



LOW-DOSE NIVOLUMAB IN ADVANCED SOLID TUMOURS: ACTIVITY, TOXICITY AND THE MISSING COMPARISON WITH STANDARD DOSE

Dr. Harkiratjit Singh Bhulla¹, Dr. Kamalpreet Kaur^{2*} Dr. Pardeep Garg³

¹PG Resident, Department of Pharmacology, GGSMC & Hospital, Faridkot, Punjab 151203, India, Email: drharkirat0@gmail.com , ORCID ID: 0009-0002-0322-5611

^{2*}Associate Professor, Department of Pharmacology, GGSMC & Hospital, Faridkot, Punjab 151203, India Email: kamalpreetaneja@ggsmch.org, ORCID ID: 0009-0003-2885-3400

³Professor and Head, Department of Radiation Oncology, GGSMC & Hospital, Faridkot, Punjab 151203, India Email: drpardeepgarg@gmail.com , ORCID ID: 0000-0001-8144-177X

13.9% objective response, low-dose nivolumab, pretreated solid tumours 95% CI 8.5–21.8 · 6 cohorts, 209 patients	137 patients in all solid-tumour comparisons with standard dose RR 0.78 (0.40–1.50), descriptive	0.80 hazard ratio for death, 20 mg q2w vs taxane (DELII) 95% CI 0.66–0.97 · 500 patients	42.5% grade ≥ 3 treatment-related events in DELII, against 0.6% in peer-reviewed cohorts retrospective cohorts under-count
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9 solid-tumour (plus 1 safety-only) and 3 Hodgkin cohorts, 2 randomised trials · cohort dose intensity 4 to 34% of approved · random-intercept logistic models (R, metafor) · JBI · ROBINS-I · GRADE

Key points		
Question	Findings	Meaning
How active and how toxic is nivolumab given at a fraction of the approved dose in pretreated solid tumours, and how does it compare with	About one patient in seven responded. Two randomised trials showed longer survival than non-immunotherapy control. Only 137 patients have ever been compared with standard dose, and observational cohorts	Low-dose nivolumab is active, and its use where standard dose is unaffordable has randomised support. Whether it costs efficacy against 240 mg is unknown and needs a

standard dose?	recorded far fewer serious events than the largest trial.	randomised dose comparison.
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Abstract

Background. Nivolumab shows a flat exposure–response relationship above about 0.3 mg/kg, and Indian and other low-resource centres have used fixed doses of 10 to 100 mg when the approved regimen is unaffordable. A systematic review of low-dose PD-(L)1 strategies did not pool data, and the only published meta-analysis covers Hodgkin lymphoma.

Methods. Cohorts treating advanced solid tumours with nivolumab monotherapy below the approved dose were eligible. Responders and treated patients were extracted from full texts, and each regimen was converted to dose intensity (mg per 4 weeks as a percentage of 480 mg). Proportions were pooled with random-intercept logistic models; comparisons with standard dose were summarised by disease with Mantel–Haenszel risk ratios. Randomised trials against non-immunotherapy control were reported narratively. All models were fitted in R (metafor).

Results. Nine solid-tumour cohorts (412 treated patients) were identified; six peer-reviewed cohorts formed the primary analysis. Dose intensity ranged from 4% to 34%. Objective response was 13.9% (95% CI 8.5 to 21.8; prediction interval 5.6 to 30.5), and 18.2% (12.9 to 25.1) with two conference abstracts and a preprint added. Response showed no increase with dose intensity, although tumour type and dose were confounded. Three cohorts compared low with standard dose in 137 patients (RR 0.78, 0.40 to 1.50). Grade ≥ 3 treatment- or immune-related events were 0.6% (0.0 to 12.4; one event in 137 patients) in peer-reviewed observational cohorts but 42.5% in the DELII trial at 8.3% dose intensity. DELII (HR 0.80, 0.66 to 0.97) and a head and neck trial (HR 0.545, 0.362 to 0.820) showed longer survival than non-immunotherapy control.

