	Safety (modelled outcomes) • Grade ≥ 3 treatment-emergent adverse events (TEAEs) • Any-grade immune-related adverse events (irAEs) • Any-grade IRRs Assessment approach • Based on ER modelling • No fixed follow-up time points reported	NR	• For any-grade irAEs, no exposure metrics were significantly associated, but the strongest (yet still insignificant) association was avelumab C_{max} after a single dose ($C_{max, sd}$), with an odds ratio of 1.000 (95% CI, 0.999 to 1.010) per mcg/mL change in concentration
Sanghavi, 2021⁵⁶	• Weight-based: nivolumab 3 mg/kg q.2.w.; • Fixed: nivolumab 240 mg q.2.w. and 480 mg q.4.w.	Efficacy • Recurrence-free survival (RFS) • Distant metastasis-free survival (DMFS) • Predicted at: ◦ 1 year ◦ 2 years Safety • Cumulative probability of: ◦ Grade ≥ 3 adverse events	RFS: 1 year: 3 mg/kg day 14 = 0.721 (0.679 to 0.766), 240 mg = 0.721 (0.679 to 0.766); 3 mg/kg day 28 = 0.721 (0.679 to 0.765), 480 mg = 0.721 (0.679 to 0.765). 2 years: 3 mg/kg day 14 = 0.644 (0.598 to 0.692), 240 mg = 0.644 (0.598 to 0.692); 3 mg/kg day 28 = 0.643 (0.598 to 0.692), 480 mg = 0.644 (0.599 to 0.693). DMFS: 1 year: 3 mg/kg day 14 = 0.8094 (0.7724 to 0.8483), 240 mg = 0.8095 (0.7724 to 0.8483); 3 mg/kg day 28 = 0.8094 (0.7724 to	NR

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
		(AEs) - Grade ≥ 2 immune-mediated adverse events (IMAEs) - Predicted at: 6 months 12 months	0.8482), 480 mg = 0.8094 (0.7724 to 0.8482). 2 years: 3 mg/kg day 14 = 0.7164 (0.6726 to 0.7631), 240 mg = 0.7165 (0.6727 to 0.7632); 3 mg/kg day 28 = 0.7165 (0.6726 to 0.7632), 480 mg = 0.7165 (0.6726 to 0.7632). Grade 3+ AEs: 6 months: 3 mg/kg 0.206 (0.1686 to 0.2975), 240 mg 0.2056 (0.1721 to 0.2985), 480 mg 0.1967 (0.1644 to 0.2863). 12 months: 3 mg/kg 0.2892 (0.2395 to 0.4076), 240 mg 0.2887 (0.2443 to 0.409), 480 mg 0.2769 (0.2339 to 0.3936). Grade 2+ IMAEs: 6 months: 3 mg/kg 0.2275 (0.1879 to 0.2877), 240 mg 0.2280 (0.1877 to 0.2841), 480 mg 0.2516 (0.2079 to 0.3124). 12 months: 3 mg/kg 0.3135 (0.2621 to 0.3905), 240 mg 0.3142 (0.2618 to 0.3861), 480 mg 0.3445 (0.2883 to 0.4212).	
Sheng, 2021 ⁵⁴	- Group 1: Nivolumab 3 mg/kg IV q.2.w.; monotherapy - Group 2: Nivolumab 240 mg/body IV q.2.w. (flat dose); monotherapy - Group 3: Nivolumab 10mg/kg IV q.2.w.; monotherapy	Safety end points - All-cause adverse events (AEs): any grade, grade 3/4, and grade 5 - All-cause serious adverse events (SAEs): any grade and grade 3/4 - Adverse events leading to discontinuation (AEs-DC): any grade and grade 3/4 Efficacy end point - Investigator-assessed objective response rate (ORR) in NSCLC - Compared across Chinese and global populations	Arm 1 (3 mg/kg q.2.w.) Chinese (CheckMate 077; n = 15): AEs any grade 15/15 (100.0%); grade 3/4 1/15 (6.7%); grade 5 4/15 (26.7%). SAEs any grade 5/15 (33.3%); grade 3/4 0/15 (0%). AEs-DC any grade 2/15 (13.3%); grade 3/4 0/15 (0%) Chinese 2L NSCLC (CheckMate 078; efficacy analysis [ORR] n = 143; safety analysis n = 241): ORR: 22.2% (responders, n: 22) for squamous and 15.4% (responders, n: 22) for nonsquamous NSCLC AEs any grade 236/241 (97.9%);	NR

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
		Based on nivolumab 3 mg/kg every 2 weeks in the referenced trials	grade 3/4 104/241 (43.2%); grade 5 10/241 (4.1%). SAEs any grade 88/241 (36.5%); grade 3/4 50/241 (20.7%). AEs-DC any grade 40/241 (16.6%); grade 3/4 29/241 (12.0%) Global Patients: ORR: 20.0% for squamous (responders, n: 27) and 19.2% for nonsquamous NSCLC (responders, n: 56), from CheckMate 017 and CheckMate 057 respectively Arm 2 (240 mg q.2.w.) Chinese (CheckMate 077; n = 20): AEs any grade 18/20 (90.0%); grade 3/4 2/20 (10.0%); grade 5 0/20 (0%). SAEs any grade 6/20 (30.0%); grade 3/4 2/20 (10.0%). AEs-DC any grade 2/20 (10.0%); grade 3/4 1/20 (5.0%) Arm 3 (10 mg/kg q.2.w.) Global (safety analysis n = 131): AEs any grade 131/131 (100.0%); grade 3/4 66/131 (50.4%); grade 5 18/131 (13.7%). SAEs any grade 73/131 (55.7%); grade 3/4 49/131 (37.4%). AEs-DC any grade 28/131 (21.4%); grade 3/4 17/131 (13.0%)	
Bei, 2020 ⁵⁷	- Group 1: Nivolumab 3 mg/kg IV q.2.w. - Group 2: Nivolumab 240 mg/body IV q.2.w. (flat dose)	Safety end points analyzed (no specific time point stated): AE leading to discontinuation or death (AE-DC/D) Grade ≥ 3 AE (AE grade 3+) Immune-mediated AE grade ≥ 2 (AE-IM grade 2+) Efficacy end points analyzed:	Arm 1 (3 mg/kg) OS (predicted mean survival probability, 95% CI) - Melanoma: 1y 0.67 (0.63, 0.77); 2y 0.47 (0.42, 0.60) - SQ NSCLC: 1y 0.56 (0.50, 0.65); 2y 0.36 (0.30, 0.45) - NSQ NSCLC: 1y 0.62 (0.57,	Safety: “no change or a negligible increase ($\leq 2\%$, not statistically significant) in the proportion of patients who may have an AE-DC/D, AE grade 3+ or AE-IM Grade 2 + for all tumour types in 240 mg compared to 3 mg/kg q.2.w.” Efficacy: “The mean OS for both

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
		OS: 1-year and 2-year predicted mean survival probability ORR: predicted and compared between doses	0.67); 2y 0.36 (0.31, 0.41) • RCC: 1y 0.76 (0.75, 0.78); 2y 0.53 (0.50, 0.55) Predicted ORR • Melanoma: 0.35 • SQ NSCLC: 0.26 • NSQ NSCLC: 0.22 Predicted proportion of AE-DC/D • Melanoma: 0.29 • SQ NSCLC: 0.35 • NSQ NSCLC: 0.34 • RCC: 0.24 • SCCHN: 0.32 • cHL: 0.1 Predicted proportion of Grade ≥ 3 AE • Melanoma: 0.56 • SQ NSCLC: 0.57 • NSQ NSCLC: 0.52 • RCC: 0.55 • SCCHN: 0.55 • cHL: 0.32 Predicted proportion of Grade > 2 AE-IM • Melanoma: 0.27 • SQ NSCLC: 0.24 • NSQ NSCLC: 0.24 • RCC: 0.39 • SCCHN: 0.17 • cHL: 0.29 Arm 2 (240 mg flat q.2.w.) OS (predicted mean survival	regimens was similar at both time points for all other tumour types. “For predicted ORR, no differences were observed between doses within each tumor type assessed.”

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			probability, 95% CI): • Melanoma: 1y 0.62 (0.57, 0.75); 2y 0.42 (0.34, 0.57) • SQ NSCLC: 1y 0.57 (0.52, 0.66); 2y 0.38 (0.33, 0.48) • NSQ NSCLC: 1y 0.62 (0.57, 0.68); 2y 0.36 (0.32, 0.41) • RCC: 1y 0.76 (0.75, 0.78); 2y 0.53 (0.51, 0.55) Predicted ORR • Melanoma: 0.35 • SQ NSCLC: 0.29 • NSQ NSCLC: 0.22 Predicted proportion of AE-DC/D • Melanoma: 0.31 • SQ NSCLC: 0.37 • NSQ NSCLC: 0.35 • RCC: 0.25 • SCCHN: 0.33 • cHL: 0.11 Predicted proportion of Grade ≥ 3 AE • Melanoma: 0.55 • SQ NSCLC: 0.56 • NSQ NSCLC: 0.51 • RCC: 0.54 • SCCHN: 0.55 • cHL: 0.31 Predicted proportion of Grade > 2 AE-IM • Melanoma: 0.29 • SQ NSCLC: 0.25	

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			• NSQ NSCLC: 0.26 • RCC: 0.41 • SCCHN: 0.18 • cHL: 0.31	
Lala, 2020 ⁵⁸	Pembrolizumab Fixed: • 400 mg q.6.w. • 200 mg q.3.w. Weight-based: • 2 mg/kg q.3.w. • 10 mg/kg q.2.w. (plus 10 mg/kg q.3.w. in pooled safety) • Switch scenario: 200 mg q.3.w. up to steady state → switch to 400 mg q.6.w.	Safety end points (pooled clinical data; time point not reported) • Any adverse events (AEs): n/N (%) • Grade III–V adverse events: n/N (%) • Serious adverse events (SAEs): n/N (%) • Discontinuation due to adverse events: n/N (%) • Death due to adverse events: n/N (%) • Selected immune-related adverse events (irAEs) and infusion-related reactions: n/N (%)	• Arm 1 (400 mg q.6.w.; simulated): Safety events NR (not reported as n/N). • Arm 2 (200 mg q.3.w.; simulated): Safety events NR (not reported as n/N). • Arm 3 (2 mg/kg q.3.w.; simulated + pooled safety; N = 740): Any AE 148/740 = 20.0%; Grade III–V AEs 37/740 = 5.0%; SAEs 41/740 = 5.5%; Discontinued due to AE 15/740 = 2.0%; Died due to AE 2/740 = 0.3%; Hypothyroidism 60/740 = 8.1%; Hyperthyroidism 21/740 = 2.8%; Pneumonitis 25/740 = 3.4%; IRR 10/740 = 1.4%; Colitis 12/740 = 1.6%. Additional arms: • Arm 4 (10 mg/kg q.2.w.; simulated + pooled safety; N = 660): Any AE 142/660 = 21.5%; Grade III–V AEs 35/660 = 5.3%; SAEs 33/660 = 5.0%; Discontinued due to AE 20/660 = 3.0%; Died due to AE 0/660 = 0%; Hypothyroidism 69/660 = 10.5%; Hyperthyroidism 28/660 = 4.2%; Pneumonitis 15/660 = 2.3%; IRR 23/660 = 3.5%; Colitis 12/660 = 1.8%.	NR

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			Arm 5 (10 mg/kg q.3.w.; pooled safety only; N = 1,399): Any AE 304/1399 = 21.7%; Grade III–V AEs 80/1399 = 5.7%; SAEs 83/1399 = 5.9%; Discontinued due to AE 47/1399 = 3.4%; Died due to AE 2/1399 = 0.1%; Hypothyroidism 118/1399 = 7.7%; Hyperthyroidism 47/1399 = 3.4%; Pneumonitis 54/1399 = 3.9%; IRR 38/1399 = 1.7%; Colitis 25/1399 = 1.8%.	
Novakovic, 2020⁵²	- Group 1: Avelumab 10 mg/kg IV q.2.w. - Group 2: Avelumab 800 mg/body IV q.2.w. (flat dose)	Safety end points (modelled, any grade): - Probability of immune-related adverse events (irAEs) using AUC_{0-336h} as the exposure metric - Probability of IRRs using C_{max} as the exposure metric - Based on the first-cycle population PK model - Reported overall and by body weight quartiles Efficacy end point (modelled): - Probability of objective response - Evaluated in mMCC and advanced/metastatic UC - Based on AUC_{0-336h} from the first-cycle model	Group 1 (weight-based): - irAE (any grade): mean probability 11.4% - irAE (any grade): simulated probability 11.9% - IRR (any grade): model probability with weight-based dosing, 24.7% Group 2 (flat): - irAE (any grade): mean probability 12.6% - irAE (any grade): observed rate across included clinical trials was similar to simulated rate for weight-based (i.e., 11.9%) - IRR (any grade): simulated probability using C_{max} strongly concordant/similar to weight-based dosing (no separate flat % given) - OR probability (weight-based): 31.8% (mMCC); 17.3% (UC)	NR

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
Zhao, 2020 ⁵⁵	- Arm 1: Nivolumab 3 mg/kg IV q.2.w. (weight-based) - Arm 2: Nivolumab 240 mg IV q.2.w. (fixed) - Arm 3: Nivolumab 480 mg IV q.4.w. (fixed, extended-interval)	Safety outcomes (modelled/predicted): Time-to-event modelled outcome: - Predicted cumulative probability at Year 2 of grade ≥ 2 IMAEs, using C_{avg} day as the exposure metric C_{avg} day = time-varying average concentration over each day a patient remains at risk for an event Other modelled safety outcomes: Grade ≥ 2 TRAEs TRAEs leading to discontinuation or death Logistic model–predicted safety outcomes: - Proportion with grade ≥ 2 IMAEs - Proportion with grade ≥ 3 adverse events (AEs) - Proportion with AEs leading to discontinuation or death Efficacy outcomes (modelled/predicted): ORR, predicted using exposure metrics such as C_{avgd28} and $C_{min-d28}$ OS, predicted as HR vs. control in referenced pivotal study contexts, using exposure metrics such as C_{avgd28} and $C_{min-d28}$	Arm 1 (3 mg/kg q.2.w.): $\geq$ Grade 2 IMAEs (using C_{avg} day as exposure), - Melanoma: 0.47 - SQ NSCLC: 0.46 - NSQ NSCLC: 0.47 - RCC: 0.54 - SCCHN: 0.36 - UC: 0.58 - cHL: 0.60 $\geq$ Grade 2 TRAEs (using C_{avg} day as exposure), - Melanoma: 0.65 - SQ NSCLC: 0.72 - NSQ NSCLC: 0.68 - RCC: 0.69 - SCCHN: 0.65 - UC: 0.73 - cHL: 0.78 TRAEs-DC/C (using C_{avg} day as exposure), - Melanoma: 0.10 - SQ NSCLC: 0.21 - NSQ NSCLC: 0.21 - RCC: 0.16 - SCCHN: 0.16 - UC: 0.15 - cHL: 0.14 OS (using C_{avgd28} as exposure) - Melanoma: 0.36 - RCC: 0.73 - SQ NSCLC: 0.59	“There were negligible differences between the three regimens in the probabilities of experiencing an AE.” “The predicted probability of experiencing grade 2 IMAEs, grade 2 TRAEs, and TRAEs-DC/D was similar with nivolumab 480mg q.4.w. compared with 3mg/kg q.2.w.”

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			• NSQ NSCLC: 0.75 ORR (using C_{avgd28} as exposure) • Melanoma: 0.43 • RCC: 0.26 • SQ NSCLC: 0.19 • NSQ NSCLC: 0.20 Arm 2 (240 mg q.2.w.): ≥ Grade 2 IMAEs (using C_{avg} day as exposure), • Melanoma: 0.47 • SQ NSCLC: 0.46 • NSQ NSCLC: 0.47 • RCC: 0.54 • SCCHN: 0.36 • UC: 0.58 • cHL: 0.60 ≥ Grade 2 TRAEs (using C_{avg} day as exposure), • Melanoma: 0.65 • SQ NSCLC: 0.72 • NSQ NSCLC: 0.68 • RCC: 0.69 • SCCHN: 0.65 • UC: 0.73 • cHL: 0.78 TRAEs-DC/C (using C_{avg} day as exposure), • Melanoma: 0.10 • SQ NSCLC: 0.21 • NSQ NSCLC: 0.21 • RCC: 0.16 • SCCHN: 0.15	

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			• UC: 0.15 • cHL: 0.14 OS (using C_{avgd28} as exposure) • Melanoma: 0.37 • RCC: 0.73 • SQ NSCLC: 0.58 • NSQ NSCLC: 0.74 ORR (using C_{avgd28} as exposure) • Melanoma: 0.43 • RCC: 0.26 • SQ NSCLC: 0.19 • NSQ NSCLC: 0.20 Arm 3 (480 mg q.4.w.): ≥ Grade 2 IMAEs (using C_{avg} day as exposure), • Melanoma: 0.47 • SQ NSCLC: 0.46 • NSQ NSCLC: 0.47 • RCC: 0.54 • SCCHN: 0.36 • UC: 0.58 • cHL: 0.60 ≥ Grade 2 TRAEs (using C_{avg} day as exposure), • Melanoma: 0.65 • SQ NSCLC: 0.73 • NSQ NSCLC: 0.68 • RCC: 0.69 • SCCHN: 0.65 • UC: 0.73 • cHL: 0.78	

Author and publication year	Intervention characteristics	Results parameters (measurement time)	Results per arm	Fixed vs. weight-based dosing effect (95% CI) [P value]
			TRAEs-DC/C (using C_{avg} day as exposure), • Melanoma: 0.10 • SQ NSCLC: 0.21 • NSQ NSCLC: 0.21 • RCC: 0.16 • SCCHN: 0.15 • UC: 0.15 • cHL: 0.14 OS (using C_{avgd28} as exposure) • Melanoma: 0.40 • RCC: 0.73 • SQ NSCLC: 0.56 • NSQ NSCLC: 0.74 ORR (using C_{avgd28} as exposure) • Melanoma: 0.42 • RCC: 0.25 • SQ NSCLC: 0.21 • NSQ NSCLC: 0.21	

AE = adverse event; AE-DC/D = adverse event leading to discontinuation or death; AESI = adverse event of special interest; all-cause AE = adverse event of any cause; alloHCT = allogeneic hematopoietic cell transplant; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC = area under the concentration–time curve; AUC_{0-336h} = area under the concentration–time curve from 0 to 336 hours; $AUC_{6wk,ss}$ = area under the concentration–time curve over 6 weeks at steady state; AUC_{ss} = area under the concentration–time curve at steady state; BICR = blinded independent central review; BMI = body mass index; BOR = best overall response; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; C_{max} = maximum drug concentration; C_{max1} = maximum concentration after the first dose or first cycle; C_{maxss} = maximum concentration at steady state; C_{min} = minimum (trough) concentration; C_{min1} = trough concentration after the first dose or first cycle (study-defined); $C_{min-d28}$ = minimum concentration over days 1 to 28; C_{minss} = minimum (trough) concentration at steady state; C_{trough} = trough concentration; $C_{trough1}$ = trough concentration at steady state; C_{avg} = average concentration; C_{avgd28} = average concentration through days 1 to 28; C_{avgss} = average concentration at steady state; CV = coefficient of variation; DCR = disease control rate; DL = dose level; DLT = dose-limiting toxicity; DOR = duration of response; dMMR = deficient mismatch repair; ED = emergency department; ER = exposure-response; FDT = fixed-dose therapy; FD = fixed dose; FU = follow-up; G = grade; $G \geq 3$ = grade 3 or higher; HCC = hepatocellular carcinoma; HR = hazard ratio; HR-QoL = health-related quality of life; ICI = immune checkpoint inhibitor; IL = interleukin; IMAE = immune-mediated adverse event; irAE = immune-related adverse event; irPR = immune-related partial response; irRECIST = immune Response Evaluation Criteria in Solid Tumours; IRR = infusion-related reaction; IPTW = inverse probability of treatment weighting; IQR = interquartile range; LA = locally advanced; mCRC = metastatic colorectal cancer; mMCC = metastatic Merkel cell carcinoma; MSS = microsatellite stable; NA = not applicable; NMA = network meta-analysis; NR = not reported; NSCLC = non–small cell lung cancer; NSQ NSCLC = nonsquamous non–small cell lung cancer; OR = odds ratio; ORR = objective response rate; OS = overall survival; PAEs = pulmonary adverse events; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; q.2.w. = every 2 weeks; q.3.w. = every 3 weeks; q.4.w. = every 4 weeks; q.6.w. = every 6 weeks; q.12.w. = every 12 weeks; rHuPH20 = recombinant human hyaluronidase PH20; RCC = renal cell carcinoma; RCT = randomized controlled trial; RD = risk difference; RECIST = Response Evaluation Criteria in Solid Tumours; RR = risk ratio; SAE = serious adverse event; SC = subcutaneous; SCLC = small cell lung cancer; SD = stable disease; SOC = standard of care; SQ NSCLC = squamous non–small cell lung cancer; ss = steady state; TEAE = treatment-emergent adverse event; Tr-PAEs = treatment-related pulmonary adverse events; TRAE = treatment-related adverse event; TTR = time to response; UC = urothelial carcinoma; UTD = unable to determine; vs. = versus; WAD = weight-adjusted dosing; WAT = weight-adjusted therapy (study-defined); WBD = weight-based dosing; WCD = weight-capped dosing.

Appendix 4: Summary of Pharmacodynamic and Pharmacokinetic Outcomes

Please note that this appendix has not been copy-edited.