Conclusions. Low-dose nivolumab is active in pretreated solid tumours and has randomised evidence of benefit over chemotherapy-based control. Observational cohorts and the one randomised trial disagree by more than an order of magnitude on serious toxicity (0.6% against 42.5%), and neither estimate is reliable. Evidence comparing low with standard dose is too small and too confounded to estimate any efficacy loss; a randomised dose-comparison trial is the necessary next step.

Keywords: Low-dose nivolumab; PD-1 inhibitors; dose intensity; solid tumours; objective response rate; systematic review and meta-analysis.

Introduction

Nivolumab, a monoclonal antibody against programmed death-1 (PD-1), is approved at 240 mg every 2 weeks or 480 mg every 4 weeks for several advanced solid tumours. Its cost puts it out of reach of most patients in low- and middle-income countries. At Tata Memorial Hospital, only 155 of 9,610 patients (1.6%) with non-melanoma solid tumours received a checkpoint inhibitor between 2015 and 2018[1].

The approved dose may be higher than needed. Early trials found no clear relationship between dose and response across 0.1 to 10 mg/kg[2],[3], and PD-1 on circulating T cells was about 85% occupied at 0.3 mg/kg[4]. On this basis, several centres have used fixed doses of 10 to 100 mg when the approved dose was unaffordable. Two randomised trials from India have since shown that nivolumab 20 mg improves survival compared with treatment without immunotherapy[5],[6]. However, neither trial compared low dose with standard dose.

A systematic review of low-dose PD-(L)1 strategies did not pool its data[7], and the only published meta-analysis is limited to Hodgkin lymphoma[8]. There is no pooled estimate for solid tumours.

Objectives

The primary objective was to estimate objective response to low-dose nivolumab monotherapy in advanced solid tumours. Secondary objectives were to estimate grade ≥ 3 treatment- or immune-related adverse events, to describe response against standard-dose anti-PD-1 therapy, to examine response across dose intensity, and to set these results against the randomised evidence.

2. Methods

Reporting was informed by the PRISMA 2020 statement[9]; the search was targeted and non-systematic. The protocol was not registered.

2.1 Eligibility

Element	Criterion
Population	Adults with advanced or metastatic solid tumours. Classical Hodgkin lymphoma was handled separately and briefly because a meta-analysis already exists.
Intervention	Nivolumab monotherapy below the approved dose, at any fixed or weight-based dose and interval.
Comparator	None for single-arm outcomes; standard-dose anti-PD-1 therapy for comparative outcomes; non-immunotherapy control for randomised trials (narrative only).
Outcomes	Responders and treated patients; grade ≥ 3 adverse events with a stated definition.
Excluded	Combinations with chemotherapy, tyrosine kinase inhibitors, brentuximab or ipilimumab; reports with no extractable responder count; and a second report of the same cohort.

2.2 Outcomes

Primary: objective response (complete plus partial response) among all treated patients. Secondary: objective response among evaluable patients; grade ≥ 3 treatment-related or immune-related adverse events; all-cause grade ≥ 3 events (reported separately); risk ratio for response against standard dose.

2.3 Information sources

Studies were identified from full-text reports held by the authors, from the reference list of the Jiménez-Labaig review, which was searched to January 2025[7], and from targeted web searches to October 2026 for reports and pooled analyses published in 2025 and 2026. Searches combined the terms nivolumab, low dose, fixed dose, reduced dose and ultra-low dose.

2.4 Extraction and handling rules

Denominators. All treated patients were the primary denominator for response, in single-arm and comparative analyses alike. Evaluable patients were used in a sensitivity analysis.

Tables over abstracts. Where an abstract and a table disagreed, the table was used (Table 5).

Dose intensity. Each regimen was converted to mg per 4 weeks and expressed as a percentage of 480 mg. Where a cohort received two doses and the split was reported, the cohort-weighted mean was used; otherwise the range was recorded and the cohort was ordered by the midpoint.

Overlap. Where two reports shared patients, the larger or later report entered the primary analysis.

Peer review. Conference abstracts and preprints were excluded from the primary models for response and toxicity and added in sensitivity analysis.

Adverse events. Treatment-related and immune-related grade ≥ 3 events were pooled; all-cause events were tabulated separately and not pooled.

Back-calculation. Counts printed only as percentages were back-calculated from the stated denominator and checked against reported totals.

Direction. Ratios reported as standard against low dose were inverted.

Pembrolizumab. Pembrolizumab regimens of about 50% dose intensity represent dose reduction rather than ultra-low dosing; they are tabulated in Table S1 and not used in any figure or pooled estimate, except the Trikha 2024 standard-dose arm, which includes some pembrolizumab (Figure 2 footnote).

2.5 Risk of bias and certainty

Single-arm cohorts were appraised with the JBI checklist for prevalence data[10] and comparative cohorts with ROBINS-I[11]. Certainty was graded with GRADE[12]. All judgements are provisional and by a single reviewer.

2.6 Statistical analysis

Proportions were pooled with a random-intercept logistic model fitted by maximum likelihood (metafor rma.glmm)[13], which uses the exact binomial likelihood and handles zero cells without correction. Freeman–Tukey and logit inverse-variance models were sensitivity analyses; the Freeman–Tukey back-transformation can mislead near zero[14]. Heterogeneity is reported as I^2 and a 95% prediction interval. Single-study proportions carry Wilson intervals[15].

Every comparative stratum contains three studies or fewer, where random-effects variance cannot be estimated usefully. These strata are summarised with fixed-effect Mantel–Haenszel risk ratios, labelled descriptive, and never combined across diseases. Dose intensity was examined by ordering the forest plot; with nine cohorts, meta-regression was not attempted. Small-study tests were not run. All models were fitted in R 4.3.3 with metafor 4.4.0.

3. Results

3.1 Study selection and characteristics

After removal of duplicate reports and reviews, 23 primary reports were assessed. Nine solid-tumour cohorts were included for response and one adjuvant cohort for safety only (Table 1); three Hodgkin cohorts (two comparative) and two randomised trials were reported separately, with Lepik 2020 contained within Fedorova 2025 and Chan 2020 taken from a published review; four pembrolizumab or mixed-agent cohorts were tabulated (Table S1); and four were excluded (combination therapy 2, no stable-disease category 1, dose split at 2.15 mg/kg 1).

Table 1. Characteristics of included solid-tumour cohorts

Study	Setting	Design	Regimen	DI, %	Treated	Source

Study	Setting	Design	Regimen	DI, %	Treated	Source
Joris 2022[16]	Mixed refractory solid tumours	Retrospective case series	10 mg q2w	4.2	18	Full text
Gauduchon 2026[17]	Mixed, 70% squamous; frail	Retrospective	20 mg q3w	5.6	53	Preprint
Mishra 2025[18]	Mixed (AIIMS Bhubaneswar)	Retrospective	20 or 40 mg q2–4w	4–17	104	Abstract
Tiwari 2024[19]	Mixed (IMS and SUM, Bhubaneswar)	Retrospective	40 mg q4w	8.3	46	Abstract
Trikha 2024[20]	MSI-high colorectal	Retrospective, comparative	20 or 40 mg q3w	10.7	30 (+35 SD)	Full text
Kumar 2025[21]	Mixed, 70% head and neck	Retrospective, consecutive	40 mg q2–3w	11–17	54	Full text
Gandhi 2024[22]	Mixed	Prospective pharmacokinetic	40 mg q2–3w	11–17	11 (+14 SD)	Full text
Yoo 2018[23]	NSCLC	Retrospective, comparative	20 or 100 mg q3w	24	18 (+29 SD)	Full text
Chen 2022[24]	HCC, BCLC C; 25% Child–Pugh B	Retrospective	20 or 100 mg q2w	34	78	Full text
Schwarze 2022[25]	Melanoma, adjuvant (safety only)	Phase II cohort	10 mg q2w then q8w	1–4	21	Full text

DI, dose intensity: mg per 4 weeks as a percentage of 480 mg (cohort-weighted where the split was reported). SD, standard-dose comparison arm.