Table 14: Summary of Pharmacodynamic and Pharmacokinetic Outcomes

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
RCTs			
Albiges, 2025²⁸	- SC: nivolumab 1,200 mg + rHuPH20 20,000 units q.4.w. - IV: nivolumab 3 mg/kg q.2.w.	NR	Nivolumab + rHuPH20 SC (n = 248) - Geometric mean of C_{avgd28}, ug/mL: 77.343 (90% CI, 74.555 to 80.297) - Geometric mean of C_{minss}, ug/mL: 122.227 (90% CI, 114.552 to 130.416) - Geometric mean of C_{max1}, ug/mL (CV%): 108 (33) - Geometric mean of $C_{min-d28}$, ug/mL (CV%): 50.8 (44) - Geometric mean of C_{maxss}, ug/mL (CV%): 230 (39) - Geometric mean of C_{avgss}, ug/mL (CV%): 182 (44) - Geometric mean of C_{trough} at week 17, ug/mL (CV%): 123 (46) Nivolumab IV (n = 247) - Geometric mean of C_{avgd28}, ug/mL: 36.875 (90% CI, 35.565 to 38.235) - Geometric mean of C_{minss}, ug/mL: 68.901 (90% CI, 64.676 to 73.402) - Geometric mean of C_{max1}, ug/mL (CV%): 91 (35) - Geometric mean of $C_{min-d28}$, ug/mL (CV%): 31.9 (30) - Geometric mean of C_{maxss}, ug/mL (CV%): 160 (28) - Geometric mean of C_{avgss}, ug/mL (CV%): 92.5 (34) - Geometric mean of C_{trough} at week 17, ug/mL (CV%): 66.3 (33) - Geometric mean ratio (90% CI) of C_{avgd28} between both arms: 2.098 (2.001 to 2.200) Geometric mean ratio (90% CI) of C_{minss} between both arms: 1.774 (1.633 to 1.927) - Nivolumab, SC - n = 56 at day 29 Median % PD-1receptor occupancy on circulating CD3+ T cells

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
			(IQR) at day 29 using the dataset with at least 8 months' follow-up: 97.0 (89.6, 104.2) • Nivolumab, IV - n = 58 at day 29 Median % PD-1receptor occupancy on circulating CD3+ T cells (IQR) at day 29 using the dataset with at least 8 months' follow-up: 94.7 (87.3, 102.4) • Nivolumab, SC - n = 55 at day 29 Median % PD-1receptor occupancy on circulating CD4+ T cells (IQR) at day 29 using the dataset with at least 8 months' follow-up: 98.3 (85.6, 106.1) • Nivolumab, IV - n = 60 at day 29 Median % PD-1receptor occupancy on circulating CD4+ T cells (IQR) at day 29 using the dataset with at least 8 months' follow-up: 93.1 (84.1, 100.1) • Nivolumab, SC - n = 56 at day 29 Median % PD-1 receptor occupancy on circulating CD8+ T cells (IQR) at day 29 using the dataset with at least 8 months' follow-up: 96.8 (84.5, 103.7) • Nivolumab, IV - n = 56 at day 29 Median % PD-1receptor occupancy on circulating CD8+ T cells (IQR) at day 29 using the dataset with at least 8 months' follow-up: 96.3 (88.4, 102.9)
Herrera, 2021 ²⁹	Avelumab IV (1-hour infusion). Arms: • 70 mg q.2.w.; • 350 mg q.2.w.; • 500 mg q.2.w.; • 500 mg q.3.w.; • 10 mg/kg q.2.w. • Premedication mandatory: antihistamine + acetaminophen 30 to 60 minute prior (alternatives per local standards allowed).	Terminal half-life reported in days (convert to hours): Cycle 1 Day 1 (geo mean, CV%) • 70 mg q.2.w.: 3.49 days (28%) = 83.8 hours; • 350 mg q.2.w.: 3.25 days (44%) = 78.0 hours; • 500 mg q.2.w.: 4.38 days (39%) = 105.1 hours; • 500 mg q.3.w.: 4.04 days (23%) = 97.0 hours; • 10 mg/kg q.2.w.: 3.88 days (38%) = 93.1 hours.	Cycle 1 Day 1: AUC_{tau} (h × mcg/mL), geo mean (CV%) • 70 mg: 1933 (64); • 350 mg: 8,450 (28); • 500 mg q.2.w.: 15,436 (38); • 500 mg q.3.w.: 15,392 (27); • 10 mg/kg: 23,780 (54). C_{max} (mcg/mL), geo mean (CV%) • 70 mg: 24.0 (35); • 350 mg: 68.4 (33); • 500 mg q.2.w.: 143 (24); • 500 mg q.3.w.: 126 (15);

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
		Cycle 2 Day 1 (geo mean, CV%) 70 mg q.2.w.: 2.92 days (13%) = 70.1 hours; 350 mg q.2.w.: 3.43 days (43%) = 82.3 hours; 500 mg q.2.w.: 4.59 days (36%) = 110.2 hours; 500 mg q.3.w.: 4.62 days (17%) = 110.9 hours; 10 mg/kg q.2.w.: 4.23 days (37%) = 101.5 hours.	10 mg/kg: 271 (16). Cycle 2 Day 1: AUC_{tau} (h × mcg/mL), geo mean (CV%) 70 mg: 2,067 (6); 350 mg: 8,789 (39); 500 mg q.2.w.: 21,053 (47); 500 mg q.3.w.: 19,173 (23); 10 mg/kg: 27,196 (59). C_{max} (mcg/mL), geo mean (CV%) 70 mg: 26.1 (21); 350 mg: 78.7 (19); 500 mg q.2.w.: 195 (46); 500 mg q.3.w.: 135 (8); 10 mg/kg: 273 (22); C_{trough} (mcg/mL), geo mean (CV%) at Cycle 2 Day 1 70 mg: 1.71 (163); 350 mg: 4.03 (110); 500 mg q.2.w.: 12.1 (93); 500 mg q.3.w.: 2.54 (125); 10 mg/kg: 14.4 (170); - Median target occupancy across all the treatment arms was > 90% throughout the dosing interval.
Nonrandomized studies			
Cohen, 2024⁶³	- Pembrolizumab Fixed dose 400 q6 for the entire cohort - Pembrolizumab model prediction of 2 mg/kg q3, 200 mg q3, 10 mg/kg q3)	NR	- The geometric mean of the observed C_{max} at 400 mg every 6 weeks was approximately 42% lower at cycle 1 and approximately 65% lower at steady state than the geometric mean of the observed C_{max} at 10 mg/kg every 2 week at cycle 1 and steady state, respectively. - The geometric mean of the observed C_{trough} at 400 mg every 6 weeks was approximately 17% lower at cycle 1 and approximately 22% lower at steady state than the geometric mean of the observed C_{trough} at 200 mg every 3 weeks and

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
			was approximately 12% higher at cycle 1 and approximately 4% higher at steady state than the geometric mean of the observed C_{trough} at 2 mg/kg every 3 weeks.
Rischin, 2024 ³⁹	- Weight-based: cemiplimab 3 mg/kg IV q.2.w. (Groups 1 and 2) - Fixed: cemiplimab 350 mg IV q.3.w. (Group 3) in patients with advanced CSCC. PK outcomes were reported as observed steady-state concentrations at weeks 17 to 19.	NR	Observed steady-state C_{trough} or C_{min}: Groups 1 and 2 (3 mg/kg q.2.w.): 68.4 mg/L mean (SD 26.1), median 72.0 (IQR 49.9 to 80.8), n = 96; Group 3 (350 mg q.3.w.): 62.7 mg/L mean (SD 28.3), median 65.3 (IQR 44.3 to 77.3), n = 34. Observed steady-state C_{max}: Groups 1 and 2: 150 mg/L mean (SD 79.0), median 141 (IQR 113 to 162), n = 96; Group 3: 151 mg/L mean (SD 46.2), median 165 (IQR 129 to 181), n = 33. AUC: not directly reported for this fixed vs. weight-based comparison.
Fujiwara, 2022 ⁴²	- Cohort 1 (weight-based): tremelimumab 10 mg/kg q.4.w. × 6 then q.12.w. × 3 + durvalumab 15 mg/kg q.4.w. × 13. - Cohort 2 (weight-based): tremelimumab 1 mg/kg q.4.w. × 4 + durvalumab 20 mg/kg q.4.w. × 4 then 10 mg/kg q.2.w. up to 22 doses. - Cohort 3 (fixed-dose): tremelimumab 75 mg q.4.w. × 4 + durvalumab 1,500 mg q.4.w. × 13.	NR	Reported as geometric mean (GMean) with geometric CV% (plus min/median/max) in the PK table. Units: AUC_{0-t} in day × mcg/mL; concentrations in mcg/mL; times in days. Combination multiple dosing: tremelimumab PK - Single-dose (Cohort 1: TRE 10 mg/kg + DUR 15 mg/kg): AUC_{0-t} 2010 (CV 24.5); C_{max} 187 (CV 24.5); C_{min} 28.8 (CV 28.1); T_{max} 0.046 days (CV 4.5). - Single-dose (Cohort 2: TRE 1 mg/kg + DUR 20 mg/kg): AUC_{0-t} 153 (CV 26.2); C_{max} 20.5 (CV 12.9); C_{min} 2.71 (CV 39.5); T_{max} 0.046 days (CV 3.6). - Single-dose (Cohort 3: TRE 75 mg + DUR 1,500 mg): AUC_{0-t} 239 (CV 15.9); C_{max} 22.9 (CV 14.2); C_{min} 3.35 (CV 40.7); T_{max} 0.044 days (CV 3.9). - Multiple-dose (Cohort 2: TRE 1 mg/kg + DUR 20 mg/kg): RAC(C_{max}) 1.18 (CV 12.8); RAC(C_{min}) 1.44 (CV 13.5); C_{ss} max 24.8 (CV 20.0); C_{ss} min 4.14 (CV 45.5); t_{ss} max 0.045 days (CV 2.8). - Multiple-dose (Cohort 3: TRE 75 mg + DUR 1,500 mg): RAC(C_{max}) 1.39 (CV 12.1); RAC(C_{min}) 2.03 (CV 41.5); C_{ss} max 36.4 (CV 12.9); C_{ss} min 9.20 (CV 12.6); t_{ss} max 0.045 days (4.7). Combination multiple dosing: Durvalumab PK (Part 2 combination):

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
			• Single-dose (Cohort 1: with TRE 10 mg/kg + DUR 15 mg/kg): AUC_{0-t} 2,980 (CV 26.2); C_{max} 278 (CV 24.1); C_{min} 40.9 (CV 45.4); T_{max} 0.12 days (85-very high CV). • Single-dose (Cohort 2: with TRE 1 mg/kg + DUR 20 mg/kg): AUC_{0-t} 3,390 (CV 22.5); C_{max} 353 (CV 16.5); C_{min} 55.4 (CV 33.6); T_{max} 0.055 days (CV 11). • Single-dose (Cohort 3: with TRE 75 mg + DUR 1,500 mg): AUC_{0-t} 4,680 (CV 15.7); C_{max} 439 (CV 15.8); C_{min} 77.7 (CV 33.6); T_{max} 0.052 days (CV 21). • Multiple-dose (Cohort 2: with TRE 1mg/kg + DUR 20 mg/kg): $RAC(C_{max})$ 1.11 (CV 13.8); $RAC(C_{min})$ 1.49 (CV 31.2); $C_{ss\ max}$ 404 (CV 14.1); $C_{ss\ min}$ 94.6 (CV 63.9); $t_{ss\ max}$ 0.049 days (CV 15). • Multiple-dose (Cohort 3: with TRE 75 mg + DUR 1,500 mg): $RAC(C_{max})$ 2.01 (CV 0.932); $RAC(C_{min})$ 1.91 (CV 26.1); $C_{ss\ max}$ 847 (CV 0.726); $C_{ss\ min}$ 200 (CV 7.55); $t_{ss\ max}$ 0.043 days (CV 3.3). (Where shown in the PK table, N differs by parameter; these values are the reported GMeans.)
Patnaik, 2022 ⁴⁶	Part 1 — Weight-Based Dose Escalation Arms • Arm 1: Dostarlimab 1 mg/kg q.2.w. • Arm 2: Dostarlimab 3 mg/kg q.2.w. • Arm 3: Dostarlimab 10 mg/kg q.2.w. Part 2A — Fixed-Dose Arms • Arm 4: Dostarlimab 500 mg q.3.w. • Arm 5: Dostarlimab 1,000 mg q.6.w.	Part 1 - weight-based dosing cohort (n = 21) • 1 mg/kg (DLT-evaluable, n = 3): $t_{1/2}$: 8.2 to 14.2 days • 1 mg/kg (PK/PDy cohort, n = 3): $t_{1/2}$: 14.5 (67.1) days • 3 mg/kg (n = 3): $t_{1/2}$: 19.1 (23.8) days • 10 mg/kg (DLT-evaluable, n = 6): $t_{1/2}$: 10.2 (35.5) days • 10 mg/kg (PK/PDy, n = 6): $t_{1/2}$: 20.5 (18.2) days Part 2A- fixed-dose regimen cohort (n = 13) • 500 mg q.3.w. (n = 6): $t_{1/2}$: 14.5 (12.3) days • 1,000 mg q.6.w. (n = 7): $t_{1/2}$: 19.6 (21.9) days	Part 1 - weight-based dosing cohort (n = 21) Cycle 1 PK parameters, Geometric mean (CV %) • 1 mg/kg (DLT-evaluable, n = 3) $AUC_{0-\infty}$: 4,440 to 9,570 mcg × h/mL; AUC_{0-tau}: 3,417 (31.7) mcg × h/mL; C_{max}: 21.78 (25.6) mcg/mL; T_{max}: 2.92 (1.52 to 2.95) h; C_{trough}: 6.382 (35.9) mcg/mL; CL: 0.336 to 0.367 L/day; V_z: 3.97 to 7.50 L; V_{ss}: 4.12 to 7.29 L • 1 mg/kg (PK/PDy cohort, n = 3) $AUC_{0-\infty}$: 5,872 (93.3) mcg × h/mL; AUC_{0-tau}: 4,219 (63.8) mcg × h/mL; C_{max}: 20.43 (17.7) mcg/mL; T_{max} (median [range]): 1.50 (0.55 to 1.50) h; C_{trough}: 2.622 (148.4) mcg/mL; CL: 0.326 (64.8) L/day; V_z: 6.84 (7.6) L; V_{ss}: 6.73 (17.8) L • 3 mg/kg (n = 3) $AUC_{0-\infty}$: 26,630 (9.4) mcg × h/mL; AUC_{0-tau}: 10,790 (9.7) mcg × h/mL; C_{max}: 66.17 (9.6) mcg/mL; T_{max} (median [range]): 1.52 (1.50 to 2.95) h; C_{trough}: 23.70 (8.9) mcg/mL; CL: 0.189 (33.5) L/day; V_z: 5.20 (33.5) L; V_{ss}: 5.11 (32.1) L

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
			10 mg/kg (DLT-evaluable, n = 6) $AUC_{0-\infty}$: 59,830 (26.7) mcg × h/mL; $AUC_{0-\tau}$: 36,480 (24.4) mcg × h/mL; C_{max}: 228.4 (22.2) mcg/mL; T_{max} (median [range]): 1.52 (1.50 to 3.07) h; C_{trough}: 60.63 (34.7) mcg/mL; CL: 0.302 (22.3) L/day; V_z: 4.43 (18.3) L; V_{ss}: 4.33 (19.8) L 10 mg/kg (PK/PDy, n = 6) $AUC_{0-\infty}$: 101,900 (35.8) mcg × h/mL; $AUC_{0-\tau}$: 63,670 (28.2) mcg × h/mL; C_{max}: 251.1 (19.2) mcg/mL; T_{max} (median [range]): 1.50 (1.43 to 3.12) h; C_{trough}: 53.15 (35.0) mcg/mL; CL: 0.160 (13.6) L/day; V_z: 4.73 (14.2) L; V_{ss}: 4.57 (14.0) L Part 2A- fixed-dose regimen cohort (n = 13) 500 mg q.3.w. (n = 6) $AUC_{0-\infty}$: 55,510 (24.2) mcg × h/mL; $AUC_{0-\tau}$: 35,730 (20.2) mcg × h/mL; C_{max}: 171.1 (20.0) mcg/mL; T_{max} (median [range]): 0.96 (0.50 to 3.02) h; C_{trough}: 39.17 (26.7) mcg/mL; CL: 0.216 (24.2) L/day; V_z: 4.51 (20.5) L; V_{ss}: 4.38 (18.0) L 1,000 mg q.6.w. (n = 7) $AUC_{0-\infty}$: 113,500 (34.4) mcg × h/mL; $AUC_{0-\tau}$: 95,820 (29.3) mcg × h/mL; C_{max}: 309.4 (30.8) mcg/mL; T_{max} (median [range]): 1.52 (0.52 to 3.00) h; C_{trough}: 40.20 (51.1) mcg/mL; CL: 0.212 (34.4) L/day; V_z: 5.97 (31.9) L; V_{ss}: 5.77 (29.8) L Part 1 - weight-based dosing cohort (n = 21) Receptor Occupancy (RO): Full PD-1 receptor occupancy was achieved across all dose levels. Mean minimum concentration for full RO: 2.44 mcg/mL 1 patient (1 mg/kg) did not achieve full RO by Day 22 (1.51 mcg/mL), partly due to antidrug antibodies Part 2A- fixed dose regimen cohort (n = 13) Receptor Occupancy (RO): Both fixed-dose regimens achieved full PD-1 receptor occupancy over the dosing cycle. IL-2 functional assays confirmed full functional RO.

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
Juergens, 2020 ⁴⁸	Durvalumab: 15 mg/kg q.3.w. (DL0 monotherapy; also in DL1 combo), 1,125 mg q.3.w. (DL2a, DL3), 1,500 mg q.3.w. (DL2b, DL4). Tremelimumab: 1 mg/kg q.3.w. (DL1, DL2a), 3 mg/kg q.3.w. (DL2b), 56 mg q.3.w. (DL3), 75 mg q.3.w. (DL4).	NR	Units: mcg/mL Durvalumab (mean [SD]) — C_{max}/C_{trough}: - DL0 (15 mg/kg, monotherapy): 320 (104) / 84.5 (23.9) - DL1 (15 mg/kg): 351 (144) / 59.7 (35.0) - DL2a (1,125 mg): 378 (164) / 56.7 (20.6) - DL2b (1,500 mg): 429 (191) / 54.6 (23.9) - DL3 (1,125 mg): 474 (205) / 64.3 (34.6) - DL4 (1,500 mg): 381 (130) / 78.5 (35.9) Tremelimumab (mean [SD]) — C_{max}/C_{trough}: - DL1 (1 mg/kg): 24.6 (5.35) / 4.66 (3.30) - DL2a (1 mg/kg): 25.6 (4.75) / 4.34 (1.85) - DL2b (3 mg/kg): 73.2 (22.5) / 13.5 (5.51) - DL3 (56 mg): 18.56 (7.76) / 3.65 (1.48) - DL4 (75 mg): 26.6 (8.53) / 5.55 (2.53) AUC: NR
Kato, 2020 ⁴⁹	- Group 1: Nivolumab weight-based dosing of 3 mg/kg q.2.w. - Group 2: Nivolumab flat dosing of 240 mg q.2.w.	NR	Group 1: Mean (SD) trough concentrations (C_{min}) before cycles 2 to 5 of nivolumab C_{min1}: 14.2 (1.9) C_{min2}: 21.5 (2.4) C_{min3}: 33.0 (4.6) C_{min4}: 31.4 (4.1) Group 2: Mean (SD) trough concentrations (C_{min}) before cycles 2 to 5 of nivolumab C_{min1}: 27.5 (2.4) C_{min2}: 43.3 (4.2) C_{min3}: 57.9 (7.0) C_{min4}: 58.6 (8.8) Group 1 vs. 2: Mean (SD) trough concentrations (C_{min}) before cycles 2 to 5 of nivolumab C_{min1}: P value < 0.01 C_{min2}: P value < 0.01

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
			C_{min} 3: P value = 0.01 C_{min} 4: P value = 0.02
PK/PD modelling or simulation studies			
Lala, 2025 ⁶⁴	Pembrolizumab IV (simulated regimens): • 4 mg/kg q.6.w. • 400 mg q.6.w. • 200 mg q.3.w. • 2 mg/kg q.3.w.	NR	C trough Group 1: 200 mg q.3.w. • < 50 kg (n = 169): Geometric mean (95% CI), ug/mL = 36.3 (33.1 to 39.9); 5th to 95th percentile = 12.8 to 82.2; 1st to 99th percentile = 6.4 to 119.3; Difference in geometric mean of 4 mg/kg q.6.w. (%): -72 • 50 to 80 kg (n = 2,109): Geometric mean (95% CI), ug/mL = 30.3 (29.6 to 31.0); 5th to 95th percentile = 11.5 to 66.6; 1st to 99th percentile = 6.8 to 85.6; Difference in geometric mean of 4 mg/kg q.6.w. (%): -58 • 80 kg (n = 1,329): Geometric mean (95% CI), ug/mL = 24.6 (23.9 to 25.3); 5th to 95th percentile = 9.9 to 50.9; 1st to 99th percentile = 5.8 to 63.3; Difference in geometric mean of 4 mg/kg q.6.w. (%): -40 • Overall (n = 3,607): Geometric mean (95% CI), ug/mL = 28.3 (27.8 to 28.8); 5th to 95th percentile = 10.7 to 63.5; 1st to 99th percentile = 6.5 to 81.9; Difference in geometric mean of 4 mg/kg q.6.w. (%): -53 Group 2: 400 mg q.6.w. • < 50 kg (n = 169): Geometric mean (95% CI), ug/mL = 22.4 (19.6 to 25.6); 5th to 95th percentile = 4.8 to 64.8; 1st to 99th percentile = 1.5 to 98.8; Difference in geometric mean of 4 mg/kg q.6.w. (%): -55 • 50 to 80 kg (n = 2,109): Geometric mean (95% CI), ug/mL = 19.1 (18.5 to 19.7); 5th to 95th percentile = 4.7 to 52.7; 1st to 99th percentile = 2.2 to 71.1; Difference in geometric mean of 4 mg/kg q.6.w. (%): -34 • 80 kg (n = 1,329): Geometric mean (95% CI), ug/mL = 15.5 (14.9 to 16.1); 5th to 95th percentile = 4.0 to 40.6; 1st to 99th percentile = 1.8 to 52.9; Difference in geometric mean of 4 mg/kg q.6.w. (%): -5