3.2 Activity in solid tumours

In the six peer-reviewed cohorts, 28 of 209 treated patients responded: 13.9% (95% CI 8.5 to 21.8; I^2 40%; prediction interval 5.6 to 30.5). Adding the Mishra and Tiwari abstracts and the Gauduchon preprint gave 18.2% (12.9 to 25.1) across 412 patients (Figure 1). The lowest rate was 5.1% in Chen 2022, a hepatocellular series in which a quarter of patients were Child–Pugh B[24]; without it the estimate was 18.3%. The Mishra abstract reported 39.7% among patients who received at least two cycles; on all 104 treated patients the rate is 27.9%[18].

Response showed no increase with dose intensity. Cohorts at 4 to 11% of the approved intensity responded at 21 to 28%, those at 11 to 34% at 5 to 17%. Tumour type and dose are confounded: the two highest-intensity cohorts are the hepatocellular and lung series.

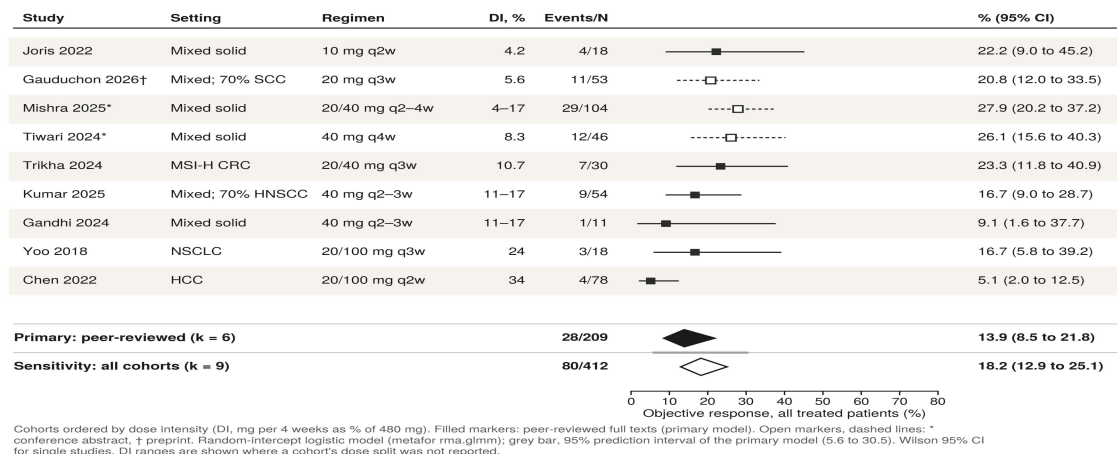


Figure 1. Objective response with low-dose nivolumab in advanced solid tumours, ordered by dose intensity.

3.3 Comparison with standard dose

Three solid-tumour cohorts compared low-dose nivolumab with standard dose[23],[22],[20]. Between them, 11 of 59 low-dose and 18 of 78 standard-dose patients responded (RR 0.78, 0.40 to 1.50; Figure 2). That interval is compatible with a 60% loss or a 50% gain in response, and dose was chosen by affordability in all three. The solid-tumour comparison is uninformative.

In Hodgkin lymphoma, the propensity-matched St Petersburg series and the Vellore cohort found near-identical response with 40 mg and with 3 mg/kg (RR 0.98, 0.79 to 1.22)[26],[27]. Both enter as abstract counts. In the Vellore cohort, lenalidomide was added in 50% of low-dose and 84% of standard-dose patients, outside the eligibility criteria, so the cohort is shown as descriptive context only.