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
			• Overall (n = 3,607): Geometric mean (95% CI), ug/mL = 17.9 (17.5 to 18.3); 5th to 95th percentile = 4.5 to 50.4; 1st to 99th percentile = 2.1 to 68.5; Difference in geometric mean of 4 mg/kg q.6.w. (%): -26 • Group 3: 2 mg/kg q.3.w. • < 50 kg (n = 169): Geometric mean (95% CI), ug/mL = 16.5 (15.0 to 18.2); 5th to 95th percentile = 5.2 to 38.4; 1st to 99th percentile = 2.9 to 50.6; Difference in geometric mean of 4 mg/kg q.6.w. (%): -38 • 50 to 80 kg (n = 2,109): Geometric mean (95% CI), ug/mL = 20 (19.6 to 20.5); 5th to 95th percentile = 7.7 to 43.2; 1st to 99th percentile = 4.5 to 53.8; Difference in geometric mean of 4 mg/kg q.6.w. (%): -37 • 80 kg (n = 1,329): Geometric mean (95% CI), ug/mL = 23.3 (22.7 to 23.9); 5th to 95th percentile = 9.2 to 47.2; 1st to 99th percentile = 5.9 to 61.0; Difference in geometric mean of 4 mg/kg q.6.w. (%): -77 • Overall (n = 3,607): Geometric mean (95% CI), ug/mL = 21 (20.6 to 21.4); 5th to 95th percentile = 8.0 to 45.0; 1st to 99th percentile = 4.7 to 57.6; Difference in geometric mean of 4 mg/kg q.6.w. (%): -37 • Group 4: 4 mg/kg q.6.w. (alternative regimen) • < 50 kg (n = 169): Geometric mean (95% CI), ug/mL = 10.2 (8.9 to 11.7); 5th to 95th percentile = 1.9 to 30.8; 1st to 99th percentile = 0.7 to 42.3 • 50 to 80 kg (n = 2,109): Geometric mean (95% CI), ug/mL = 12.6 (12.2 to 13.0); 5th to 95th percentile = 3.2 to 34.5; 1st to 99th percentile = 1.5 to 44.6 • 80 kg (n = 1,329): Geometric mean (95% CI), ug/mL = 14.7 (14.2 to 15.3); 5th to 95th percentile = 3.9 to 37.5; 1st to 99th percentile = 2.0 to 50.0 • Overall (n = 3,607): Geometric mean (95% CI), ug/mL = 13.2 (12.9 to 13.5); 5th to 95th percentile = 3.4 to 35.9; 1st to 99th percentile = 1.4 to 47.7 AUC

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
			Group 1: 200 mg q.3.w. • < 50 kg (n = 169): Geometric mean (95% CI), ug/mL = 2,285 (2,149 to 2,430); 5th to 95th percentile = 1,107 to 3,979; 1st to 99th percentile = 862 to 5,433; Difference in geometric mean of 4 mg/kg q.6.w. (%): -54 • 50 to 80 kg (n = 2,109): Geometric mean (95% CI), ug/mL = 1,867 (1,838 to 1,897); 5th to 95th percentile = 976 to 3,355; 1st to 99th percentile = 719 to 3,993; Difference in geometric mean of 4 mg/kg q.6.w. (%): -34 • 80 kg (n = 1,329): Geometric mean (95% CI), ug/mL = 1,513 (1,484 to 1,541); 5th to 95th percentile = 816 to 2,541; 1st to 99th percentile = 626 to 3,004; Difference in geometric mean of 4 mg/kg q.6.w. (%): -5 • Overall (n = 3,607): Geometric mean (95% CI), ug/mL = 1,744 (1,723 to 1,766); 5th to 95th percentile = 917 to 3,204; 1st to 99th percentile = 674 to 3,961; Difference in geometric mean of 4 mg/kg q.6.w. (%): -25 Group 2: 400 mg q.6.w. • < 50 kg (n = 169): Geometric mean (95% CI), ug/mL = 2,302 (2,162 to 2,450); 5th to 95th percentile = 1,103 to 4,025; 1st to 99th percentile = 862 to 5,545; Difference in geometric mean of 4 mg/kg q.6.w. (%): -55 • 50 to 80 kg (n = 2,109): Geometric mean (95% CI), ug/mL = 1,880 (1,850 to 1,910); 5th to 95th percentile = 974 to 3,408; 1st to 99th percentile = 720 to 4,126; Difference in geometric mean of 4 mg/kg q.6.w. (%): -34 • 80 kg (n = 1,329): Geometric mean (95% CI), ug/mL = 1,523 (1,494 to 1,552); 5th to 95th percentile = 814 to 2,592; 1st to 99th percentile = 626 to 3,069; Difference in geometric mean of 4 mg/kg q.6.w. (%): -5 • Overall (n = 3,607): Geometric mean (95% CI), ug/mL = 1,756 (1,734 to 1,778); 5th to 95th percentile = 917 to 3,529; 1st to 99th percentile = 668 to 4,050; Difference in geometric mean of 4 mg/kg q.6.w. (%): -26 Group 3: 2mg/kg q.3.w.

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
			• < 50 kg (n = 169): Geometric mean (95% CI), ug/mL = 1,036 (973 to 1,104); 5th to 95th percentile = 491 to 1,861; 1st to 99th percentile = 383 to 2,366; Difference in geometric mean of 4 mg/kg q.6.w. (%): 1 • 50 to 80 kg (n = 2,109): Geometric mean (95% CI), ug/mL = 1,233 (1,213 to 1,252); 5th to 95th percentile = 651 to 2,150; 1st to 99th percentile = 487 to 2,538; Difference in geometric mean of 4 mg/kg q.6.w. (%): 1 • 80 kg (n = 1,329): Geometric mean (95% CI), ug/mL = 1,433 (1,407 to 1,460); 5th to 95th percentile = 797 to 2,403; 1st to 99th percentile = 616 to 2,951; Difference in geometric mean of 4 mg/kg q.6.w. (%): 1 • Overall (n = 3,607): Geometric mean (95% CI), ug/mL = 1,293 (1,277 to 1,308); 5th to 95th percentile = 677 to 2,260; 1st to 99th percentile = 499 to 2,695; Difference in geometric mean of 4 mg/kg q.6.w. (%): 1 Group 4: 4 mg/kg q.6.w. (alternative regimen) • < 50 kg (n = 169): Geometric mean (95% CI), ug/mL = 1,044 (979 to 1,113); 5th to 95th percentile = 491 to 1,891; 1st to 99th percentile = 383 to 2,423 • 50 to 80 kg (n = 2,109): Geometric mean (95% CI), ug/mL = 1,241 (1,221 to 1,261); 5th to 95th percentile = 651 to 2,191; 1st to 99th percentile = 487 to 2,608 • 80 kg (n = 1,329): Geometric mean (95% CI), ug/mL = 1,443 (1,416 to 1,470); 5th to 95th percentile = 796 to 2,456; 1st to 99th percentile = 615 to 3,025 Overall (n = 3,607): Geometric mean (95% CI), ug/mL = 1,301 (1,285 to 1,317); 5th to 95th percentile = 676 to 2,299; 1st to 99th percentile = 498 to 2,757 • Target saturation for 400 mg q.6.w. is typically predicted to be > 90%, similar to 200 mg and 2 mg/kg q.3.w.
Gandhi, 2024⁵³	• Arm 1 (conventional): nivolumab 3 mg/kg IV (60-minute infusion) q.2.w. or q.3.w. • Arm 2 (low-dose): nivolumab 40 mg	• Conventional dose: 11.0 days $\approx$ 264 hour (GeoMean; CV 60.8%) • Low-dose: 11.8 days $\approx$ 283 hour (GeoMean; CV 92.2%)	• C_{max}: Conventional 47.3 mcg/mL (GeoCV 61.3%); Low-dose 9.06 mcg/mL (GeoCV 16.3%) • $AUC_{0-\infty}$ ((mcg*d)/mL): Conventional 238 mcg $\times$ day/mL (GeoCV 43.1%); Low-dose 44.3 mcg $\times$ day/mL (GeoCV 60%)

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
	flat IV (60-minute infusion) q.2.w. or q.3.w.		Dose-normalized AUC_{0-t} (mcg*d/mL/mg): 0.0014 vs. 0.0011 day/mL/mg (conventional vs. low-dose)
Zhao, 2024 ⁶²	Weight-based comparator: nivolumab 3 mg/kg IV q.2.w. (also benchmarked against 10 mg/kg IV q.2.w. as an upper safe-exposure reference) Fixed-dose regimens: nivolumab 720 mg SC q.4.w., 960 mg SC q.4.w., and 1,200 mg SC q.4.w. (with rHuPH20) in model-based simulations	NR	3 mg/kg IV q.2.w.: $C_{min-d28}$ 27.5 mcg/mL, C_{max1} 40.4 mcg/mL, C_{avgd28} 57.9 mcg/mL. 10 mg/kg IV q.2.w.: $C_{min-d28}$ 91.6 mcg/mL, C_{max1} 135 mcg/mL, C_{avgd28} 193 mcg/mL. 720 mg SC q.4.w.: $C_{min-d28}$ 24.3 mcg/mL, C_{max1} 39.4 mcg/mL, C_{avgd28} 55.8 mcg/mL. 960 mg SC q.4.w.: $C_{min-d28}$ 32.4 mcg/mL, C_{max1} 52.5 mcg/mL, C_{avgd28} 74.4 mcg/mL. 1,200 mg SC q.4.w.: $C_{min-d28}$ 40.5 mcg/mL, C_{max1} 65.6 mcg/mL, C_{avgd28} 93.0 mcg/mL. AUC was not directly reported in the main paper; C_{avgd28} was used instead as the 28-day exposure summary. The paper states that SC dosing had reduced and delayed C_{max} vs. IV, with peak concentrations occurring by about 7 days, and that 960 mg and 1,200 mg SC q.4.w. generally produced higher C_{avgd28} and $C_{min-d28}$ than 3 mg/kg IV q.2.w., while remaining less than 10 mg/kg IV q.2.w.
Hwang, 2023 ⁶⁵	Pooled population PK modelling of tremelimumab given IV as monotherapy and in combination with durvalumab across multiple phase I to 3 solid-tumour studies. Dosing regimens included weight-based (e.g., 1/3/10 mg/kg q.4.w.) and flat dose (e.g., 750 mg q.4.w. monotherapy; 75 mg q.4.w. combination). Maintenance schedules in some trials included q.12.w. after initial q.4.w. dosing. Objective was to evaluate the adequacy of exposure coverage when converting 1 mg/kg to a flat dose of 75 mg.	~18 days ≈ 432 hour (variability not reported).	Figures show reported/used exposure metrics include cycle 1 C_{min} and C_{max} (by dose group) and model-based exposure comparisons for 75 mg vs. 1 mg/kg using average exposure over the first 16 weeks (overlap proportions). Specific numeric C_{min}/C_{max}/AUC values were not consistently presented as a single summary in the extracted sections.) Exposure overlap (simulation-based): ~86.3% overlap for patients > 90 kg ~73.7% overlap for > 110 kg ~72.0% overlap for < 50 kg ~63.6% overlap for < 40 kg Study concluded that a flat dose (75 mg) was projected to provide comparable exposure to weight-based dosing (1 mg/kg) in adults.
Ter Heine, 2023 ⁵⁹	Reference dosing regimen: - Atezolizumab q.3.w.: 1,200 mg - Durvalumab q.2.w.: 10 mg/kg - Durvalumab q.4.w.: 20 mg/kg - Ipilimumab q.6.w.: 1 mg/kg	NR	Ratios of the alternative ICI dose regimen to the reference ICI dose regimen for the following metrics Atezolizumab (q.3.w.): Geometric mean C trough at end of 1st dosing cycle (CV%) = 0.82

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
	• Nivolumab q.2.w.: 3 mg/kg • Nivolumab q.3.w.: 360 mg • Pembrolizumab q.3.w.: 2 mg/kg Alternative dosing regimens: • Atezolizumab: < 70 kg: 840 mg, ≥ 70 kg: 1,200 mg • Durvalumab (q.2.w.): < 60 kg: 480 mg, 60 to 80 kg: 600 mg, > 80 kg: 720 mg • Durvalumab (q.4.w.): < 60 kg: 960 mg, 60 to 80 kg: 1,200 mg, > 80 kg: 1,440 mg • Ipilimumab: < 60 kg: 50 mg, 60 to 90 kg: 75 mg, > 90 kg: 100 mg • Nivolumab (q.2.w.): < 50 kg: 120 mg, 50 to 75 kg: 160 mg, 75 to 100 kg: 200 mg, > 100 kg: 240 mg • Nivolumab (q.3.w.): < 60 kg: 280 mg, 60 to 90 kg: 320 mg, > 90 kg: 360 mg • Pembrolizumab (q.3.w.): < 60 kg: 100 mg, > 60 kg: 150 mg		• Geometric mean C trough at steady state (CV%) = 0.82 • Geometric mean AUC at end of 1st dosing cycle (CV%) = 0.82 • Geometric mean AUC at steady state (CV%) = 0.82 Durvalumab (q.2.w.): • Geometric mean C trough at end of 1st dosing cycle (CV%) = 0.87 • Geometric mean C trough at steady state (CV%) = 0.87 • Geometric mean AUC at end of 1st dosing cycle (CV%) = 0.87 • Geometric mean AUC at steady state (CV%) = 0.87 Durvalumab (q.4.w.): • Geometric mean C trough at end of 1st dosing cycle (CV%) = 0.87 • Geometric mean C trough at steady state (CV%) = 0.87 • Geometric mean AUC at end of 1st dosing cycle (CV%) = 0.87 • Geometric mean AUC at steady state (CV%) = 0.87 Ipilimumab (q.6.w.): • Geometric mean C trough at end of 1st dosing cycle (CV%) = 1.0 • Geometric mean C trough at steady state (CV%) = 1.0 • Geometric mean AUC at end of 1st dosing cycle (CV%) = 1.0 • Geometric mean AUC at steady state (CV%) = 1.0 Nivolumab (q.2.w.): • Geometric mean C trough at end of 1st dosing cycle (CV%) = 0.90 • Geometric mean C trough at steady state (CV%) = 0.91 • Geometric mean AUC at end of 1st dosing cycle (CV%) = 0.87 • Geometric mean AUC at steady state (CV%) = 0.90 Nivolumab (q.3.w.): • Geometric mean C trough at end of 1st dosing cycle (CV%) = 0.82 • Geometric mean C trough at steady state (CV%) = 0.81 • Geometric mean AUC at end of 1st dosing cycle (CV%) = 0.83

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
			- Geometric mean AUC at steady state (CV%) = 0.82 Pembrolizumab (q.3.w.): - Geometric mean C trough at end of 1st dosing cycle (CV%) = 1.0 - Geometric mean C trough at steady state (CV%) = 1.0 - Geometric mean AUC at end of 1st dosing cycle (CV%) = 1.0 - Geometric mean AUC at steady state (CV%) = 1.0"
Masters, 2022 ⁵¹	- Weight-based: avelumab 10 mg/kg IV q.2.w. - Flat dose: avelumab 800 mg IV q.2.w. (simulated/reference flat-dose exposures)	NR	Exposure metrics evaluated after single dose and at steady state: AUC, C_{max} , C_{trough} (and $C_{avg,ss}$ in simulations). Units shown: AUC _{tau,ss} (mg × h/L); $C_{max,ss}$ (mcg/mL); $C_{trough,ss}$ (mcg/mL). Numeric mean/CV% for C_{min}/C_{max} /AUC are not tabulated in text (presented mainly as boxplots/distributions).
Paccaly, 2021 ⁶¹	- Weight-based: cemiplimab 3 mg/kg IV q.2.w. - Fixed: cemiplimab 350 mg IV q.3.w.	Not reported in hours. Reported as: $t_{1/2}$ after first dose = 12.5 days; $t_{1/2}$ at steady state = 19.2 days. Converting to hours: 300 hour and 460.8 hour. These half-lives are overall cemiplimab PK parameters from the final PopPK model, not arm-specific.	After first dose: 3 mg/kg q.2.w.: C_{max} 69.5 mg/L, C_{trough} 18.9 mg/L, AUC _{0-6wk} 1,880 day × mg/L; 350 mg q.3.w.: C_{max} 107 mg/L, C_{trough} 20.4 mg/L, AUC _{0-6wk} 2,050 day × mg/L. At steady state: 3 mg/kg q.2.w.: $C_{max,ss}$ 135 mg/L, $C_{trough,ss}$ 65.7 mg/L, AUC _{6wk,ss} 3,710 day × mg/L; 350 mg q.3.w.: $C_{max,ss}$ 166 mg/L, $C_{trough,ss}$ 58.7 mg/L, AUC _{6wk,ss} 3,800 day × mg/L. Authors conclude exposures were similar at steady state.
Sanghavi, 2021 ⁵⁶	- Weight-based: nivolumab 3 mg/kg q.2.w. - Fixed: nivolumab 240 mg q.2.w. and 480 mg q.4.w.; model-predicted PK exposure in adjuvant melanoma	NR	3 mg/kg q.2.w.: C_{min1} 24.7 mcg/mL; $C_{min-d28}$ 42.8 mcg/mL; C_{minss} 95.6 mcg/mL; C_{max1} 69.5 mcg/mL; C_{maxss} 169 mcg/mL; C_{avgd28} 45 mcg/mL; C_{avg1} 34.4 mcg/mL; C_{avgss} 118 mcg/mL. 240 mg q.2.w.: C_{min1} 25.0 mcg/mL; $C_{min-d28}$ 43.3 mcg/mL; C_{minss} 96.8 mcg/mL; C_{max1} 70.6 mcg/mL; C_{maxss} 171 mcg/mL; C_{avgd28} 45.6 mcg/mL; C_{avg1} 34.9 mcg/mL; C_{avgss} 119 mcg/mL. 480 mg q.4.w.: C_{min1} 36.6 mcg/mL; $C_{min-d28}$ 36.6 mcg/mL; C_{minss} 81.8 mcg/mL; C_{max1} 141 mcg/mL; C_{maxss} 227 mcg/mL; C_{avgd28} 56.4 mcg/mL; C_{avg1} 56.4 mcg/mL; C_{avgss} 119 mcg/mL
Sheng, 2021 ⁵⁴	- Group 1: Nivolumab 3 mg/kg IV q.2.w.; monotherapy - Group 2: Nivolumab 240 mg/body IV q.2.w. (flat dose); monotherapy	NR	Geometric mean (CV %) reported for the following metrics: Group 1: Chinese 3 mg/kg q.2.w. (n = 294) C_{min1}: 16.3 (23.4) C_{max1}: 56.2 (13.8) C_{avg1}: 25.6 (17.5)

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
	Group 3: Nivolumab 10mg/kg IV q.2.w.; monotherapy		C_{minss}: 62.0 (73.5) C_{maxss}: 120.0 (44.8) C_{avgss}: 80.2 (61.5) Group 2: Chinese 240 mg q.2.w. (n = 314) C_{min1}: 20.7 (24.1) C_{max1}: 71.2 (18.9) C_{avg1}: 32.4 (18.3) C_{minss}: 78.3 (71.8) C_{maxss}: 152.0 (44.7) C_{avgss}: 101.0 (58.1) Group 3: Global patients 10mg/kg q.2.w. (n = 148) C_{min1}: 53.6 (27.5) C_{max1}: 178.0 (25.2) C_{avg1}: 85.7 (22.0) C_{minss}: 206.0 (64.0) C_{maxss}: 393.0 (39.6) C_{avgss}: 268.0 (52.3) Difference in Geometric Mean (%) 240 mg q.2.w. vs. 3 mg/kg q.2.w. (Group 2 vs. Group 1): C_{min1} = 27 C_{max1} = 27 C_{avg1} = 27 C_{minss} = 26 C_{maxss} = 27 C_{avgss} = 26 Difference in Geometric Mean (%) 240 mg q.2.w. vs. 10 mg/kg q.2.w. (Group 2 vs. Group 3): C_{min1} = -61 C_{max1} = -60 C_{avg1} = -62 C_{minss} = -62

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
			• $C_{maxss} = -61$ • $C_{avgss} = -62$
Yang, 2021 ⁶⁰	Cemiplimab weight-based • 1 mg/kg • 3 mg/kg • 10 mg/kg q.2.w • 3 mg/kg q.3.w. fixed • 200 mg q.2.w. • 350 mg q.3.w.	Elimination half-life reported as mean 22.7 days (responders) vs. 18.7 days (others) at steady state → ~544.8 hour vs. ~448.8 hour, respectively.	C_{min} ($C_{trough'ss}$) and $AUC_{6wk,ss}$ reported by body weight quartiles for 3 mg/kg q.2.w. and 350 mg q.3.w. Weight quartiles, kg: Q1 (30.9, 65.5), Q2 (65.5, 76.2), Q3 (76.2, 88.5), Q4 (88.5, 172) Summary across quartiles: 3 mg/kg q.2.w.: Mean $AUC_{6wk,ss}$ (SD) day × mg/L: • Q1 = 3,280 (2,220) • Q2 = 3,750 (1,330) • Q3 = 3,960 (1,220) • Q4 = 4,200 (1,430) Mean $C_{trough'ss}$ (SD) mg/L • Q1 = 58.4 (51.6) • Q2 = 66.8 (28.2) • Q3 = 70.6 (26.3) • Q4 = 74.0 (30.5) 350 mg q.3.w.: Mean $AUC_{6wk,ss}$ (SD) day × mg/L: • Q1 = 4,510 (3,180) • Q2 = 4,100 (1,440) • Q3 = 3,760 (1,190) • Q4 = 3,190 (1,110) Mean $C_{trough'ss}$ (SD) mg/L • Q1 = 70.3 (72.6) • Q2 = 64.0 (29.1) • Q3 = 58.8 (24.5) • Q4 = 49.0 (22.3) C_{max}: not numerically reported in the extracted tables (figure shows C_{max} conceptually).

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
Bei, 2020 ⁵⁷	- Group 1: Nivolumab 3 mg/kg IV q.2.w. - Group 2: Nivolumab 240 mg/body IV q.2.w. (flat dose)	NR	Group 1: 3 mg/kg q.2.w. - Geometric mean (CV %) for C_{avgd28} (ug/mL): 32.5 (20.6) - Geometric mean (CV %) for $C_{min-d28}$ (ug/mL): 27.9 (25.8) - Geometric mean (CV %) for C_{max1} (ug/mL): 55.3 (18.3) Group 2: 240 mg q.2.w. - Geometric mean (CV %) for C_{avgd28} (ug/mL): 44.6 (21.4) - Geometric mean (CV %) for $C_{min-d28}$ (ug/mL): 38.4 (27.7) - Geometric mean (CV %) for C_{max1} (ug/mL): 76.1 (21.0) % Difference (240 mg q.2.w. vs. 3 mg/kg q.2.w.): C_{avgd28}: 37.2; $C_{min-d28}$: 37.6; C_{max1}: 37.6
Lala, 2020 ⁵⁸	Pembrolizumab Fixed: 400 mg q.6.w. 200 mg q.3.w. Weight-based: 2 mg/kg q.3.w. 10 mg/kg q.2.w.; (plus 10 mg/kg q.3.w. in pooled safety) - Switch scenario: 200 mg q.3.w. up to steady state → switch to 400 mg q.6.w.	NR	Absolute values/units not reported; results are presented as % differences and described as based on geometric means from simulations. Key comparisons for 400 mg q.6.w. vs. 200 mg q.3.w.: $C_{avg,ss}$ (AUC_{ss}) + 0.7%; $C_{min,ss}$ -34%; $C_{max,ss}$ + 59%; $C_{avg,wk6}$ + 16%; $C_{min,wk6}$ - 41%; $C_{max,wk6}$ + 108%. Key comparisons for 400 mg q.6.w. vs. 2 mg/kg q.3.w.: $C_{avg,ss}$ + 35%; $C_{min,ss}$ -12%; $C_{max,ss}$ + 113%; $C_{avg,wk6}$ + 56%; $C_{min,wk6}$ - 21%; $C_{max,wk6}$ + 179% Key comparisons for 400 mg q.6.w. vs. 10 mg/kg q.2.w. (safety bound; only C_{avg} and C_{max} shown): $C_{avg,ss}$ -81.8%; $C_{max,ss}$ -65.6%;

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
			$C_{avg, wk6}$ –77.5%; $C_{max, wk6}$ – 44.1%. AUC integrated over 42 days (trapezoidal), C_{min} at end of interval (day 42 early; day 210 ss), C_{max} at end of infusion (30 minutes after the dose; day 1 early; day 169 ss).
Novakovic, 2020⁵²	- Group 1: Avelumab 10 mg/kg IV q.2.w. - Group 2: Avelumab 800 mg/body IV q.2.w. (flat dose)	NR	Paper reports simulation/analysis of C_{trough}, C_{max}, $AUC_{0-\tau}$ (τ = 336 hours) after single dose (first-cycle model) and multiple dose (steady-state model). Numeric AUC_{0-336h} (mg × h/L), first dosing interval: Overall (N = 1,663): 10 mg/kg: 23,160 (range: 7,438 to 51,742) vs. 800 mg: 25,913 (range: 5,689 to 54,763). Weight Q1 (30.4 to ≤ 60.0 kg) [n = 415]: 10 mg/kg: 19,102 (8,271 to 36,965); 800 mg: 29,418 (14,191 to 54,763) Weight Q2 (60.0 to ≤ 60.0 kg) [n = 404]: 10 mg/kg: 22,221 (9,057 to 35,556); 800 mg: 27,170 (10,893 to 45,739) Weight Q3 (70.6 to ≤ 84.6 kg) [n = 435]: 10 mg/kg: 24,720 (12,970 to 51,742); 800 mg: 25,280 (13,627 to 51,103) Weight Q4 (84.4 to ≤ 204 kg) [n = 409]: 10 mg/kg: 27,681 (7,438 to 44,938); 800 mg: 22,583 (5,689 to 38,309) Variability AUC_{0-336h} CV%): 27.1% (800 mg) vs. 29.0% (10 mg/kg).
Zhao, 2020⁵⁵	- Nivolumab 3 mg/kg IV q.2.w. (weight-based) - Nivolumab 240 mg IV q.2.w. (fixed) - Nivolumab 480 mg IV q.4.w. (fixed, extended-interval)	NR	Steady state (geometric mean [CV%], ug/mL): 3 mg/kg q.2.w.: C_{minss} 67.2 (52.8); C_{maxss} 129.1 (46.1); C_{avgss} 86.7 (44.2) 240 mg q.2.w.: C_{minss} 70.6 (55.7); C_{maxss} 136.0 (50.0); C_{avgss} 91.2 (47.3) 480 mg q.4.w.: C_{minss} 56.3 (63.9); C_{maxss} 185.1 (58.3); C_{avgss} 91.2 (47.3) After the first dose (geometric mean [CV%], ug/mL): 3 mg/kg q.2.w.: C_{avg1} 27.5 (23.6); C_{min1} 18.0 (28.1); C_{max1} 58.7 (72.9) 240 mg q.2.w.: C_{avg1} 29.0 (27.2); C_{min1} 19.0 (32.6); C_{max1} 61.8

Author and publication year	Intervention characteristics	$t_{1/2}$ (h)	C_{min} , C_{max} , AUC, PD / target occupancy (%)
			(76.4) 480 mg q.4.w.: C_{avg1} 44.0 (29.4); C_{min1} 22.6 (39.2); C_{max1} 123.5 (76.4) Over the first 28 days (geometric mean [CV%], ug/mL): 3 mg/kg q.2.w.: C_{avgd28} 34.7 (24.5); $C_{min-d28}$ 29.0 (30.0) 240 mg q.2.w.: C_{avgd28} 36.5 (28.4); $C_{min-d28}$ 30.6 (34.6) 480 mg q.4.w.: C_{avgd28} 44.0 (29.4); $C_{min-d28}$ 22.6 (39.3) Difference between 3 mg/kg q.2.w. and 240 mg q.2.w., %: C_{minss} 5.1%; C_{maxss} 5.4%; C_{avgss} 5.2%; C_{avg1} 5.5; C_{min1} 5.6; C_{max1} 5.3; C_{avgd28} 5.2; $C_{min-d28}$ 5.5 Difference between 3 mg/kg q.2.w. and 480 mg q.4.w., %: C_{minss} -16.2%; C_{maxss} 43.4%; C_{avgss} 5.2%; C_{avg1} 59.6; C_{min1} 25.5; C_{max1} 110.4; C_{avgd28} 26.7; $C_{min-d28}$ -22.1 - AUC: NR (not reported; paper emphasizes $C_{min}/C_{max}/C_{avg}$ metrics).

AUC = area under the concentration–time curve; $AUC_{0-\infty}$ = area under the curve from time 0 to infinity; $AUC_{0-\tau}$ = area under the curve over one dosing interval (τ); AUC_{0-t} = area under the curve from time 0 to last measurable time point; $AUC_{6wk,ss}$ = area under the curve over 6 weeks at steady state; AUC_{ss} = area under the curve at steady state; AUC_{τ} = area under the curve over the dosing interval (τ); $AUC_{\tau,ss}$ = area under the curve over the dosing interval at steady state; CL = clearance; CR = complete response; CSCC = cutaneous squamous cell carcinoma; CTCAE = Common Terminology Criteria for Adverse Events; C_{avg} = Average (Mean) Concentration; C_{avg1} = average concentration after first dose or first cycle (study-defined); C_{avgd28} = average concentration over 28 days; C_{avgss} = average concentration at steady state; $C_{avg1,week6}$ = average concentration over week 6 (study-defined window); C_{max} = Maximum Concentration; C_{max1} = maximum concentration after first dose or first cycle; C_{maxss} = maximum concentration at steady state; C_{min} = Minimum (Trough) Concentration; C_{min1} = minimum concentration after first dose or first cycle (study-defined); C_{min1} = minimum concentration after first dose or first cycle; $C_{min-d28}$ = minimum concentration over 28 days (study-defined); C_{minss} = minimum (trough) concentration at steady state; C_{trough} = trough concentration; $C_{trough,ss}$ = trough concentration at steady state; CV = coefficient of variation; DL = dose level; DLT = dose-limiting toxicity; ICI = immune checkpoint inhibitor; NSCLC = Non–Small Cell Lung Cancer; ORR = objective response rate; OS = overall survival; PD = Pharmacodynamics; PK = Pharmacokinetics; PK/PD = Pharmacokinetics/Pharmacodynamics; PK/PDy = pharmacokinetics and pharmacodynamics (as labelled in study); PopPK = population pharmacokinetic; PR = partial response; q.2.w. = every 2 weeks; q.3.w. = every 3 weeks; q.4.w. = every 4 weeks; q.6.w. = every 6 weeks; q.12.w. = every 12 weeks; RAC = accumulation ratio; RCT = randomized controlled trial; RECIST = Response Evaluation Criteria in Solid Tumours; rHuPH20 = recombinant human hyaluronidase PH20; SC = subcutaneous; SD = Stable Disease; STRIDE = Single Tremelimumab Regular Interval Durvalumab (regimen name); T_{max} = time to maximum concentration; vs. = versus; V_{ss} = volume of distribution at steady state; V_z = volume of distribution during terminal phase; WAT = weight-adjusted therapy (study-defined); irRECIST = Immune-Related Response Evaluation Criteria in Solid Tumours; $t_{1/2}$ = elimination half-life.

Appendix 5: List of Included Studies

Please note that this appendix has not been copy-edited.

Table 15: Included Studies

Study	Citation
Review articles	
Hoyek, 2025	Hoyek C, Zheng-Lin B, Bauernfeind JJ, et al. Overcoming Financial and Access Barriers in Global Cancer Care With Low-Dose Immunotherapy: A Systematic Review. <i>JCO Glob Oncol</i> . 2025;11:e2400409.
Tan, 2025	Tan Z, Voller S, Sancho-Araiz A, Knibbe CAJ, Moes D. A Systematic Evaluation of the Dosing Regimens for Approved Targeted Therapies and Immune Checkpoint Inhibitors in Metastatic Renal Cell Carcinoma From a Project OPTIMUS Perspective. <i>J Clin Pharmacol</i> . 2025;02:02.
Mao, 2024	Mao YT, Wang Y, Chen XX, Liu CJ, Bao Q. Comparative severe dermatologic toxicities of immune checkpoint inhibitors in malignant melanoma: A systematic review and network meta-analysis. <i>J</i> . 2024;23(4):1165-1177.
Hong, 2023	Hong B, Zheng J, Chen R, et al. Pulmonary Toxicity Associated with Immune Checkpoint Inhibitors-Based Therapy: Current Perspectives and Future Directions. <i>Drug Saf</i> . 2023;46(12):1313-1322.
Li, 2023	Li Y, Liang X, Li H, Chen X. Comparative efficacy and safety of immune checkpoint inhibitors for unresectable advanced melanoma: A systematic review and network meta-analysis. <i>Int Immunopharmacol</i> . 2023;115:109657.
Wesevich, 2023	Wesevich A, Goldstein DA, Paydary K, Peer CJ, Figg WD, Ratain MJ. Interventional pharmacoeconomics for immune checkpoint inhibitors through alternative dosing strategies. <i>Br J Cancer</i> . 2023;129(9):1389-96.
Jiang, 2022	Jiang M, Hu Y, Lin G, Chen C. Dosing Regimens of Immune Checkpoint Inhibitors: Attempts at Lower Dose, Less Frequency, Shorter Course. <i>Front Oncol</i> . 2022;12:906251
Lee, 2020	Lee A, Duggan S, Deeks ED. Cemiplimab: A Review in Advanced Cutaneous Squamous Cell Carcinoma. <i>Drugs</i> . 2020;80(8):813-819.
Sehgal, 2020	Sehgal K, Costa DB, Rangachari D. Extended-Interval Dosing Strategy of Immune Checkpoint Inhibitors in Lung Cancer: Will it Outlast the COVID-19 Pandemic? <i>Front</i> . 2020;10:1193.
Randomized controlled trials	
Albiges, 2024	Albiges L, Bournon MT, Chacon M, et al. Subcutaneous versus intravenous nivolumab for renal cell carcinoma. <i>Ann Oncol</i> . 2025;36(1):99-107.
Herrera, 2021	Herrera AF, Burton C, Radford J, et al. Avelumab in relapsed/refractory classical Hodgkin lymphoma: phase 1b results from the JAVELIN Hodgkins trial. <i>Blood Adv</i> . 2021;5(17):3387-3396.
Nonrandomized studies	
Campo Le Brun, 2025	Le Brun IC, Dalle S, Mortier L, et al. Methods of nivolumab administration in advanced melanoma: A comparison of patients' clinical outcomes treated with flat dose or weight-adjusted dose, a multicenter observational study. <i>Cancer</i> . 2025;131(1):e35679.
Horisaki, 2025	Horisaki K, Yoshikawa S, Omata W, Tsutsumida A, Kiyohara Y. The Real-World Efficacy and Side Effects of Different Nivolumab Regimens in Japanese Patients with Advanced Melanoma: A Single-Center Retrospective Study. <i>Cancers (Basel)</i> . 2025;17(14):10.

Study	Citation
Hughes, 2025	Hughes BGM, Guminski A, Bowyer S, et al. A phase 2 open-label study of cemiplimab in patients with advanced cutaneous squamous cell carcinoma (EMPOWER-CSCC-1): Final long-term analysis of groups 1, 2, and 3, and primary analysis of fixed-dose treatment group 6. <i>J Am Acad Dermatol</i> . 2025;92(1):68-77.
Smeenk, 2025	Smeenk MM, van der Noort V, Hendriks JMA, Abedian Kalkhoran H, Smit EF, Theelen W. Pembrolizumab hybrid dosing is non-inferior to flat dosing in advanced non-small cell lung cancer: a real-world, retrospective bicenter cohort study. <i>J Immunother Cancer</i> . 2025;13(2):06.
Staender, 2025	Staender HF, Langan EA. Fixed-Dose vs. Weight-Adapted Immune Checkpoint Inhibitor Therapy in Melanoma: A Retrospective Monocentric Analysis of Efficacy and Immune-Related Adverse Events. <i>Cancers (Basel)</i> . 2025;17(7):28.
Chaitesipaseut, 2024	Chaitesipaseut L, Shah N, Truong TG, et al. Outcomes of weight-based vs. fixed dose of Pembrolizumab among patients with non-small cell lung cancer. <i>J Oncol Pharm Pract</i> . 2024;30(8):1352-1357.
Cohen, 2024	Cohen G, Rapoport B, Chan SW, et al. Pembrolizumab 400 mg every 6 weeks as first-line therapy for advanced melanoma (KEYNOTE-555): Results from cohort B of an open-label, phase 1 study. <i>PLoS ONE</i> . 2024;19(11):e0309778.
Grit, 2024	Grit GF, van Geffen E, Malmberg R, et al. Real-world overall survival after alternative dosing for pembrolizumab in the treatment of non-small cell lung cancer: A nationwide retrospective cohort study with a non-inferiority primary objective. <i>Lung Cancer</i> . 2024;196:107950.
Leroy, 2024	Leroy, M., Desmedt, E., Deramoudt, L., Vasseur, M., Odou, P., Béhal, H., ... and Simon, N. (2024). Retrospective comparison of a weight-based dose every 2 weeks with a fixed dose every month: a real-life analysis of nivolumab in the treatment of advanced melanoma. <i>Melanoma Research</i> , 34(3), 258-264.
Patel, 2024	Patel A, Hande V, Mr K, et al. Effectiveness of Immune Checkpoint Inhibitors in Various Tumor Types Treated by Low, Per-Weight, and Conventional Doses at a Tertiary Care Center in Mumbai. <i>JCO Glob Oncol</i> . 2024;10:e2300312.
Rischin, 2024	Rischin D, Hughes BGM, Basset-Seguin N, et al. High response rate with extended dosing of cemiplimab in advanced cutaneous squamous cell carcinoma. <i>J Immunother Cancer</i> . 2024;12(3):11.
Berard, 2023	Berard G, Guevremont C, Marcotte N, Schroeder C, Bouchard N, Rajan R. Descriptive Analysis of First-Line Non-Small Cell Lung Cancer Treatment with Pembrolizumab in Tumors Expressing PD-L1 $\geq 50\%$ in Patients Treated in Quebec's University Teaching Hospitals (DALP-First Study). <i>Curr</i> . 2023;30(3):3251-3262.
Samlowski, 2023	Samlowski W, Robert NJ, Chen L, et al. Real-World nivolumab dosing patterns and safety outcomes in patients receiving adjuvant therapy for melanoma. <i>Cancer Med</i> . 2023;12(3):2378-2388.
Fujiwara, 2022	Fujiwara Y, Takahashi Y, Okada M, et al. Phase I Study of Tremelimumab Monotherapy or in Combination With Durvalumab in Japanese Patients With Advanced Solid Tumors or Malignant Mesothelioma. <i>Oncologist</i> . 2022;27(9):e703-e722.
Hijmering-Kappelle, 2022	Hijmering-Kappelle LBM, Hiltermann TJN, Bensch F. Safety and Efficacy of Extended Interval Dosing for Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer During the COVID-19 Pandemic. <i>Clin Lung Cancer</i> . 2022;23(2):143-150.
Iikura, 2022	Iikura Y, Aoyama T, Hiraide M, et al. Safety evaluation of fixed-dose nivolumab in patients with gastric cancer. <i>Health Sci Rep</i> . 2022;5(4):e673.
Okada, 2022	Okada T, Fushimi C, Matsuki T, et al. Comparison of Dosage of Nivolumab in Efficacy and Safety for Recurrent Metastatic Squamous Cell Carcinoma. <i>Anticancer Res</i> . 2022;42(3):1607-1613.

Study	Citation
Patnaik, 2022	Patnaik A, Weiss GJ, Rasco DW, et al. Safety, antitumor activity, and pharmacokinetics of dostarlimab, an anti-PD-1, in patients with advanced solid tumors: a dose-escalation phase 1 trial. <i>Cancer Chemother Pharmacol.</i> 2022;89(1):93-103.
To, 2022	To SY, Kao LT, Shih JH, et al. Modified-Dose Pembrolizumab and Prognostic Outcomes among Non-Small Cell Lung Cancer Patients: A Chart Review Study. <i>Int J Environ Res Public Health.</i> 2022;19(10):15.
Juergens, 2020	Juergens RA, Hao D, Ellis PM, et al. A phase IB study of durvalumab with or without tremelimumab and platinum-doublet chemotherapy in advanced solid tumours: Canadian Cancer Trials Group Study IND226. <i>Lung Cancer.</i> 2020;143:1-11.
Kato, 2020	Kato R, Ikarashi D, Matsuura T, et al. Analyses of Nivolumab Exposure and Clinical Safety Between 3-mg/kg Dosing and 240-mg Flat Dosing in Asian Patients with Advanced Renal Cell Carcinoma in the Real-World Clinical Setting. <i>Transl Oncol.</i> 2020;13(6):100771.
Rischin, 2020	Rischin D, Migden MR, Lim AM, et al. Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing. <i>J Immunother Cancer.</i> 2020;8(1):06.
PK/PD modelling or simulation studies	
Lala, 2025	Lala M, Bardia A, Calles A, et al. Weight-Based Pembrolizumab Dosing at 4 mg/kg Every 6 Weeks Leads to Exposures Below Approved Doses with Unestablished Efficacy: A Pharmacokinetic Model-Based Simulation Analysis. <i>Target Oncol.</i> 2025;20(6):955-965.
Gandhi, 2024	Gandhi KA, Shirsat A, Hj SK, et al. Pharmacokinetics and clinical outcomes of low-dose nivolumab relative to conventional dose in patients with advanced cancer. <i>Cancer Chemother Pharmacol.</i> 2024;94(5):659-668.
Zhao, 2024	Zhao Y, Sanghavi K, Roy A, et al. Model-Based Dose Selection of Subcutaneous Nivolumab in Patients with Advanced Solid Tumors. <i>Clin Pharmacol Ther.</i> 2024;115(3):488-497.
Hwang, 2023	Hwang M, Chia YL, Zheng Y, et al. Population pharmacokinetic modelling of tremelimumab in patients with advanced solid tumours and the impact of disease status on time-varying clearance. <i>Br J Clin Pharmacol.</i> 2023;89(5):1601-1616.
Ter Heine, 2023	Ter Heine R, van den Heuvel MM, Piet B, et al. A Systematic Evaluation of Cost-Saving Dosing Regimens for Therapeutic Antibodies and Antibody-Drug Conjugates for the Treatment of Lung Cancer. <i>Target.</i> 2023;18(3):441-450.
Masters, 2022	Masters JC, Khandelwal A, di Pietro A, Dai H, Brar S. Model-informed drug development supporting the approval of the avelumab flat-dose regimen in patients with advanced renal cell carcinoma. <i>CPT Pharmacometrics Syst Pharmacol.</i> 2022;11(4):458-468.
Paccaly, 2021	Paccaly AJ, Migden MR, Papadopoulos KP, et al. Fixed Dose of Cemiplimab in Patients with Advanced Malignancies Based on Population Pharmacokinetic Analysis. <i>Adv Ther.</i> 2021;38(5):2365-2378.
Sanghavi, 2021	Sanghavi, K., Vuppala, P., Ivaturi, V., Hamuro, L., Roy, A., and Suryawanshi, S. (2021). Nivolumab exposure–response analysis for adjuvant treatment of melanoma supporting a change in posology. <i>CPT: Pharmacometrics and Systems Pharmacology</i> , 10(7), 748-759.
Sheng, 2021	Sheng J, Zhang J, Baudalet C, Roy A. Clinical Benefit-Risk Assessment of Nivolumab 240 mg Every 2 Weeks in Chinese Patients With Advanced and Metastatic Solid Tumors. <i>J Clin Pharmacol.</i> 2021;61(8):1045-1053.
Yang, 2021	Yang F, Paccaly AJ, Rippley RK, Davis JD, DiCioccio AT. Population pharmacokinetic characteristics of cemiplimab in patients with advanced malignancies. <i>J Pharmacokinet Pharmacodyn.</i> 2021;48(4):479-494.

Study	Citation
Bei, 2020	Bei D, Osawa M, Uemura S, et al. Benefit-risk assessment of nivolumab 240 mg flat dose relative to 3 mg/kg Q2W regimen in Japanese patients with advanced cancers. <i>Cancer Sci.</i> 2020;111(2):528-535.
Lala, 2020	Lala M, Li TR, de Alwis DP, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. <i>Eur J Cancer.</i> 2020;131:68-75.
Novakovic, 2020	Novakovic AM, Wilkins JJ, Dai H, et al. Changing Body Weight-Based Dosing to a Flat Dose for Avelumab in Metastatic Merkel Cell and Advanced Urothelial Carcinoma. <i>Clin Pharmacol Ther.</i> 2020;107(3):588-596.
Zhao, 2020	Zhao X, Shen J, Ivaturi V, et al. Model-based evaluation of the efficacy and safety of nivolumab once every 4 weeks across multiple tumor types. <i>Ann Oncol.</i> 2020;31(2):302-309.