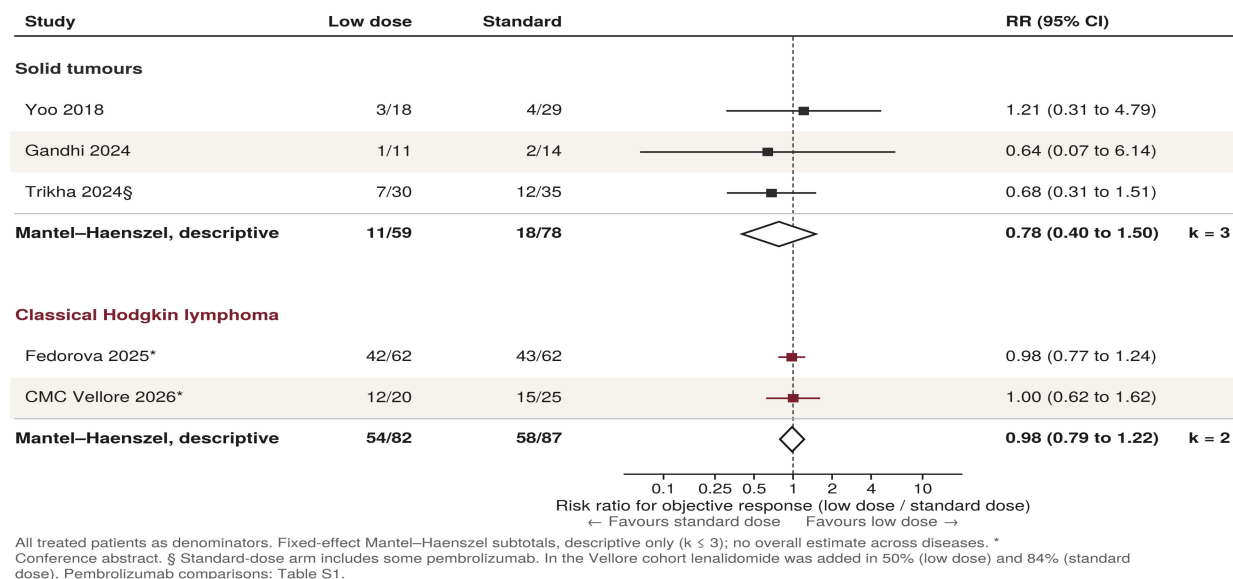


Figure 2. Objective response, low versus standard dose nivolumab, by disease. No estimate is pooled across diseases.

3.4 Toxicity

Four peer-reviewed observational cohorts recorded one grade ≥ 3 treatment- or immune-related event among 137 patients: 0.6% (0.0 to 12.4; Figure 3). Adding the Gauduchon preprint, which reported 2 events in 53 patients, gives 1.4% (0.3 to 6.2). Schwarze 2022 recorded one treatment-related grade ≥ 3 event in 21 patients given nivolumab 10 mg after resection of melanoma metastases[25]; it is outside the primary pool because adjuvant patients without measurable disease are not comparable with advanced disease, and adding it gives 1.2% (0.2 to 6.2). In DELII, at a lower dose intensity than most of these cohorts, 42.5% of 250 patients had grade ≥ 3 treatment-related events, against 60.8% with docetaxel or paclitaxel[6]. Two cohorts that counted all-cause events reported 11.1% (Kumar 2025, all hyponatraemia) and 20.2% (Mishra 2025)[21],[18].

A gap of this size between observational cohorts and a randomised trial of the same regimen cannot be explained by case mix alone. Retrospective chart review in compassionate-use cohorts almost certainly under-ascertains toxicity, and the 0.6% should be read as a lower bound of recorded immune-related events, not as the rate patients experience. DELII's definition of "treatment-related" in a pretreated population will also capture events that a chart reviewer would attribute to disease.

Only two studies compared serious events by dose, one in each disease. In Gandhi 2024, 0 of 11 low-dose and 4 of 14 standard-dose patients had grade ≥ 3 events; in Fedorova 2025, 4 of 62 and 8 of 62 (RR 0.50, 0.16 to 1.58). They are not combined.

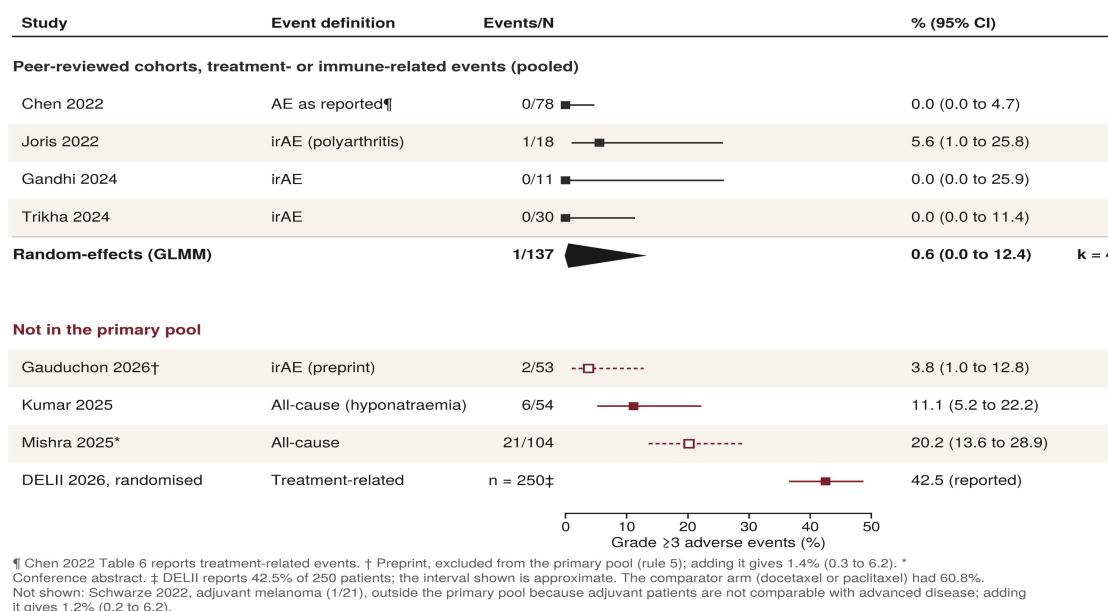


Figure 3. Grade ≥ 3 adverse events: pooled observational cohorts (black) against all-cause cohorts and the DELII trial (dark red, not pooled).

3.5 Randomised evidence

Both trials were single-centre and open-label. Adding nivolumab 20 mg every 3 weeks to triple metronomic chemotherapy in 151 patients with head and neck cancer reduced the hazard of death (HR 0.545, 0.362 to 0.820; Figure 4)[5]. In DELII, 500 patients with progression after at least one line, 52% with head and neck and 36% with lung cancer, were randomised to nivolumab 20 mg every 2 weeks or

a taxane. Overall survival improved (HR 0.80, 0.66 to 0.97; median 5.88 against 4.70 months), progression-free survival did not differ (HR 1.03, 0.86 to 1.23) and quality of life was better[6]. A further phase III trial, in which 422 patients received metronomic chemotherapy with nivolumab 20 mg every 3 weeks or paclitaxel–carboplatin, was presented in 2026 and has not been extracted[28].

3.6 Hodgkin lymphoma

Nivolumab 40 mg every 2 weeks (16.7% dose intensity) produced responses in 47 of 68 patients in two cohorts, 69.1% (57.2 to 78.9)[26],[29],[30]. A published meta-analysis reported 87% overall and 83.8% for nivolumab[8]. The gap has identifiable sources. That analysis pooled five small series totalling 84 patients, included pembrolizumab, and pooled untransformed proportions with DerSimonian–Laird weights, which gives heavy weight to small series reporting 100% response. Our estimate is dominated by the 62-patient St Petersburg series, which reported 68% with 40 mg and 70% with 3 mg/kg[26]; it is the larger and more conservative figure. This section adds the two comparative cohorts to that literature.