Appendix 6: List of Excluded Studies

Please note that this appendix has not been copy-edited.

Table 16: Excluded Studies

Reason for exclusion	Citation
Ineligible immune checkpoint inhibitor	1. Anonymous. Phase I/IIa Dose Finding Study of Triplet Regimen of Relatlimab Ipilimumab and Nivolumab in First Line Therapy of Metastatic Melanoma (TRINITY). <i>clinicaltrials.gov</i>. 2024;08. 2. Luke JJ, Gelmon K, Siu LL, et al. Phase 1/2 Study of the Indoleamine 2,3-Dioxygenase 1 Inhibitor Linrodostat Mesylate Combined with Nivolumab or Nivolumab and Ipilimumab in Advanced Solid Tumors or Hematologic Malignancies. <i>Clin Cancer Res</i>. 2025;31(11):2134-2144.
Ineligible outcomes	1. Diaz-Rangel M, Sanchez-Rubio F, Drozd-Vergara A, et al. Fixed or weight-adjusted dose in immunotherapy? <i>Eur</i>. 2025;32(4):338-341. 2. Duerinck J, Lescrauwaet L, Dirven I, et al. Intracranial administration of anti-PD-1 and anti-CTLA-4 immune checkpoint-blocking monoclonal antibodies in patients with recurrent high-grade glioma. <i>Neuro-oncol</i>. 2024;26(12):2208-2221. 3. Anonymous. Medico-economic Evaluation Comparing the Impact of the New Fixed-dose Nivolumab Regimen With the Old mg/kg Regimen in the Management of Patients With Metastatic Cancer. <i>clinicaltrials.gov</i>. 2022;05. 4. Hall E, Zhang J, Kim EJ, et al. Economics of alternative dosing strategies for pembrolizumab and nivolumab at a single academic cancer center. <i>Cancer Med</i>. 2020;9(6):2106-2112. 5. Oliveira G, Egloff AM, Afeyan AB, et al. Preexisting tumor-resident T cells with cytotoxic potential associate with response to neoadjuvant anti-PD-1 in head and neck cancer. <i>Science Immunology</i>. 2023;8(87) (no pagination).
Ineligible population	1. Du S, Zhao Y, Hu Z, et al. Pediatric model-based dose optimization using a pooled exposure-response safety analysis for nivolumab and nivolumab plus ipilimumab combination in melanoma. <i>CPT Pharmacometrics Syst Pharmacol</i>. 2024;13(1):168-179. 2. Qi Z, Zhao J, Li Y, et al. Live-attenuated Japanese encephalitis virus inhibits glioblastoma growth and elicits potent antitumor immunity. <i>Front Immunol</i>. 2023;14:982180. 3. van den Haak DAC, Otten LS, Koenen H, et al. Evidence-based rationale for low dose nivolumab in critically ill patients with sepsis-induced immunosuppression. <i>Clin Transl Sci</i>. 2023;16(6):978-986. 4. Davis KL, Fox E, Isikwei E, et al. A Phase I/II Trial of Nivolumab plus Ipilimumab in Children and Young Adults with Relapsed/Refractory Solid Tumors: A Children's Oncology Group Study ADVL1412. <i>Clin Cancer Res</i>. 2022;28(23):5088-5097. 5. Low Dose Nivolumab in Adults Living With HIV on Antiretroviral Therapy. Safety, Immunogenicity and Efficacy of Low Dose Nivolumab in Adults Living With HIV on Antiretroviral Therapy (ART). NCT05187429. 2021. 6. Davis KL, Fox E, Merchant MS, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1-2 trial. <i>Lancet Oncol</i>. 2020;21(4):541-550. 7. Watanabe E, Nishida O, Kakihana Y, et al. Pharmacokinetics, Pharmacodynamics, and Safety of Nivolumab in Patients With Sepsis-Induced

Reason for exclusion	Citation
	Immunosuppression: A Multicenter, Open-Label Phase 1/2 Study. Shock. 2020;53(6):686-694. 8. Huang W, Stader F, Chan P, et al. Development of a pediatric physiologically-based pharmacokinetic model to support recommended dosing of atezolizumab in children with solid tumours. Front Pharmacol. 2022;13:974423. 9. Loeb DM, Lee JW, Morgenstern DA, et al. Avelumab in paediatric patients with refractory or relapsed solid tumours: dose-escalation results from an open-label, single-arm, phase 1/2 trial. Cancer Immunol Immunother. 2022;71(10):2485-2495.
Ineligible study design	1. Arora A, Seenu V, Parshad R, et al. A phase II, randomized, open-labeled study to evaluate low-dose pembrolizumab in addition to neoadjuvant chemotherapy for triple-negative breast cancer (TNBC). Trials. 2025;26(1):73. 2. Proctor JR, Wong H. Clinical study design strategies to mitigate confounding effects of time-dependent clearance on dose optimization of therapeutic antibodies. CPT Pharmacometrics Syst Pharmacol. 2025;14(2):365-375. 3. Pembrolizumab Low dose in Addition to NACT in TNBC. <i>A phase- II randomised open labelled study to evaluate low dose pembrolizumab plus chemotherapy versus chemotherapy as neoadjuvant therapy for localised triple negative breast cancer(TNBC) - PLANeT.</i> CTRI/2024/01/062088. 2024. 4. Head SA, Johnson C, Sarkar S, et al. Comparison of dose selection based on target engagement versus inhibition of receptor-ligand interaction for checkpoint inhibitors. CPT Pharmacometrics Syst Pharmacol. 2024;13(6):919-925. 5. Yohannan B, Rios A, Buja M. Durable Remission in Hodgkin Lymphoma Treated With One Cycle of Bleomycin, Vinblastine, Dacarbazine and Two Doses of Nivolumab and Brentuximab Vedotin. J Hematol (Brossard). 2022;11(4):154-158. 6. Dose Tapering and Early Discontinuation to InCreAse cost-effectiveness Of Immunotherapy for NSCLC. Dose Tapering and Early Discontinuation to InCreAse cost-effectiveness Of Immunotherapy for Non-small Cell Lung Carcinoma. 2021. 7. Anonymous. Dose Tapering and Early Discontinuation to InCreAse cost-effectiveness Of Immunotherapy for Non-small Cell Lung Carcinoma. clinicaltrials.gov. 2021;26.
Irrelevant comparator	1. Pembro-FLASH – phase II trial of pembrolizumab in first-line treatment of advanced-stage classic hodgkin lymphoma. EUCT number:2022-501458-13-01. Protocol code:Uni-Koeln-4938. 2025; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2022-501458-13-01. Accessed 2026 May 29. 2. A phase IIIb study of durvalumab as consolidation treatment for patients diagnosed with limited stage small cell lung cancer who have not progressed following definitive concurrent or sequential platinum-based chemoradiation therapy in Spain (ALBORAN). EUCT number: 2025-521340-37-00. Protocol code: D419QL00009. 2025; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2025-521340-37-00. Accessed 2026 May 29. 3. Public title: Effect of smaller doses of drug Nivolumab in cancer patients who have failed to standard treatment. Scientific title: Efficacy of low dose Nivolumab in combination with chemotherapy as remission-induction therapy in primary progressive and relapsed Hodgkin lymphoma - NA. Trial number: CTRI/2025/06/089253. 2025. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=135021. Accessed 2025 Oct 1. 4. Nivolumab dose optimization in patients with a complete, partial or stable response (NIVOPTIMIZE-trial). Trial number: CTIS2024-516718-39-00. 2025. https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-516718-39-00, https://trialsearch.who.int/Trial2.aspx?TrialID=CTIS2024-516718-39-00. Accessed 2026 May 29.

Reason for exclusion	Citation
	5. Abhyankar AV, Ahn MJ, Dy GK. CLO25-097: randomized phase II study of pembrolizumab 200mg q12 weeks versus standard-of-care (soc) dosing in stage IV non-small cell lung cancer (NSCLC) with prior clinical benefit to pembrolizumab monotherapy. <i>J.</i> 2025;23(3.5):28. 6. Anonymous. Circadian rhythm impact on triple negative breast cancer response to neoadjuvant immunotherapy - a feasibility randomized trial. <i>ClinicalTrial.gov.</i> 2025;11. 7. Anonymous. An open-label, randomized study of bms-986489 (atigotatug + nivolumab fixed-dose combination) vs durvalumab as consolidation therapy following chemoradiotherapy in limited-stage small-cell lung cancer (TIGOS-LS). <i>ClinicalTrial.gov.</i> 2025;08. 8. Anonymous. An open-label, single-arm, multicenter, phase 1 study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of BMS-986489 (BMS-986012 + nivolumab fixed dose combination) in chinese participants with relapsed/refractory small cell lung cancer. <i>ClinicalTrial.gov.</i> 2025;24. 9. Blank C, Hoeijmakers L, Dimitriadis P, et al. Long-term survival after neoadjuvant low-dose ipilimumab plus high-dose nivolumab in resectable stage III melanoma: the 5-year survival-update and biomarker analysis from the PRADO-trial [PRE-PRINT]. <i>Research Square.</i> 2025. 10. de Vries F, Franssen EJJ, Smit AAJ, et al. TDM-Based tailored dosing of durvalumab in lung cancer patients: a comprehensive population pharmacokinetic-pharmacoeconomic evaluation. <i>Clin Pharmacokinet.</i> 2025;25:25. 11. Felip E, Rojas CI, Schenker M, et al. Subcutaneous versus intravenous pembrolizumab, in combination with chemotherapy, for treatment of metastatic non-small-cell lung cancer: the phase III 3475A-D77 trial. <i>Ann Oncol.</i> 2025;36(7):775-785. 12. Frenel JS, Mathiot L, Cropet C, et al. Durvalumab and tremelimumab in combination with metronomic oral vinorelbine for recurrent advanced cervical cancer: an open-label phase I/II study. <i>J Immunother Cancer.</i> 2025;13(1):07. 13. Gaillard S, Verma N, Berg M, et al. A clinical study of tremelimumab, alone or in combination with olaparib, for recurrent epithelial ovarian cancer. <i>Gynecol Oncol.</i> 2025;194:41-47. 14. Garje R, Ravindra A, Rahim B, et al. Avelumab and taxol chemotherapy in platinum-refractory or ineligible metastatic urothelial carcinoma (AVETAX trial). <i>Urologic Oncology: Seminars and Original Investigations.</i> 2025. 15. Georgy JT, Regi SS, Georgy RV, et al. Low-Dose Nivolumab with Induction Chemotherapy Improves Responses and Conversion to Radical Therapy in Locally Advanced/Unresectable HNSCC: An Ambispective Real-world Study [PRE-PRINT]. <i>Research Square.</i> 2025. 16. Hoeijmakers LL, Rozeman EA, Lopez-Yurda M, et al. Durable responses upon short-term addition of targeted therapy to anti-PD1 in advanced melanoma patients: 5-year progression-free and overall survival update of the IMPemBra trial. <i>European Journal of Cancer.</i> 2025;222:115431. 17. Horisaki K, Yoshikawa S, Omata W, Tsutsumida A, Kiyohara Y. Comparison of efficacy and adverse events by treatment cycles of nivolumab and ipilimumab in Japanese melanoma patients: A single-centre, retrospective study. <i>J Dermatol.</i> 2025;52(4):651-662. 18. Jimenez-Labaig P, Mohamed F, Tan NJI, et al. Expanding access to cancer immunotherapy: a systematic review of low-dose PD-(L)1 inhibitor strategies. <i>Eur J Cancer.</i> 2025;225:115564. 19. Kumar A, Kapoor A, Noronha V, et al. Efficacy and Safety of Low-Dose Nivolumab in Treatment of Advanced Solid Tumors: A Retrospective Audit from Resource-Constrained Settings. <i>South Asian J.</i> 2025;14(1):70-76. 20. Long GV, Larkin J, Schadendorf D, et al. Pooled Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone in Patients With Advanced Melanoma. <i>J Clin Oncol.</i> 2025;43(8):938-948. 21. Long GV, Tang H, Desai K, et al. Pretreatment and on-treatment ctDNA and tissue biomarkers predict recurrence in patients with stage IIIB-D/IV

Reason for exclusion	Citation
	melanoma treated with adjuvant immunotherapy: CheckMate 915. <i>J Immunother Cancer</i>. 2025;13(7). 22. Menzies AM, Salman P, Frontera OA, et al. Administration of nivolumab plus ipilimumab: Infusion of the fixed-ratio combination versus sequential infusions in two randomized controlled trials of metastatic melanoma (CheckMate 742) and renal cell carcinoma (CheckMate 800). <i>Cancer</i>. 2025;131(14):e35962. 23. Motzer RJ, Bex A, Russo P, et al. Adjuvant Nivolumab for Localized Renal Cell Carcinoma at High Risk of Recurrence After Nephrectomy: Part B of the Randomized, Placebo-Controlled, Phase III CheckMate 914 Trial. <i>J Clin Oncol</i>. 2025;43(2):189-200. 24. Oppelt PJ, Puram SV, Liu J, Ley JC, Adkins D. Tazemetostat, a Selective EZH2 Inhibitor, in Combination with Pembrolizumab for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: A Phase 1 Trial. <i>Cancers (Basel)</i>. 2025;17(3):27. 25. Sekar P, Ashok Kumar A, Hughes I, Mason R, Dzienis M. The safety of extended dosing pembrolizumab when compared to traditional dosing: A review and meta-analysis of retrospective studies. <i>Lung Cancer</i>. 2025;204:108585. 26. Slee AL, Coutsouvelis J, Tong B, Poole S, Zalberg J. A cost comparison of pembrolizumab: Fixed and weight-based dosing. <i>J Oncol Pharm Pract</i>. 2025;31(5):687-692. 27. Smeenk MM, van Diessen JNA, Boellaard TN, et al. Tremelimumab plus Durvalumab prior to Chemoradiotherapy in Unresectable, Locally Advanced Non-Small Cell Lung Cancer: The Induction Trial. <i>Clin Cancer Res</i>. 2025;31(6):1037-1046. 28. van Rijssen L, Nagtegaal IEC, Ploos van Amstel FK, et al. Safety of accelerated infusion of nivolumab and pembrolizumab. <i>Eur J Cancer</i>. 2025;220:115373. 29. Vaquera-Alfaro HA, Montelongo-Cepeda JE, Vega-Mateos A, et al. Low-Dose Anti-PD1 Immune Checkpoint Inhibitors in Relapsed/Refractory Hodgkin Lymphoma: A Systematic Review. <i>JCO Glob Oncol</i>. 2025;11:e2400538. 30. Williamson J, Fadlullah MZH, Kovacs-Bankowski M, et al. Dramatic Responses to High-Dose Ipilimumab Plus Temozolomide After Progression on Standard- or Low-Dose Ipilimumab in Advanced Melanoma. <i>Curr Oncol</i>. 2025;32(3):28. 31. Yamada A, Choules MP, Brightman FA, et al. A multiple-model-informed drug-development approach for optimal regimen selection of an oncolytic virus in combination with pembrolizumab. <i>CPT Pharmacometrics Syst Pharmacol</i>. 2025;14(3):572-582. 32. ABIMMUNE: A Phase I/II study evaluating the safety and clinical activity of anti-PDL1 (Durvalumab [MEDI4736]) + Anti CTLA-4 (Tremelimumab) antibodies administered in combination with stereotactic body radiotherapy (SBRT) in patients with metastatic squamous cell carcinoma of head and neck, lung, oesophagus, cervix, vagina, vulva or anus. EUCT number: 2024-514920-18-00. Protocol code: CSET N°2016/2454. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-514920-18-00. Accessed 2026 May 29. 33. Clinical trial to compare subcutaneous pembrolizumab given with hyaluronidase to intravenous pembrolizumab in patients with newly diagnosed stage IV (non-small cell) lung cancer who are PD-L1 Strong. <i>A phase 3 randomized, open-label clinical study to evaluate the pharmacokinetics and safety of subcutaneous pembrolizumab coformulated with hyaluronidase (MK-3475A) versus intravenous pembrolizumab, in the first-line treatment of participants with metastatic non-small cell lung cancer with pd-l1 tps 50% or greater - MK-3475A-F84</i>. 2024. 34. Dostarlimab for locally advanced or metastatic cancer (non-colorectal/non-endometrial) with tumor dMMR/MSI. NCT06333314. <i>Dostarlimab as first-line treatment for patients with dMMR/MSI (Non-colorectal/Non-endometrial) locally advanced or metastatic cancer: a randomized phase 2 trial (Cohort Pan-MSI ACSE) with crossover in the standard arm at progression</i>. 2024. 35. Durvalumab (MEDI4736) plus tremelimumab in resectable, locally advanced squamous cell carcinoma of the oral cavity: a window of opportunity

Reason for exclusion	Citation
	study. EUCT number: 2024-511511-25-0. Protocol code: ESR-16-12192. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-511511-25-00. Accessed 2026 May 29. 36. NEOSTART Study - neoadjuvant pembrolizumab in patients with high risk, stage iib/iic cutaneous melanoma: a single arm proof of concept phase iia study. EUCT number: 2024-519573-19-00. Protocol code: 2024/880. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-519573-19-00. Accessed 2026 May 29. 37. Pembrolizumab and olaparib in recurrent/metastatic, platinum resistant nasopharyngeal cancer. POINT study. EUCT number: 2024-511901-52-00. Protocol code:POINT. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-511901-52-00. Accessed 2026 May 29. 38. Phase 1b/ii trial of checkpoint inhibitor (pembrolizumab and anti pd-1 antibody) plus standard imrt in hpv induced stage iii squamous cell carcinoma of anus. EUCT number: 2024-515369-33-00. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-515369-33-00. Accessed 2026 May 29. 39. A Phase 2 BIOMarker driven trial with Nivolumab and Ipilimumab or VEGFR tKi in naïve metastatic Kidney cancer. EUCT number:2024-520045-23-00. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-520045-23-00. Accessed 2026 May 29. 40. A Phase IB/II, 2-Stage, open-label, multicenter study to determine the efficacy and safety of durvalumab (MEDI4736) + paclitaxel and durvalumab (MEDI4736) in combination with novel oncology therapies with or without paclitaxel for first-line metastatic triple negative breast cancer (BEGONIA). EUCT number:2024-511646-40-00. Protocol code:D933LC00001. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-511646-40-00. Accessed 2026 May 29. 41. Phase II study of nivolumab (Group 1) and nivolumab plus relatlimab (Group 2) in patients with locally advanced/ metastatic squamous cell carcinoma of the skin. EUCT number: 2024-513637-20-00. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-513637-20-00. Accessed 2026 May 29. 42. A phase II, open label, randomized trial of ipilimumab and nivolumab with concurrent intracranial stereotactic radiotherapy vs. ipilimumab and nivolumab alone in patients with melanoma brain metastases. EUCT number: 2024-518545-13-00. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-518545-13-00. Accessed 2026 May 29. 43. A phase IIIb, single arm, open-label, multicentre study of durvalumab in combination with chemotherapy for the first line treatment for patients with advanced biliary tract cancers (TOURMALINE). EUCT number: 2022-502043-35-01. Protocol code:D4191C00140. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2022-502043-35-01. Accessed 2026 May 29. 44. PREventing Second Cancers With DOSTARlimab. (PREDOSTAR). A multicenter, open-label, randomized phase ii study aiming to assess the clinical impact of dostarlimab on occurrence of second primary cancer in patients with cured primary cancer. NCT05855811. 2023. <i>ClinicalTrials.gov</i>. 2024. 45. A randomized open-label phase II study on the effect of durvalumab and tremelimumab combined with personalized SIRT (p-SIRT), standard-dose SIRT (sd-SIRT) or immunotherapy followed by on-demand loco-regional SIRT (od-SIRT) in non-resectable hepatocellular carcinoma (HCC) patients. EUCT number: 2024-515127-11-00. Protocol code: ESR-19-14451. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-515127-11-00. Accessed 2026 May 29. 46. A randomized, double-blind, placebo-controlled, phase III study evaluating the efficacy and safety of pembrolizumab plus platinum-based doublet chemotherapy with or without canakinumab as first line therapy for locally advanced or metastatic non-squamous and squamous non-small cell lung cancer subjects (CANOPY-1). EUCT number: 2024-511490-29-00. Protocol code: CACZ885U2301. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-511490-29-00. Accessed 2026 May 29.