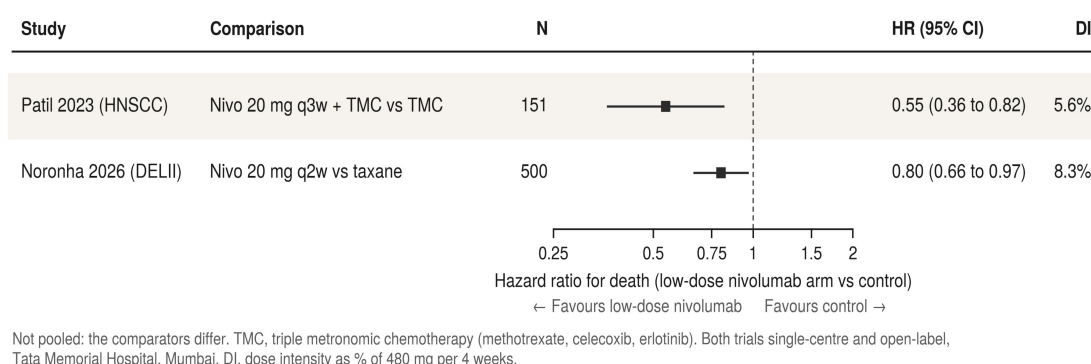


Figure 4. Randomised trials of low-dose nivolumab against non-immunotherapy control.

3.7 Summary of findings

Table 2. Summary of findings and certainty of evidence (GRADE)

Outcome	Studies (patients)	Estimate	Certainty	Reasons
Objective response, low dose, solid tumours	6 (209)	13.9% (8.5 to 21.8)	Very low	Single-arm retrospective data; inconsistency (prediction interval 5.6 to 30.5)
Response, low vs standard, solid tumours	3 (137)	RR 0.78 (0.40 to 1.50), descriptive	Very low	Confounding by affordability; very serious imprecision

Outcome	Studies (patients)	Estimate	Certainty	Reasons
Grade ≥ 3 related events, low dose	4 (137)	0.6% (0.0 to 12.4)	Very low	One event; under-ascertainment; contradicted by randomised data (42.5%)
Survival, low-dose nivolumab vs no immunotherapy	2 RCTs (651)	HR 0.545 and 0.80, not pooled	Moderate	Single centre, open label

GRADE: moderate, the true effect is probably close to the estimate; very low, the true effect is likely to be substantially different.

3.8 Sensitivity analyses

Table 3. Sensitivity analyses

Analysis	k	Estimate (95% CI)	Conclusion changed?
Objective response, solid tumours (primary 13.9%, 8.5 to 21.8)			
All nine cohorts, all treated patients	9	18.2% (12.9 to 25.1)	No
All nine cohorts, evaluable patients	9	19.7% (13.1 to 28.4)	No; highest estimate
Peer-reviewed cohorts, evaluable patients	6	14.4% (8.8 to 22.7)	No
Without Chen 2022 (hepatocellular, Child–Pugh B)	5	18.3% (12.6 to 25.9)	No
Without Gandhi 2024 (possible overlap with Kumar 2025)	5	14.4% (8.5 to 23.3)	No
Freeman–Tukey, REML	6	13.8% (6.9 to 22.3)	No
Logit, REML with HKSJ interval	6	14.9% (8.0 to 26.2)	No
Leave-one-out range	5	12.1% to 18.3%	No
Grade ≥ 3 related events (primary 0.6%, 0.0 to 12.4)			
Adding the Gauduchon preprint	5	1.4% (0.3 to 6.2)	No
Adding the adjuvant cohort	5	1.2% (0.2 to 6.2)	No
Hodgkin lymphoma (primary 69.1%, 57.2 to 78.9)			

Analysis	k	Estimate (95% CI)	Conclusion changed?
Adding the Vellore cohort	3	67.0% (56.6 to 76.0)	No
Lepik 2020 in place of Fedorova 2025	2	72.2% (55.6 to 84.4)	No

3.9 Risk of bias

All cohorts were retrospective except Gandhi 2024, a prospective pharmacokinetic study[22]. Response assessment was investigator-reported throughout, and dose in the comparative cohorts followed affordability, a confounder no study adjusted for (Table 4).