Reason for exclusion	Citation
	47. A randomized, run-in, phase II study of nivolumab combined with ipilimumab and oral decitabine/cedazuridine (ASTX727) or nivolumab combined with ipilimumab in melanoma and NSCLC patients resistant to anti-PD-1/PD-L1. EUCT number: 2024-518891-29-00. Protocol code: NIBIT-ML-1. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-518891-29-00. Accessed 2026 May 29. 48. A study of dostarlimab vs placebo after chemoradiation in adult participants with locally advanced unresected head and neck squamous cell carcinoma. CTRI/2024/06/068865. <i>A randomized, double-blind, placebo-controlled phase 3 study to evaluate dostarlimab as sequential therapy after chemoradiation in participants with locally advanced unresected head and neck squamous cell carcinoma - JADE</i>. 2024. 49. Study of imdusiran (AB-729) in combination with intermittent dosing of durvalumab in subjects with chronic hbv infection. NCT06245291. <i>A phase 2a, open-label multiple dose study evaluating the safety, tolerability, and pharmacodynamics of imdusiran (AB-729) in combination with intermittent dosing of durvalumab, a pd-l1 monoclonal antibody, in subjects with chronic hbv infection</i>. 2024. 50. A two-part randomized, phase 3 study of combinations of cemiplimab (Anti- PD-1 Antibody) and platinum-based doublet chemotherapy in first-line treatment of patients with advanced or metastatic non-small cell lung cancer. EUCT number: 2024-515051-38-00. Protocol code: R2810-ONC-16113. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-515051-38-00. Accessed 2026 May 29. 51. Algazi A, Papadopoulos KP, Tsai F, et al. Safety and clinical activity of durvalumab combined with tremelimumab in recurrent/metastatic head and neck squamous cell carcinoma: a multicenter phase I study. <i>ESMO open</i>. 2024;9(8):103646. 52. Anonymous. Phase I/IIa dose finding study of triplet regimen of relatlimab ipilimumab and nivolumab in first line therapy of metastatic melanoma (TRINITY). <i>ClinicalTrial.gov</i>. 2024;08. 53. Anonymous. A value-driven study on reducing immune checkpoint inhibitor dosing frequency in advanced cancers: phase 2 randomized trial (VALUE-CHECK). <i>ClinicalTrial.gov</i>. 2024;15. 54. Brahmer JR, Long GV, Hamid O, et al. Safety profile of pembrolizumab monotherapy based on an aggregate safety evaluation of 8937 patients. <i>European Journal of Cancer</i>. 2024;199:113530. 55. Bryant AK, Lewy JR, Bressler RD, et al. Projected environmental and public health benefits of extended-interval dosing: an analysis of pembrolizumab use in a US national health system. <i>Lancet Oncol</i>. 2024;25(6):802-810. 56. Burotto M, Zvirbule Z, Alvarez R, et al. Brief report: updated data from IMscin001 part 2, a randomized phase iii study of subcutaneous versus intravenous atezolizumab in patients with locally advanced or metastatic NSCLC. <i>J Thorac Oncol</i>. 2024;19(10):1460-1466. 57. Colunga-Pedraza PR, Vaquera-Alfaro HA, Guzman-Martinez Z, et al. Optimizing resources: low-dose nivolumab combinations in the management of relapsed/refractory Hodgkin lymphoma. <i>Ann Hematol</i>. 2024;103(12):5607-5614. 58. Corbaux P, Freyer G, Glehen O, et al. Intraperitoneal nivolumab after debulking surgery and hyperthermic intraperitoneal chemotherapy in advanced ovarian cancer: a phase i study with expansion cohort. <i>Clin Cancer Res</i>. 2024;30(16):3438-3446. 59. Elez E, Cubillo A, Alfonso PG, et al. Binimetinib in combination with nivolumab or nivolumab and ipilimumab in patients with previously treated microsatellite-stable metastatic colorectal cancer with RAS mutations in an open-label phase 1b/2 study. <i>BMC Cancer</i>. 2024;24(1):446. 60. Elijah J, Puzanov I, Cresanti B, et al. Evaluation of safety outcomes between nivolumab regimens with differing dosing patterns. <i>J Oncol Pharm Pract</i>. 2024;10781552241264817. 61. Gok V, Aydin F, Ozcan A, et al. The effect of nivolumab in pediatric malignant tumors: a single center experience with nine children. <i>UHOD - Uluslararası Hematoloji-Onkoloji Dergisi</i>. 2024;34(4):184-94.

Reason for exclusion	Citation
	62. Grimm MO, Schostak M, Grun CB, et al. Nivolumab + ipilimumab as immunotherapeutic boost in metastatic urothelial carcinoma: a nonrandomized clinical trial. <i>JAMA Oncology</i>. 2024;10(6):755-764. 63. Huang WK, Tang YJ, Wu CE, et al. Real-world effectiveness and prognostic factors of durvalumab plus chemotherapy in a multicentric cohort with advanced biliary tract cancer. <i>Oncologist</i>. 2024;20:20. 64. Kao CH, Lin H, Liu CT, et al. Real-world efficacy and safety of low-dose pembrolizumab in patients with advanced and refractory gynecologic cancers. <i>J Formos Med Assoc</i>. 2024;123(4):487-495. 65. Khushalani NI, Ott PA, Ferris RL, et al. Final results of urelumab, an anti-CD137 agonist monoclonal antibody, in combination with cetuximab or nivolumab in patients with advanced solid tumours. <i>J Immunother Cancer</i>. 2024;12(3):07. 66. Kicken MP, Deenen MJ, Moes D, et al. An evidence-based rationale for dose de-escalation of subcutaneous atezolizumab. <i>Target</i>. 2024;19(5):779-787. 67. Lai KC, Chen YH, Hung YP, Chiang NJ, Chen MH, Chen SC. Efficacy and safety of durvalumab rechallenge in advanced hepatocellular carcinoma patients refractory to prior anti-PD-1 therapy. <i>Hepatol Int</i>. 2024;18(6):1804-1814. 68. Lakhani NJ, Papadopoulos KP, Johnson ML, et al. First-in-human dose-escalation study of fianlimab, an antilymphocyte activation gene-3 antibody, with cemiplimab in patients with advanced malignancies. <i>Clin Cancer Res</i>. 2024;30(24):5601-5611. 69. Long GV, Carlino MS, McNeil C, et al. Pembrolizumab versus ipilimumab for advanced melanoma: 10-year follow-up of the phase III KEYNOTE-006 study. <i>Ann Oncol</i>. 2024;35(12):1191-1199. 70. Melero I, Yau T, Kang YK, et al. Nivolumab plus ipilimumab combination therapy in patients with advanced hepatocellular carcinoma previously treated with sorafenib: 5-year results from CheckMate 040. <i>Ann Oncol</i>. 2024;35(6):537-548. 71. Murashima Y, Yamamoto S, Hirose T, et al. Efficacy and safety of salvage-line nivolumab monotherapy for advanced esophageal squamous cell carcinoma: comparison of 240 mg versus 480 mg doses. <i>J Gastrointest Cancer</i>. 2024;55(3):1345-1351. 72. Nagase T, Shima O, Maruhana N, et al. Analysis and evaluation of factors contributing to the occurrence of immune-related adverse events with immune checkpoint inhibitors. <i>Pharmazie</i>. 2024;79(7):163-168. 73. Necchi A, Ramlau R, Falcon Gonzalez A, et al. Derazantinib alone and with atezolizumab in metastatic urothelial carcinoma with activating FGFR aberrations. <i>JNCI Cancer Spectr</i>. 2024;8(3):30. 74. Nguyen CB, Reimers MA, Perera C, et al. Evaluating immune checkpoint blockade in metastatic castration-resistant prostate cancers with deleterious cdk12 alterations in the phase 2 IMPACT trial. <i>Clin Cancer Res</i>. 2024;30(15):3200-3210. 75. Oaknin A, Moore K, Meyer T, et al. Nivolumab with or without ipilimumab in patients with recurrent or metastatic cervical cancer (CheckMate 358): a phase 1-2, open-label, multicohort trial. <i>Lancet Oncol</i>. 2024;25(5):588-602. 76. Perez-Lamas L, de Paz Arias R, Diaz RMA, et al. Hepatotoxicity as dose-limiting toxicity of the combination of bosutinib and atezolizumab in patients with chronic myeloid leukemia. Results of the ZEROLMC study. <i>Ann Hematol</i>. 2024;103(10):4045-4055. 77. Pierre C, Le Guen Y, Giordanengo C, et al. Safety and efficacy of immunotherapy using a double-dose regimen in advanced non-small cell lung cancer (NSCLC): results of IDEE study. <i>Transl Lung Cancer Res</i>. 2024;13(8):1807-1815. 78. Pouw JEE, Hashemi SMS, Huisman MC, et al. First exploration of the on-treatment changes in tumor and organ uptake of a radiolabeled anti PD-L1 antibody during chemoradiotherapy in patients with non-small cell lung cancer using whole body PET. <i>J Immunother Cancer</i>. 2024;12(2):01.

Reason for exclusion	Citation
	79. Puszkiel A, Bianconi G, Pasquiers B, et al. Extending the dosing intervals of nivolumab: model-based simulations in unselected cancer patients. <i>Br J Cancer</i>. 2024;130(11):1866-1874. 80. Riess JW, Lara MS, Lopez de Rodas M, et al. Immune cell dynamics in egfr-mutated nscl treated with afatinib and pembrolizumab: results from a phase IB study. <i>JTO Clin Res Rep</i>. 2024;5(10):100706. 81. Smithy JW, Kalvin HL, Ehrich FD, et al. Early on-treatment assessment of t cells, cytokines, and tumour dna with adaptively dosed nivolumab + ipilimumab: final results from the phase 2 ADAPT-IT study. <i>Clin Cancer Res</i>. 2024;30(16):3407-3415. 82. Tasaki Y, Ito N, Mimura Y, et al. Real-world data on efficacy/safety and economic impact of nivolumab administered every 2 and 4 weeks among Japanese patients. <i>Asia Pac J Clin Oncol</i>. 2024;20(4):515-521. 83. Truong J, Yeung SST, Kletas V, de Lemos M, Schaff K, Nakashima L. Utilization and toxicity patterns of 2-weekly (Q2W) versus 4-weekly (Q4W) nivolumab for treatment of adjuvant and metastatic melanoma at BC cancer. <i>J Oncol Pharm Pract</i>. 2024;30(6):1016-1022. 84. Wheatley DA, Berardi R, Climent Duran MA, et al. First-line avelumab plus chemotherapy in patients with advanced solid tumors: results from the phase Ib/II JAVELIN chemotherapy medley Study. <i>Cancer Res Commun</i>. 2024;4(6):1609-1619. 85. White O, Dent S, Westbrook K, Lee HJ, Yang C, Moore HN. Assessment of efficacy and safety of dose-dense doxorubicin and cyclophosphamide (ddAC) in combination with immunotherapy in early-stage triple-negative breast cancer. <i>Breast Cancer Res Treat</i>. 2024;207(1):179-185. 86. Adjuvant MK-7684A vs pembrolizumab for resected high-risk melanoma. a phase 3, randomized, double-blind, active-comparator-controlled clinical study of adjuvant MK-7684A (Vibostolimab With Pembrolizumab) versus adjuvant pembrolizumab in participants with high-risk Stage II-IV melanoma (KEYVIBE-010) - MK7684A-010/KEYVIBE-010. 2023. 87. CA209-8KX Phase I/II pharmacokinetic multi-tumor study of subcutaneous formulation of nivolumab monotherapy. EUCT number: 2023-503554-12-00. Protocol code: CA209-8KX. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-503554-12-00. Accessed 2026 May 29. 88. Evaluation of low dose immunotherapy for lung cancer. <i>Evaluation of low dose nivolumab with neoadjuvant chemotherapy in non small cell lung cancer - ELoN</i>. 2023. 89. An Open-label, Multicenter, phase 2 study to evaluate the efficacy and safety of pembrolizumab plus lenvatinib in combination with belzutifan in multiple solid tumours. EUCT number: 2023-503905-12-00. Protocol code: MK-6482-016. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-503905-12-00. Accessed 2026 May 29. 90. An open-label, prospective, multi-center clinical trial to evaluate the efficacy and safety of TheraSphere™ followed by durvalumab (Imfinzi®) with tremelimumab (Imjudo®) for hepatocellular carcinoma (HCC). EUCT number: 2023-508945-41-00. Protocol code: S2472. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-508945-41-00. Accessed 2026 May 29. 91. Pembrocabosarc: Combination of pembrolizumab and cabozantinib in patients with advanced sarcomas. EUCT number: 2023-509496-16-00. Protocol code: IB 2020-02. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-509496-16-00. Accessed 2026 May 29. 92. A pharmacokinetics (PK) study to compare GME751 (proposed pembrolizumab biosimilar) and United States (US)-licensed and European Union (EU)-approved Keytruda® in participants with stage II and III skin cancer requiring adjuvant treatment (therapy applied after initial treatment of cancer to suppress the regrowth of tumor) with pembrolizumab. EUCT number: 2023-506881-30-00. Protocol code: CGME751A12101. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-506881-30-00. Accessed 2026 May 29.

Reason for exclusion	Citation
	93. A phase 1 dose finding and phase 2 randomized, open-label trial to evaluate the safety and clinical activity of immunoradiotherapy combinations as a treatment option for subjects with metastatic solid tumours. EUCT number: 2023-508529-29-00. Protocol code: GCT1042-02. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-508529-29-00. Accessed 2026 May 29. 94. A phase 1/2 open-label, umbrella platform design study of investigational agents with or without pembrolizumab (MK-3475) and/or chemotherapy in participants with advanced esophageal cancer previously exposed to PD-1/PD-L1 treatment (KEYMAKER-U06): substudy 06B. EUCT number: 2023-505189-26-00. Protocol code: MK-3475-06B. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-505189-26-00. Accessed 2026 May 29. 95. A phase 1b/2 study to evaluate the efficacy and safety of investigational agents as monotherapy or in combination with pembrolizumab for the treatment of participants with pd-1/l1-refractory extensive-stage small cell lung cancer in need of second-line therapy (KEYNOTE-B98). EUCT number: 2023-507687-38-00. Protocol code: MK-3475-B98. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-507687-38-00. Accessed 2026 May 29. 96. A phase 2 study of tremelimumab (day 1 only), durvalumab (MEDI4736) and trans-arterial catheter chemoembolization (TACE) in patients with advanced hepatocellular carcinoma (HCC). EUCT number: 2023-510117-26-00. Protocol code: UCDCRC/23/06. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-510117-26-00. Accessed 2026 May 29. 97. A phase 2, single-arm, open-label study with dostarlimab monotherapy in participants with untreated stage II/III dMMR/MSI-H locally advanced rectal cancer. EUCT number: 2023-509583-22-00. Protocol code: 219369. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-509583-22-00. Accessed 2026 May 29. 98. A phase 3 randomized, controlled study of IMC-F106C plus nivolumab versus nivolumab regimens in HLA-A*02:01-positive participants with previously untreated advanced melanoma (PRISM-MEL-301). EUCT number: 2023-505306-42-01. Protocol code: IMC-F106C-301. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-505306-42-01. Accessed 2026 May 29. 99. A phase 3 trial of fianlimab (anti-LAG-3) and cemiplimab versus pembrolizumab in the adjuvant setting in patients with completely resected high-risk melanoma. EUCT number: 2022-501576-25-00. Protocol code: R3767-ONC-2055. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2022-501576-25-00. Accessed 2026 May 29. 100. A phase 3, open-label, randomized, noninferiority trial of the subcutaneous formulation of nivolumab versus intravenous nivolumab in participants with advanced or metastatic clear cell renal cell carcinoma who had received prior systemic therapy. EUCT number: 2023-503280-42-00. Protocol code: CA209-67T. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-503280-42-00. Accessed 2026 May 29. 101. A phase 3, randomized, double-blind, placebo-controlled, multicenter study comparing niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in participants whose disease has remained stable or responded to first-line platinum based chemotherapy with pembrolizumab for stage IIIB/IIIC or IV non-small cell lung cancer (ZEAL 1L). EUCT number: 2023-508443-40-00. Protocol code: 213400. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-508443-40-00. Accessed 2026 May 29. 102. Phase I/II, open-label, multicenter study to evaluate the safety, tolerability, and preliminary efficacy of durvalumab monotherapy or durvalumab in combination with tremelimumab in pediatric patients with advanced solid tumors and hematological malignancies. EUCT number: 2023-510424-68-00. Protocol code: D419EC00001. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-510424-68-00. Accessed 2026 May 29. 103. Phase IB study with the combination of LB-100 (PP2A inhibitor) and atezolizumab (PD-L1 INHIBI-TOR) in metastatic colorectal cancer patients: the

Reason for exclusion	Citation
	CoLBA trial. EUCT number: 2023-505534-98-00. Protocol code: N22CLB. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-505534-98-00. 104. Phase II study of Atezolizumab plus Tiragolumab in combination with chemoradiotherapy in localized squamous cell carcinoma of the anal canal. EUCT number: 2023-509485-38-00. Protocol code: GEMCAD - 2103//MO4. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-509485-38-00. Accessed 2026 May 29. 105. A phase II, multicenter, randomized, open label, parallel-arm, umbrella study of avelumab (MSB0010718C) in combination with other antitumor agents as a maintenance treatment in participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy (JAVELIN Bladder Medley). EUCT number: 2023-510139-12-00. Protocol code: MS100070_0119. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-510139-12-00. Accessed 2025 Oct 1. 106. A phase II, randomized, double-blind study of atezolizumab plus tiragolumab and atezolizumab plus placebo as first-line treatment in patients with recurrent/metastatic PD-L1-positive squamous cell carcinoma of the head and neck. EUCT number: 2023-509449-10-00. Protocol code: BO42533. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-509449-10-00. Accessed 2026 May 29. 107. A phase II, single-arm, open-label study evaluating the safety and pharmacokinetics of the IV fixed-dose combination (IV FDC) of tiragolumab and atezolizumab in participants with locally advanced, recurrent or metastatic solid tumors. EUCT number: 2023-508489-14-00. Protocol code: GO44096. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-508489-14-00. Accessed 2026 May 29. 108. A randomized, double-blind, phase III clinical trial of neoadjuvant chemotherapy with atezolizumab or placebo in patients with triple-negative breast cancer followed by adjuvant continuation of atezolizumab or placebo “GeparDouze.” EUCT number: 2023-508472-11-00. Protocol code: NSABP B-59/GBG 96. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-508472-11-00. Accessed 2026 May 29. 109. Randomized, double-blind, placebo-controlled phase 3 study to evaluate dostarlimab as sequential therapy after chemoradiation in participants with locally advanced unresected head and neck squamous cell carcinoma. EUCT number: 2023-508613-17-00. Protocol code: 221530. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-508613-17-00. Accessed 2026 May 29. 110. A randomized, phase 2, double-blind study to evaluate the efficacy of dostarlimab plus chemotherapy versus pembrolizumab plus chemotherapy in metastatic non-squamous non-small cell lung cancer. EUCT number: 2023-505894-33-00. Protocol code: 213403. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-505894-33-00. Accessed 2026 May 29. 111. Roll over study for patients who have completed a previous oncology study with durvalumab and are judged by the investigator to clinically benefit from continued treatment. EUCT number: 2023-507337-22-00. Protocol code: D4191C00137 ROSY-D. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-507337-22-00. 112. Single cell characterization of persistent cells upon treatment with durvalumab (MEDI4736) with or without tremelimumab in MSS and MSI colorectal and endometrial tumors: the SERPENTINE clinical trial (Single cell pRoFiling PErsistaNce To ImmuNoThErapy). EUCT number: 2023-509619-10-00. Protocol code: ESR 21-21165. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-509619-10-00. Accessed 2025 Oct 1. 113. A study of ZL-1218 with or without pembrolizumab in subjects with advanced solid tumor cancers to find a suitable dose and to test how different doses of these medications can be tolerated by the body. EUCT number: 2022-503102-20-00. Protocol code: ZL-1218-001. 2023; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2022-503102-20-00. Accessed 2026 May 29. 114. Aguiar-Ibanez R, Scherrer E, Grebennik D, et al. Time and productivity loss associated with immunotherapy infusions for the treatment of melanoma in the United States: a survey of health care professionals and patients. <i>BMC Health Serv Res</i>. 2023;23(1):136.

Reason for exclusion	Citation
	115. Anonymous. Cemiplimab/PEG-Interferon-alpha combination for advanced cutaneous squamous cell carcinoma (aCSCC). <i>ClinicalTrials.gov</i>. 2023. 116. Anonymous. Nivolumab dose optimization in patients with a complete, partial or stable response. <i>ClinicalTrials.gov</i>. 2023;04. 117. Anonymous. A phase 2 open-label, two-cohort study to evaluate patient preference for nivolumab + relatlimab fixed-dose combination subcutaneous versus nivolumab + relatlimab fixed-dose combination intravenous and nivolumab subcutaneous versus nivolumab intravenous in participants with melanoma. <i>ClinicalTrials.gov</i>. 2023;20. 118. Bendell J, LoRusso P, Overman M, et al. First-in-human study of oleclumab, a potent, selective anti-CD73 monoclonal antibody, alone or in combination with durvalumab in patients with advanced solid tumors. <i>Cancer Immunol Immunother</i>. 2023;72(7):2443-2458. 119. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. <i>J Clin Oncol</i>. 2023;41(4):715-723. 120. Burotto M, Zvirbulis Z, Mochalova A, et al. IMscin001 part 2: a randomised phase III, open-label, multicentre study examining the pharmacokinetics, efficacy, immunogenicity, and safety of atezolizumab subcutaneous versus intravenous administration in previously treated locally advanced or metastatic non-small-cell lung cancer and pharmacokinetics comparison with other approved indications. <i>Ann Oncol</i>. 2023;34(8):693-702. 121. Cantini L, Paoloni F, Pecci F, et al. Safety of extended interval dosing immune checkpoint inhibitors: a multicenter cohort study. <i>J Natl Cancer Inst</i>. 2023;115(7):796-804. 122. Dunkel IJ, Doz F, Foreman NK, et al. Nivolumab with or without ipilimumab in pediatric patients with high-grade CNS malignancies: safety, efficacy, biomarker, and pharmacokinetics-CheckMate 908. <i>Neuro-oncol</i>. 2023;25(8):1530-1545. 123. Grimm MO, Grun CB, Niegisch G, et al. Tailored immunotherapy approach with nivolumab with or without ipilimumab in patients with advanced transitional cell carcinoma after platinum-based chemotherapy (TITAN-TCC): a multicentre, single-arm, phase 2 trial. <i>Lancet Oncol</i>. 2023;24(4):347-359. 124. Hanna L, Moffat GT, Hopman W, Gaudreau PO, Fung AS. A study of the efficacy and toxicity outcomes of extended durvalumab dosing in patients with stage III unresectable non-small cell lung cancer (NSCLC) during the COVID-19 pandemic. <i>Cancer Treat Res Commun</i>. 2023;34:100678. 125. Ito T, Kaku-Ito Y, Ohno F, Nakahara T. A real-world study on the safety profile of extended-interval dosing of immune checkpoint inhibitors for melanoma: a single-center analysis in Japan. <i>Front Med (Lausanne)</i>. 2023;10:1293397. 126. Kenniscentrum voor de Gezondheidszorg [Belgian Health Care Knowledge Centre]. PULSE: maintenance pembrolizumab at usual or low dose in non-squamous lung cancer: a non-inferiority study (KCE-231395). 2023; https://kce.fgov.be/en/kce-trials/funded-trials/pulse-maintenance-pembrolizumab-at-usual-or-low-dose-in-non-squamous-lung-cancer-a-non-inferiority. Accessed 2026 May 29. 127. Kuah CY, Monfries R, Quartagno M, Seckl MJ, Ghorani E. What is the optimal duration, dose and frequency for anti-PD1 therapy of non-small cell lung cancer? <i>Therapeutic Advances in Medical Oncology</i>. 2023;15:17588359231210271. 128. Lai-Kwon J, Jacques S, Carlino M, et al. Efficacy of ipilimumab 3 mg/kg following progression on low-dose ipilimumab in metastatic melanoma. <i>Eur J Cancer</i>. 2023;186:12-21. 129. Lim K, Abegesah A, Fan C, et al. Population pharmacokinetics and exposure-response analysis of tremelimumab 300 mg single dose combined with durvalumab 1500 mg Q4W (STRIDE) in patients with unresectable hepatocellular carcinoma. <i>J Clin Pharmacol</i>. 2023;63(11):1221-1231. 130. Marolleau S, Mogenet A, Boeri C, Hamimed M, Ciccolini J, Greillier L. Killing a fly with a sledgehammer: atezolizumab exposure in real-world lung cancer patients. <i>CPT Pharmacometrics Syst Pharmacol</i>. 2023;12(11):1795-1803.

Reason for exclusion	Citation
	131. McLouth LE, Zheng Y, Smith S, et al. Patient-reported tolerability of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon alfa-2b for resected high-risk stage III-IV melanoma in phase III trial E1609. <i>Qual Life Res.</i> 2023;32(1):183-196. 132. Merrick S, Nankivell M, Quartagno M, et al. REFINE (REDuced Frequency ImmuNE checkpoint inhibition in cancers): a multi-arm phase II basket trial testing reduced intensity immunotherapy across different cancers. <i>Contemp Clin Trials.</i> 2023;124:107030. 133. Nubel C, Amaral T, Leiter U, Flatz L, Forschner A. Outcome and treatment-related adverse events of combined immune checkpoint inhibition with flipped dosing in a real-world cohort of 79 patients with metastasized melanoma. <i>Front.</i> 2023;13:1256800. 134. Oliveira G, Egloff AM, Afeyan AB, et al. Preexisting tumor-resident T-cells with cytotoxic potential associate with response to neoadjuvant anti-PD-1 in head and neck cancer. <i>Science Immunology.</i> 2023;8(87) (no pagination). 135. Peer CJ, Schmidt KT, Arisa O, et al. In Silico Re-optimization of atezolizumab dosing using population pharmacokinetic simulation and exposure-response simulation. <i>J Clin Pharmacol.</i> 2023;63(6):672-680. 136. Psyrri A, Fayette J, Harrington K, et al. Durvalumab with or without tremelimumab versus the EXTREME regimen as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck: KESTREL, a randomized, open-label, phase III study. <i>Ann Oncol.</i> 2023;34(3):262-274. 137. Sangro B, Yau T, El-Khoueiry AB, et al. Exposure-response analysis for nivolumab plus ipilimumab combination therapy in patients with advanced hepatocellular carcinoma (CheckMate 040). <i>Clin Transl Sci.</i> 2023;16(8):1445-1457. 138. Schadendorf D, Tawbi H, Lipson EJ, et al. Health-related quality of life with nivolumab plus relatlimab vs. nivolumab monotherapy in patients with previously untreated unresectable or metastatic melanoma: RELATIVITY-047 trial. <i>Eur J Cancer.</i> 2023;187:164-173. 139. Song X, Kelley RK, Green M, et al. Modeling of proliferating CD4 and CD8 T-cell Changes to tremelimumab exposure in patients with unresectable hepatocellular carcinoma. <i>Clin Pharmacol Ther.</i> 2023;114(4):874-882. 140. Song X, Kelley RK, Khan AA, et al. Exposure-response analyses of tremelimumab monotherapy or in combination with durvalumab in patients with unresectable hepatocellular carcinoma. <i>Clin Cancer Res.</i> 2023;29(4):754-763. 141. Strauss J, Deville JL, Sznol M, et al. First-in-human phase Ib trial of M9241 (NHS-IL12) plus avelumab in patients with advanced solid tumors, including dose expansion in patients with advanced urothelial carcinoma. <i>J Immunother Cancer.</i> 2023;11(5):05. 142. van Dorp J, Pipinikas C, Suelmann BBM, et al. High- or low-dose preoperative ipilimumab plus nivolumab in stage III urothelial cancer: the phase 1B NABUCCO trial. <i>Nat Med.</i> 2023;29(3):588-592. 143. Versluis JM, Menzies AM, Sikorska K, et al. Survival update of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma in the OpACIN and OpACIN-neo trials. <i>Ann Oncol.</i> 2023;34(4):420-430. 144. Wang N, Zheng L, Li M, et al. Clinical efficacy and safety of individualized pembrolizumab administration based on pharmacokinetic in advanced non-small cell lung cancer: a prospective exploratory clinical trial. <i>Lung Cancer.</i> 2023;178:183-190. 145. Williamson J, Fadlullah MZH, Kovacs-Bankowski M, et al. Response to high dose ipilimumab plus temozolomide after progression on standard or low dose ipilimumab in advanced melanoma: a retrospective analysis. <i>Research Square.</i> 2023;01:01. 146. Woodcock VK, Chen JL, Purshouse K, et al. PemBla: a Phase 1 study of intravesical pembrolizumab in recurrent non-muscle-invasive bladder cancer. <i>BJUI Compass.</i> 2023;4(3):322-330. 147. Zhai Y, Chopra P, Kang D, Robert NJ, Zhang W. Impact of COVID-19 pandemic on non-small cell lung cancer care. <i>Curr Oncolog.</i> 2023;30(1):769-785.

Reason for exclusion	Citation
	148. Zhao Y, Roy A, Kondic AG. Time-dependent pharmacokinetics of immune checkpoint inhibitors and their implications and considerations for exposure-response analysis. <i>Current Pharmacology Reports</i>. 2023;9(6):397-403. 149. Assessing the safety of atezolizumab being directly administered to the bladder in bladder cancer patients undergoing radical cystectomy. ISRCTN15842444. https://doi.org/10.1186/ISRCTN15842444. 2022. 150. A Phase 2 clinical trial of Pembrolizumab in combination with carboplatin and cabazitaxel in aggressive variant metastatic castration resistant prostate cancer. EUCT number: 2022-501139-17-01. Protocol code: PEAPOD-FOS04/2022. 2022; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2022-501139-17-01. Accessed 2026 May 29. 151. Phase 3 study of pembrolizumab SC versus pembrolizumab IV, administered with platinum doublet chemotherapy, in 1L metastatic squamous or nonsquamous NSCLC. <i>A Randomized, Phase 3, Open-label Study to Investigate the Pharmacokinetics and Safety of Subcutaneous Pembrolizumab versus Intravenous Pembrolizumab, Administered with Platinum Doublet Chemotherapy, in the First-Line Treatment of Participants with Metastatic Squamous or Nonsquamous Non-Small-Cell Lung Cancer</i>. 2022. 152. A Randomized, Double-Blind, Phase II Study of BMS-986315 and Nivolumab in Combination with Chemotherapy Versus Nivolumab in Combination with Chemotherapy as First-line Treatment for Participants with Stage IV or Recurrent Non-Small-Cell Lung Cancer (NSCLC). EUCT number: 2022-503007-22-00. Protocol code: CA0471009. 2022; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2022-503007-22-00. Accessed 2026 May 29. 153. Anonymous. HPV 16-positive and/or HPV 18-positive recurrent and/or for patients with metastatic head and neck cancer to evaluate gx-188e dna vaccination, GX-I7 and nivolumab combination therapy open-label phase 2 clinical trial with lead-in safety cohort. <i>ClinicalTrial.gov</i>. 2022;11. 154. Anonymous. Maintenance Pembrolizumab at usual or low dose in non-squamous lung cancer: a non-inferiority study. <i>ClinicalTrial.gov</i>. 2022;20. 155. Anonymous. A phase 3, open label, randomized, non-inferiority pharmacokinetic study of nivolumab subcutaneous (Nivo SC) versus intravenous (Nivo IV) administration in participants with stage iiiia/b/c/d or stage iv adjuvant melanoma following complete resection. <i>ClinicalTrial.gov</i>. 2022;17. 156. Anonymous. A phase 3, randomized, open-label, study of subcutaneous nivolumab + relatlimab fixed-dose combination versus intravenous nivolumab + relatlimab fixed-dose combination in participants with previously untreated metastatic or unresectable melanoma. <i>ClinicalTrial.gov</i>. 2022;15. 157. Chang KC, Shao SC, Chen HY, Chan YY, Fang YF. comparative effectiveness and safety of standard-dose and low-dose pembrolizumab in patients with non-small-cell lung cancer: a multi-institutional cohort study in Taiwan. <i>Cancers (Basel)</i>. 2022;14(5):24. 158. Chen YH, Wang CC, Chen YY, Wang JH, Hung CH, Kuo YH. Low-dose nivolumab in advanced hepatocellular carcinoma. <i>BMC Cancer</i>. 2022;22(1):1153. 159. Cruz-Merino Ldl, Gion M, Cruz J, et al. Pembrolizumab in combination with gemcitabine for patients with HER2-negative advanced breast cancer: GEICAM/2015-04 (PANGAEA-Breast) study [Pre-Print]. <i>Research Square</i>. 2022. 160. Dercle L, Zhao B, Gonen M, et al. Early readout on overall survival of patients with melanoma treated with immunotherapy using a novel imaging analysis. <i>JAMA Oncology</i>. 2022;8(3):385-392. 161. Doki Y, Ueno M, Hsu CH, et al. Tolerability and efficacy of durvalumab, either as monotherapy or in combination with tremelimumab, in patients from Asia with advanced biliary tract, esophageal, or head-and-neck cancer. <i>Cancer Med</i>. 2022;11(13):2550-2560. 162. Hamuro L, Hu Z, Passarell J, et al. Exposure-response analysis to support nivolumab once every 4 weeks dosing in combination with cabozantinib

Reason for exclusion	Citation
	in renal cell carcinoma. <i>Clin Cancer Res.</i> 2022;28(8):1603-1613. 163. Higashiyama RI, Yoshida T, Yagishita S, et al. Safety implications of switching pembrolizumab dosage from 200 mg every 3 weeks to 400 mg every 6 weeks in patients with advanced NSCLC. <i>J Thorac Oncol.</i> 2022;17(10):1227-1232. 164. Jones L, Rittberg R, Leung B, et al. Alternate pembrolizumab dosing interval in advanced nsclc with pd-l1 tps $\geq$ 50%: 3 weekly compared to 6 weekly dosing. <i>Curr Oncolog.</i> 2022;29(11):8686-8692. 165. Joris S, Fontaine C, Decoster L, et al. Efficacy of a flat low dose of nivolumab in advanced cancer: a retrospective case series. <i>Anticancer Res.</i> 2022;42(3):1433-1437. 166. Kaseb AO, Hasanov E, Cao HST, et al. Perioperative nivolumab monotherapy versus nivolumab plus ipilimumab in resectable hepatocellular carcinoma: a randomised, open-label, phase 2 trial. <i>Lancet Gastroenterol Hepatol.</i> 2022;7(3):208-218. 167. Lee JY, Kim BG, Kim JW, et al. Biomarker-guided targeted therapy in platinum-resistant ovarian cancer (AMBITION; KGOG 3045): a multicentre, open-label, five-arm, uncontrolled, umbrella trial. <i>J Gynecol Oncol.</i> 2022;33(4):e45. 168. Liu SN, Marchand M, Liu X, et al. Extension of the alternative intravenous dosing regimens of atezolizumab into combination settings through modeling and simulation. <i>J Clin Pharmacol.</i> 2022;62(11):1393-1402. 169. Morimoto K, Yamada T, Morimoto Y, et al. A real-world study on the safety of the extended dosing schedule for nivolumab and pembrolizumab in patients with solid tumors. <i>Int Immunopharmacol.</i> 2022;108:108775. 170. Peer CJ, Heiss BL, Goldstein DA, Goodell JC, Figg WD, Ratain MJ. Pharmacokinetic simulation analysis of less frequent nivolumab and pembrolizumab dosing: pharmacoeconomic rationale for dose deescalation. <i>J Clin Pharmacol.</i> 2022;62(4):532-540. 171. Riudavets M, Naigeon M, Texier M, et al. Gefitinib plus tremelimumab combination in refractory non-small cell lung cancer patients harbouring EGFR mutations: the GEFTREM phase I trial. <i>Lung Cancer.</i> 2022;166:255-264. 172. Schwarze JK, Garaud S, Jansen YJL, et al. Low-dose nivolumab with or without ipilimumab as adjuvant therapy following the resection of melanoma metastases: a sequential dual cohort phase ii clinical trial. <i>Cancers (Basel).</i> 2022;14(3):28. 173. Udo K. Nivolumab in combination with cisplatin and 5-fluorouracil as induction therapy in children and adults with EBV-positive nasopharyngeal carcinoma. German Clinical Trials Register; 2022. 174. Vugmeyster Y, Griscic AM, Brockhaus B, et al. Avelumab dose selection for clinical studies in pediatric patients with solid tumors. <i>Clin Pharmacokinet.</i> 2022;61(7):985-995. 175. Wu YL, Cheng Y, Chen H, et al. Phase I/Ib dose-escalation study of avelumab in Chinese patients with advanced solid tumors. <i>Fut Oncol.</i> 2022;18(17):2053-2062. 176. DPX-survivac and pembrolizumab with and without intermittent low-dose cyclophosphamide, in subjects with relapsed/refractory diffuse large B-Cell lymphoma. <i>A phase 2b, open-label, multicenter, randomized parallel-group, two-stage, study of an immunotherapeutic treatment dpx-survivac and pembrolizumab, with and without intermittent low-dose cyclophosphamide, in subjects with relapsed/refractory diffuse large b-cell lymphoma (VITALIZE).</i> 2021. 177. A phase 3, randomized study to evaluate the efficacy and safety of pembrolizumab (MK-3475) + lenvatinib (E7080/MK-7902) + chemotherapy compared with standard of care as first-line intervention in participants with metastatic esophageal carcinoma. EUCT number: 2022-501342-29-00. Protocol code:MK 7902-014. 2021; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2022-501342-29-00. Accessed 2026 May 29.

Reason for exclusion	Citation
	178. A randomized, multicenter, phase IB/III study to investigate the pharmacokinetics, efficacy, and safety of atezolizumab subcutaneous compared with atezolizumab intravenous in patients with previously treated locally advanced or metastatic nonsmall cell lung cancer. 2021. 179. A study to evaluate the similarity in pharmacokinetics and safety of IBI310 and Ipilimumab(YERVOY) in adult healthy Chinese male volunteers. <i>compare IBI310 and Ipilimumab on the pharmacokinetics, safety, tolerance and immunogenicity of a single dose in healthy male subjects: a randomized double-blind parallel controlled phase I clinical study</i>. 2021. 180. Temozolomide and atezolizumab as second or third line for the treatment of metastatic or recurrent small cell lung cancer. <i>A randomized, multi-cohort phase II trial of temozolomide and atezolizumab as second or third line treatment for small cell lung cancer</i>. 2021. 181. Abou Dalle I, Kantarjian H, Daver N, et al. Phase II study of single-agent nivolumab in patients with myelofibrosis. <i>Ann Hematol</i>. 2021;100(12):2957-2960. 182. Ak N, Aydinler A. Nivolumab treatment for metastatic thymic epithelial tumors. <i>J Oncol Pharm Pract</i>. 2021;27(7):1710-1715. 183. Anonymous. Boosting immune response with copanlisib in locally advanced unresectable non-small cell lung cancer receiving durvalumab, A phase Ib study. <i>ClinicalTrial.gov</i>. 2021;17. 184. Anonymous. A First-in-Human, Multicenter, Phase 1/2, Open-Label Study of Vilastobart (XTX101) Monotherapy and Vilastobart (XTX101) and Atezolizumab Combination Therapy in Patients with Advanced Solid Tumors. <i>ClinicalTrial.gov</i>. 2021;06. 185. Anonymous. Maintenance ipilimumab + nivolumab post induction chemotherapy + SBRT for first line. <i>ClinicalTrial.gov</i>. 2021;22. 186. Anonymous. Nivolumab and pembrolizumab dose optimisation in solid tumours with curate.ai platform and sequential ctDNA measurements. <i>ClinicalTrial.gov</i>. 2021;14. 187. Anonymous. A Phase 1 Clinical Study to Evaluate the Bioavailability of Pembrolizumab Via Subcutaneous Injection of MK-3475A, a Formulation of Pembrolizumab With MK-5180, in Participants With Advanced Solid Tumors. <i>ClinicalTrial.gov</i>. 2021;18. 188. Anonymous. Phase 1 study of the administration of ipilimumab intra-lymphatically using the Sofusa DoseConnect™ device with nivolumab administered iv in patients with metastatic melanoma. <i>ClinicalTrial.gov</i>. 2021;08. 189. Anonymous. Phase II trial evaluating the association of peripheral blood immunologic response to therapeutic response to adjuvant treatment with immune checkpoint inhibition (ICI) in patients with newly diagnosed glioblastoma or gliosarcoma. <i>ClinicalTrial.gov</i>. 2021;25. 190. Anonymous. A randomised open-label phase III trial of reduced frequency pembrolizumab immunotherapy for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) utilising a novel multi-arm frequency-response optimisation design. <i>ClinicalTrial.gov</i>. 2021;05. 191. Anonymous. A randomized, multi-cohort phase II trial of temozolomide and atezolizumab as second or third line treatment for small cell lung cancer. <i>ClinicalTrial.gov</i>. 2021;03. 192. Baa AK, Rastogi S. Combination doxorubicin and pembrolizumab in patients with advanced anthracycline-naïve sarcoma. <i>JAMA Oncology</i>. 2021;7(3):465. 193. Bauman JE, Harris J, Uppaluri R, et al. NRG-HN003: phase I and expansion cohort study of adjuvant pembrolizumab, cisplatin and radiation therapy in pathologically high-risk head and neck cancer. <i>Cancers (Basel)</i>. 2021;13(12):09. 194. Chou CH, Hsu LF. Model-based simulation to support the extended dosing regimens of atezolizumab. <i>Eur J Clin Pharmacol</i>. 2021;77(1):87-93. 195. Do KT, Chow LQM, Reckamp K, et al. First-in-human, first-in-class, phase I trial of the fucosylation inhibitor SGN-2FF in patients with advanced solid

Reason for exclusion	Citation
	tumors. <i>Oncologist</i>. 2021;26(11):925-e1918. 196.Dudnik E, Moskovitz M, Agbarya A, et al. Alternative nivolumab duration and scheduling in advanced nonsmall cell lung cancer: a real-world evidence. <i>Int J Cancer</i>. 2021;148(5):1183-1191. 197.Felip E, Burotto M, Zvirbule Z, et al. Results of a dose-finding phase 1b study of subcutaneous atezolizumab in patients with locally advanced or metastatic non-small cell lung cancer. <i>Clin</i>. 2021;10(10):1142-1155. 198.Foldi J, Silber A, Reisenbichler E, et al. Neoadjuvant durvalumab plus weekly nab-paclitaxel and dose-dense doxorubicin/cyclophosphamide in triple-negative breast cancer. <i>NPJ Breast Cancer</i>. 2021;7(1):9. 199.Gordon SE, Bryan WE, 3rd, Hammond JM. Use and toxicity of checkpoint inhibitors for solid tumour treatment in a veteran population. <i>Fed Pract</i>. 2021;38(Suppl 3):S46-S51. 200.Hurkmans DP, Sassen SDT, de Joode K, et al. Prospective real-world study on the pharmacokinetics of pembrolizumab in patients with solid tumors. <i>J Immunother Cancer</i>. 2021;9(6). 201.Jang A, Nakashima L, Ng T, et al. A real-world data approach to determine the optimal dosing strategy for pembrolizumab. <i>J Oncol Pharm Pract</i>. 2021;27(3):635-643. 202.Li TR, Chatterjee M, Lala M, et al. Pivotal dose of pembrolizumab: a dose-finding strategy for immuno-oncology. <i>Clin Pharmacol Ther</i>. 2021;110(1):200-209. 203.Long GV, Robert C, Butler MO, et al. Standard-dose pembrolizumab plus alternate-dose ipilimumab in advanced melanoma: KEYNOTE-029 cohort 1C, a phase 2 randomized study of two dosing schedules. <i>Clin Cancer Res</i>. 2021;27(19):5280-5288. 204.Low JL, Huang Y, Sooi K, et al. Low-dose pembrolizumab in the treatment of advanced non-small cell lung cancer. <i>Int J Cancer</i>. 2021;149(1):169-176. 205.Lu S, Bowsher RR, Clancy A, et al. An integrated analysis of dostarlimab immunogenicity. <i>AAPS J</i>. 2021;23(5):96. 206.Ma Y, Fang W, Zhao H, et al. A phase I dose escalation study of the safety, tolerability, and pharmacokinetics of ipilimumab in chinese patients with select advanced solid tumors. <i>Oncologist</i>. 2021;26(4):e549-e566. 207.Owonikoko TK, Park K, Govindan R, et al. Nivolumab and ipilimumab as maintenance therapy in extensive-disease small-cell lung cancer: CheckMate 451. <i>J Clin Oncol</i>. 2021;39(12):1349-1359. 208.Pujade-Lauraine E, Fujiwara K, Ledermann JA, et al. Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study. <i>The Lancet Oncology</i>. 2021;22(7):1034-1046. 209.Somekawa K, Horita N, Kaneko A, et al. Adverse events induced by nivolumab and ipilimumab combination regimens. <i>Ther Adv Med Oncol</i>. 2021;13(no pagination). 210.Xu Y, Hezam K, Ali MG, Wang Y, Zhang J. The efficacy and safety of Nivolumab combined with Ipilimumab in the immunotherapy of cancer: a meta-analysis. <i>Immunopharmacol Immunotoxicol</i>. 2021;43(3):386-394. 211.Zhao JJ, Kumarakulasinghe NB, Muthu V, et al. Low-dose nivolumab in renal cell carcinoma: a real-world experience. <i>Oncology</i>. 2021;99(3):192-202.

Reason for exclusion	Citation
	212. Dose tapering and early discontinuation to increase cost-effectiveness of immunotherapy trial number 1. <i>Dose tapering and early discontinuation to increase cost-effectiveness of immunotherapy trial number 1 - Dedication-1 NVALT30</i>. 2020. 213. Public title: To study how nivolumab behaves in Indian cancer patients. Scientific title: To study the pharmacokinetics of Nivolumab in Indian patients with solid tumours. CTRI/2020/06/026176. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2020/06/026176. 2020; http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=27778. Accessed 2025 Oct 2. 214. A study to investigate the pharmacokinetics, efficacy, and safety of atezolizumab subcutaneous compared with atezolizumab intravenous in patients with previously treated locally advanced or metastatic non-small cell lung cancer. <i>A randomized, multicenter, phase Ib/III study to investigate the pharmacokinetics, efficacy, and safety of atezolizumab subcutaneous compared with atezolizumab intravenous in patients with previously treated locally advanced or metastatic non-small cell lung cancer</i>. 2020. 215. ACTRN12620000063910. Public title: SUBurothelial DURvalumab injEction-1 (SUBDUE-1). Scientific title: A phase 1 open label dose-escalation study to evaluate the tolerability, safety, and immunological efficacy of sub-urothelial durvalumab injection in adult subjects with muscle invasive bladder cancer or high-risk non-muscle invasive bladder tumours. 2020. https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12620000063910; https://anzctr.org.au/ACTRN12620000063910.aspx. Accessed 2025 Oct 2. 216. Anonymous. A phase II study of biomarker driven early discontinuation of Anti-PD-1 therapy in patients with advanced melanoma (PET-Stop). <i>ClinicalTrial.gov</i>. 2020;26. 217. Anonymous. A randomized study investigating the pharmacokinetics of standard interval dosing compared to extended interval dosing of nivolumab or pembrolizumab in locally advanced or metastatic cancers. <i>ClinicalTrial.gov</i>. 2020;14. 218. Anonymous. Releasing the brakes on CD8+ T-cells in the melanoma sentinel lymph node by pre-operative local administration of low-dose Anti-CTLA-4 (tremelimumab). <i>ClinicalTrial.gov</i>. 2020;06. 219. Anonymous. SCANDIUM II Trial - a phase I randomized controlled multicentre trial of isolated hepatic perfusion in combination with ipilimumab and nivolumab in patients with uveal melanoma metastases. <i>ClinicalTrial.gov</i>. 2020;05. 220. Anonymous. A single arm, pilot of neoadjuvant checkpoint inhibition followed by adjuvant checkpoint inhibition in children and young adults with recurrent or progressive high grade glioma (HGG). <i>ClinicalTrial.gov</i>. 2020;24. 221. Ascierto PA, Del Vecchio M, Mackiewicz A, et al. Overall survival at 5 years of follow-up in a phase III trial comparing ipilimumab 10 mg/kg with 3 mg/kg in patients with advanced melanoma. <i>J Immunother Cancer</i>. 2020;8(1):06. 222. Awada G, Ben Salama L, De Cremer J, et al. Axitinib plus avelumab in the treatment of recurrent glioblastoma: a stratified, open-label, single-center phase 2 clinical trial (GliAvAx). <i>J Immunother Cancer</i>. 2020;8(2):10. 223. Carlino MS, Menzies AM, Atkinson V, et al. Long-term follow-up of standard-dose pembrolizumab plus reduced-dose ipilimumab in patients with advanced melanoma: KEYNOTE-029 part 1B. <i>Clin Cancer Res</i>. 2020;26(19):5086-5091. 224. Chang CY, Park H, Malone DC, et al. Immune checkpoint inhibitors and immune-related adverse events in patients with advanced melanoma: a systematic review and network meta-analysis. <i>JAMA network open</i>. 2020;3(3):e201611-NA. 225. Fukuoka S, Hara H, Takahashi N, et al. Regorafenib plus nivolumab in patients with advanced gastric or colorectal cancer: an open-label, dose-escalation, and dose-expansion phase Ib trial (REGONIVO, EPOC1603). <i>J Clin Oncol</i>. 2020;38(18):2053-2061. 226. Kato K, Narita Y, Mitani S, et al. Efficacy of Cytotoxic Agents After Progression on Anti-PD-(L)1 Antibody for Pre-treated Metastatic Gastric Cancer.

Reason for exclusion	Citation
	<i>Anticancer Res.</i> 2020;40(4):2247-2255. 227. Klajer E, Garnier L, Goujon M, et al. Targeted and immune therapies among patients with metastatic renal carcinoma undergoing hemodialysis: a systemic review. <i>Semin Oncol.</i> 2020;47(2-3):103-116. 228. Miah MK, Imedio ER, Ottesen L, Kumar S, Mugundu G. Clinical pharmacokinetics of adavosertib in the presence or absence of PD-L1 inhibitor durvalumab in patients with refractory solid tumors. <i>Eur J Cancer.</i> 2020;138(Supplement 2):S45. 229. Nehra J, Bradbury PA, Ellis PM, et al. A Canadian cancer trials group phase IB study of durvalumab (anti-PD-L1) plus tremelimumab (anti-CTLA-4) given concurrently or sequentially in patients with advanced, incurable solid malignancies. <i>Invest New Drugs.</i> 2020;38(5):1442-1447. 230. Papadopoulos KP, Johnson ML, Lockhart AC, et al. First-in-human study of cemiplimab alone or in combination with radiotherapy and/or low-dose cyclophosphamide in patients with advanced malignancies. <i>Clin Cancer Res.</i> 2020;26(5):1025-1033. 231. Ready NE, Ott PA, Hellmann MD, et al. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: results from the CheckMate 032 randomized cohort. <i>J Thorac Oncol.</i> 2020;15(3):426-435. 232. Rogers JE, Xiao L, Trail A, Blum Murphy M, Palmer M, Ajani JA. Nivolumab in combination with irinotecan and 5-fluorouracil (folfiri) for refractory advanced gastroesophageal cancer. <i>Oncology.</i> 2020;98(5):289-294. 233. Rozeman EA, Prevoo W, Meier MAJ, et al. Phase Ib/II trial testing combined radiofrequency ablation and ipilimumab in uveal melanoma (SECIRA-UM). <i>Melanoma Research.</i> 2020;30(3):252-260. 234. Senan S, Okamoto I, Lee GW, et al. Design and rationale for a phase III, randomized, placebo-controlled trial of durvalumab with or without tremelimumab after concurrent chemoradiotherapy for patients with limited-stage small-cell lung cancer: the ADRIATIC study. <i>Clin Lung Cancer.</i> 2020;21(2):e84-e88. 235. Sureda M, Mata JJ, Catalan A, Escudero V, Martinez-Navarro E, Rebollo J. Therapeutic drug monitoring of nivolumab in routine clinical practice. A pilot study. <i>Farm Hosp.</i> 2020;44(3):81-86. 236. Vogelzang NJ, Olsen MR, McFarlane JJ, et al. Safety and efficacy of nivolumab in patients with advanced non-clear cell renal cell carcinoma: results from the phase IIIb/IV CheckMate 374 study. <i>Clin Genitourin Cancer.</i> 2020;18(6):461-468.e463. 237. Waterhouse DM, Garon EB, Chandler J, et al. Continuous Versus 1-Year Fixed-Duration Nivolumab in Previously Treated Advanced Non-Small-Cell Lung Cancer: CheckMate 153. <i>J Clin Oncol.</i> 2020;38(33):3863-3873. 238. Yau T, Kang YK, Kim TY, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. <i>JAMA Oncol.</i> 2020;6(11):e204564. 239. Zamarin D, Hamid O, Nayak-Kapoor A, et al. Mogamulizumab in combination with durvalumab or tremelimumab in patients with advanced solid tumors: a phase I study. <i>Clin Cancer Res.</i> 2020;26(17):4531-4541. 240. Zimmer L, Livingstone E, Hassel JC, et al. Adjuvant nivolumab plus ipilimumab or nivolumab monotherapy versus placebo in patients with resected stage IV melanoma with no evidence of disease (IMMUNED): a randomised, double-blind, placebo-controlled, phase 2 trial. <i>Lancet.</i> 2020;395(10236):1558-1568. 241. EUCTR2015-004920-67-DE. Public title: A randomized, double blinded, study of two different dose combinations of nivolumab in combination with ipilimumab in subjects with previously untreated, unresectable or metastatic melanoma. Scientific title: Phase IIIb/IV, randomized, double blinded, study of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg vs nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in subjects with

Reason for exclusion	Citation
	previously untreated, unresectable or metastatic melanoma - CheckMate 511: CHECKpoint pathway and nivolumab clinical trial evaluation 511. 2016. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2015-004920-67-DE; https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-004920-67. Accessed 2025 Oct 1. 242. LIGHTBEAM-U01-Substudy 01B: a phase 1/2 substudy to evaluate the safety and efficacy of pembrolizumab in combination with investigational agents in pediatric and young adult participants with hematologic malignancies or solid tumors. EUCT number: 2023-507179-23-00. Protocol code: MK-9999-01B. https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-507179-23-00. Accessed 2026 May 29. 243. A phase 1/2 open-label rolling-arm umbrella platform design of investigational agents with or without pembrolizumab or pembrolizuma alone in participants with melanoma (KEYMAKER-U02): substudy 02B. EUCT number: 2023-506313-21-00. Protocol code: MK-3475-02B. https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-506313-21-00. Accessed 2026 May 29. 244. A phase 2, single-arm, open-label clinical trial of pembrolizumab plus lenvatinib in participants with first-line advanced/metastatic non-clear cell renal cell carcinoma (nccRCC) (KEYNOTE-B61). EUCT number: 2023-504944-32-00. Protocol code: MK-3475-B61. https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-504944-32-00. Accessed 2026 May 29. 245. A phase 3, randomized, double-blind, multicenter study of dostarlimab (tsr-042) plus carboplatin-paclitaxel vs. placebo plus carboplatin-paclitaxel in patients with recurrent or primary advanced endometrial cancer (RUBY). EUCT number: 2023-506551-23-00. Protocol code: 4010-03-001. https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-506551-23-00. Accessed 2026 May 29. 246. A phase III, randomized, double-blind, placebo-controlled study of atezolizumab plus carboplatin and etoposide with or without tiragolumab (Anti-Tigit Antibody) in patients with untreated extensive-stage small cell lung cancer. EUCT number: 2022-502988-37-00. Protocol code: GO41767. https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2022-502988-37-00. Accessed 2026 May 29. 247. A phase IIIB single arm, open-label, multicentre study of durvalumab and tremelimumab as first line treatment in participants with advanced hepatocellular carcinoma (SIERRA). EUCT number: 2022-502012-37-00. Protocol code: D419CR00030. https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2022-502012-37-00. Accessed 2026 May 29. 248. Public title: Low dose nivolumab in advanced cancers. Scientific title: A phase 2 single arm study evaluating the safety and efficacy of fixed low dose nivolumab in advanced malignancy. - NIL. Trial number: CTRI/2022/05/042895. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=65821. Accessed 2025 Oct 2. 249. Public title: To study the effect of drug nivolumab in patients with cancers. Scientific title: Efficacy of low dose nivolumab as remission-induction therapy in primary progressive and relapsed Hodgkin lymphoma. Trial number: CTRI/2022/04/042179. 2022. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=67091. Accessed 2025 Oct 2.
Not full publication	1. Smeenk MM, van der Noort V, Hendriks J, Abedian Kalkhoran H, Smit EF, Theelen W. Response to: Comment on 'Pembrolizumab hybrid dosing is non-inferior to flat dosing in advanced non-small cell lung cancer: a real-world, retrospective bicenter cohort study' by Zhu. <i>J Immunother Cancer</i>. 2025;13(7):22. 2. van den Heuvel M, van der Noort V, Ter Heine R. 1258MO Low dose versus standard dose pembrolizumab for treatment of stage IV stage non-small cell lung carcinoma: Results of the pre-planned interim analysis of the NVALT-30 clinical trial. <i>Annals of Oncology</i>. 2024;35(NA):S806-S806. 3. van Dorp J, Pipinikas C, Suelmann BBM, et al. Author Correction: High- or low-dose preoperative ipilimumab plus nivolumab in stage III urothelial cancer: the phase 1B NABUCCO trial. <i>Nat Med</i>. 2024;30(1):304.

Reason for exclusion	Citation
	4. Gupta AK, Mann A, Vincent K, Abramovits W, Libtayo R (Cemiplimab-rwlc) Injection for intravenous Use. <i>Skinmed</i>. 2024;22(2):138-143. 5. Anonymous. A Feasibility Multicenter Phase I Study of Therapeutic Drug Monitoring-Based Atezolizumab Dosing. <i>clinicaltrials.gov</i>. 2023;03. 6. Ghorani E, Quartagno M, Blackhall F, et al. REFINE-Lung implements a novel multi-arm randomised trial design to address possible immunotherapy overtreatment. <i>Lancet Oncol</i>. 2023;24(5):e219-e227. 7. Noronha V. Dosing of nivolumab in India. <i>Clin</i>. 2023;21(5):228-243. 8. Fukumoto T, Horita N. The best dosage of nivolumab plus ipilimumab combination for melanoma brain metastases. <i>Transl Oncol</i>. 2022;22:101449. 9. Gower A, Garon EB. Pembrolizumab in advanced non-small cell lung cancer: safety implications of dose adjustments. <i>Transl</i>. 2022;11(12):4479-4481. 10. Iqbal A, Abbasi ZA, Naeem F. Benefits of six week and personalized dosing of pembrolizumab considering ongoing delta variant surge. <i>JPMA J Pak Med Assoc</i>. 2022;72(3):595. 11. Malmberg R, Zietse M, Dumoulin DW, et al. Alternative dosing strategies for immune checkpoint inhibitors to improve cost-effectiveness: a special focus on nivolumab and pembrolizumab. <i>Lancet Oncol</i>. 2022;23(12):e552-e561. 12. Mountzios G, Aggarwal C. Pembrolizumab Administration Frequency, Dose Exposure, and Toxicity: Is Switching Safe? <i>J Thorac Oncol</i>. 2022;17(10):1155-1157. 13. Ratain MJ, Peer CJ, Figg WD, Goldstein DA. Dose Optimization of Pembrolizumab: Less May Be More. <i>Clin Pharmacol Ther</i>. 2022;111(5):993. 14. Takamoto K, Komori T, Ishida Y, Kambe N, Kabashima K. Up-dosing of nivolumab may induce serious immune-related adverse events. <i>J Eur Acad Dermatol Venereol</i>. 2022;36(2):e141-e142. 15. Anonymous. A Phase 1/2a, Open-label, Multicenter Study to Evaluate the Safety, Pharmacokinetics, and Preliminary Efficacy of Subcutaneous Durvalumab in Patients With Non-Small Cell and Small Cell Lung Cancer - SCoPe-D1. <i>clinicaltrials.gov</i>. 2021;16. 16. Anonymous. Correction to: Benefit-risk assessment of nivolumab 240 mg flat dose relative to 3 mg/kg Q2W regimen in Japanese patients with advanced cancers (Cancer Science, (2020), 111, 2, (528-535), 10.1111/cas.14252). <i>Cancer Science</i>. 2021;112(5):2063. 17. Jameson-Lee M, Luke JJ. Ipilimumab Combination Dosing: Less is More. <i>Clin Cancer Res</i>. 2021;27(19):5153-5155. 18. A study of atezolizumab and tiragolumab compared with durvalumab in patients with unresectable stage iii non-small cell lung cancer who have not progressed after concurrent platinum-based chemoradiation. <i>A phase III, open-label, randomized study of atezolizumab and tiragolumab compared with durvalumab in patients with locally advanced, unresectable stage iii non-small cell lung cancer who have not progressed after concurrent platinum-based chemoradiation - SKYSCRAPER-03</i>. 2020. 19. Dose tapering and early discontinuation to increase cost-effectiveness of immunotherapy trial number 1. <i>Dose tapering and early discontinuation to increase cost-effectiveness of immunotherapy trial number 1 - Dedication-1 NVALT30</i>. 2020. 20. Buma AIG, Piet B, Ter Heine R, van den Heuvel MM. Integrating treatment cost reduction strategies and biomarker research to reduce costs and personalize expensive treatments: an example of a self-funding trial in non-small cell lung cancer. <i>Front Pharmacol</i>. 2023;14:1274532.

Appendix 7: PRISMA Checklist

Please note that this appendix has not been copy-edited.

Table 17: PRISMA Checklist

Section and topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	Refer to the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 8
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 9
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 10 and 11
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 10
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 10
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 12
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 13
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 12
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 12 and 13
Study risk-of-bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 13

Section and topic	Item #	Checklist item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	Page 13
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 13
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 13
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 13
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 13
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	Page 13
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 13
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 13 and 14
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 13 and 14
Study characteristics	17	Cite each included study and present its characteristics.	Page 16 and 17
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 17 to page 20
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Page 21 to Page 38
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	Page 21 to Page 38
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 21 to Page 38
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 21 to Page 38

Section and topic	Item #	Checklist item	Location where item is reported
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 21 to Page 38
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 38 to 51
	23b	Discuss any limitations of the evidence included in the review.	Page 38
	23c	Discuss any limitations of the review processes used.	Page 38
	23d	Discuss implications of the results for practice, policy, and future research.	Page 38
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 9
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 9
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 9
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 156
Competing interests	26	Declare any competing interests of review authors.	Page 156
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 156

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>

Appendix 8: Overlap Between Flagged Systematic Reviews

Please note that this appendix has not been copy-edited.

Table 18: Overlap in Relevant Primary Studies Between Selected Systematic Reviews

Primary Study Ref	Hoyek, 2025 ¹⁸	Tan, 2025 ¹⁹	Mao, 2024 ²⁰	Hong, 2023 ²¹	Li, 2023 ²²	Wesevich, 2023 ²³	Jiang, 2022 ²⁴	Lee, 2020 ²⁵	Sehgal, 2020 ²⁶
RCTs									
Albiges, 2025²⁸	No	No	No	No	No	No	No	No	No
Herrera, 2021²⁹	No	No	No	No	No	No	No	No	No
Nonrandomized studies									
Campo Le Brun, 2025³⁰	No	No	No	No	No	No	No	No	No
Horisaki, 2025³¹	No	No	No	No	No	No	No	No	No
Hughes, 2025³²	No	No	No	No	No	No	No	No	No
Smeenck, 2025³³	No	No	No	No	No	No	No	No	No
Staender, 2025³⁴	No	No	No	No	No	No	No	No	No
Chaitesipaseut, 2024³⁵	No	No	No	No	No	No	No	No	No
Cohen, 2024³⁶	No	No	No	No	No	No	No	No	No
Grit, 2024³⁷	No	No	No	No	No	No	No	No	No
Leroy, 2024³⁸	No	No	No	No	No	No	No	No	No
Patel, 2024³⁹	No	No	No	No	No	No	No	No	No
Rischin, 2024⁴⁰	No	No	No	No	No	No	No	No	No
Berard, 2023⁴¹	No	No	No	No	No	No	No	No	No
Samlowski, 2023⁴²	No	No	No	No	No	No	No	No	No
Fujiwara, 2022⁴³	No	No	No	No	No	No	No	No	No

Primary Study Ref	Hoyek, 2025 ¹⁸	Tan, 2025 ¹⁹	Mao, 2024 ²⁰	Hong, 2023 ²¹	Li, 2023 ²²	Wesevich, 2023 ²³	Jiang, 2022 ²⁴	Lee, 2020 ²⁵	Sehgal, 2020 ²⁶
Hijmering-Kappelle et al., 2022 ⁴⁴	No	No	No	No	No	No	Yes	No	No
Iikura, 2022 ⁴⁵	No	No	No	No	No	No	No	No	No
Okada, 2022 ⁴⁶	No	No	No	No	No	No	No	No	No
Patnaik, 2022 ⁴⁷	No	No	No	No	No	Yes	No	No	No
To, 2022 ⁴⁸	No	No	No	No	No	No	No	No	No
Juergens, 2020 ⁴⁹	No	No	No	No	No	No	No	No	No
Kato, 2020 ⁵⁰	No	No	No	No	No	No	No	No	No
Rischin, 2020 ⁵¹	No	No	No	No	No	No	No	Yes	No
PK/PD modelling or simulation studies									
Lala, 2025 ⁵²	No	No	No	No	No	No	No	No	No
Gandhi, 2024 ⁵³	No	No	No	No	No	No	No	No	No
Zhao, 2024 ⁵⁴	No	Yes	No	No	No	No	No	No	No
Hwang, 2023 ⁵⁶	No	No	No	No	No	No	No	No	No
Ter Heine, 2023 ⁵⁵	No	Yes	No	No	No	No	No	No	No
Masters, 2022 ⁵⁷	No	No	No	No	No	No	No	No	No
Paccaly, 2021 ⁵⁸	No	No	No	No	No	Yes	No	No	No
Sanghavi, 2021 ⁵⁹	No	No	No	No	No	No	No	No	No
Sheng, 2021 ⁶⁰	No	No	No	No	No	No	No	No	No
Yang, 2021 ⁶¹	No	No	No	No	No	No	No	No	No
Bei, 2020 ⁶⁵	No	Yes	No	No	No	No	No	No	No
Lala, 2020 ⁶²	No	No	No	No	No	No	Yes	No	Yes
Novakovic, 2020 ⁶³	No	No	No	No	No	No	No	No	No
Zhao, 2020 ⁶⁴	No	Yes	No	No	No	No	Yes	No	No



Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

ISSN: 2563-6596

This work was conducted by the Knowledge Translation Program (KTP) team, with collaborative contributions from the Canadian Cancer Real-world Evaluation (CCRE) Platform, through the Post-Market Drug Evaluation CoLab Network. It was supported by Canada's Drug Agency (CDA-AMC) and its Post-Market Drug Evaluation Program through funding provided by Health Canada.

CDA-AMC is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

CoLab is a pan-Canadian network of experts in applied research, scientific methods, and data analysis. CoLab members work with the Post-Market Drug Evaluation Program to produce credible and timely evidence on postmarket drug safety and effectiveness.

Disclaimer: CDA-AMC has taken care to ensure that the information in this document was accurate, complete, and up to date when it was published, but does not make any guarantee to that effect. Your use of this information is subject to this disclaimer and the Terms of Use at cda-amc.ca.

The information in this document is made available for informational and educational purposes only and should not be used as a substitute for professional medical advice, the application of clinical judgment in respect of the care of a particular patient, or other professional judgments in any decision-making process. You assume full responsibility for the use of the information and rely on it at your own risk.

CDA-AMC does not endorse any information, drugs, therapies, treatments, products, processes, or services. The views and opinions of third parties published in this document do not necessarily reflect those of CDA-AMC. The copyright and other intellectual property rights in this document are owned by the Canadian Agency for Drugs and Technologies in Health (operating as CDA-AMC) and its licensors.

This document is the property of the KTP Team. CDA-AMC has a nonexclusive, limited, royalty-free, worldwide, nontransferable, fully paid-up, and irrevocable license to use the report in support of its objects, mission, and reasonable operational requirements.