Table 4. Risk of bias, provisional single-reviewer judgements

Study	Tool	Judgement	Principal concerns
Schwarze 2022	JBI	Moderate	Single-arm phase II; adjuvant melanoma, so not comparable with advanced disease; 21 patients; safety outcome only
Chen 2022	JBI	Moderate	Two doses mixed; quarter Child–Pugh B; consecutive series, RECIST 1.1
Joris 2022	JBI	High	18 heterogeneous patients; text and table disagree on complete responders
Gauduchon 2026	JBI	High	Not peer reviewed, so excluded from the primary models for response and toxicity (rule 5); frail population; retrospective
Mishra 2025	JBI	High	Abstract only; response counted after at least two cycles
Tiwari 2024	JBI	High	Abstract only; 28.5% of 46 is not a whole number
Kumar 2025	JBI	Moderate	Compassionate use; 4 of 54 not evaluable; all-cause adverse events
Gandhi 2024	JBI / ROBINS-I	Moderate / serious	Abstract labels disease control as response; dose by affordability
Trikha 2024	JBI / ROBINS-I	Moderate / serious	Standard-dose arm mixes nivolumab and pembrolizumab; dose by affordability

Study	Tool	Judgement	Principal concerns
Yoo 2018	JBIC / ROBINS-I	Moderate / serious	Dose by affordability; no adjustment; no safety data

JBIC, checklist for prevalence data (single-arm outcome). ROBINS-I, comparative outcome; confounding domain judged serious in all three. To be repeated by a second reviewer.

3.10 Reporting errors found during extraction

Table 5. Reporting errors and inconsistencies

Report	Error	Handling
Gandhi 2024	Abstract gives 5/11 vs 4/9 as response; Table 3 shows these are complete, partial and stable responses combined	Table 3 used: 2/14 vs 1/11 on treated patients
Gandhi 2024	Abstract gives 19 evaluable patients; text and Table 3 give 20	Treated patients used
Joris 2022	Text names patients 5 and 18 as complete responders; Table I names 5 and 12	No effect on 4/18
Mishra 2025	29/73 counts only patients given at least two cycles	29/104 used; sensitivity only
Tiwari 2024	28.5% of 46 is not a whole number; implies 12 of 42 evaluable	12/46 used; sensitivity only
Gauduchon 2026	Grade 3 events given as 3.7%; 2 of 53 is 3.8%	2/53 used
Souza 2024	Hazard ratios below 1 alongside medians favouring standard dose	Direction inferred; Table S1 only
Low 2021	Single-agent PFS HR 0.72 in abstract, 0.60 in results	PFS not used
Patel 2024	Response table has no stable-disease category	Excluded
Devabhaktuni 2023	Two reports of the cohort give different response counts	Excluded

4. Discussion

Principal findings

About one patient in seven with a pretreated solid tumour responded to nivolumab at 4 to 34% of the approved dose intensity, with no sign that response rose with dose. Two randomised trials show that ultra-low doses prolong survival over non-immunotherapy control. The comparison that matters to prescribers, low against standard dose, rests on 137 patients in three confounded cohorts and cannot be estimated.

Why the toxicity estimates disagree

Compassionate-use cohorts record what the treating team chose to document, usually immune-related events that changed management. A trial with scheduled visits and CTCAE grading records everything, including fatigue, anaemia and electrolyte disturbance in patients with advanced disease. The observational estimate and DELII differ by more than an order of magnitude, and the two figures are best read as bounds. The observational 0.6% is a floor set by what chart review captured. The DELII 42.5% may be inflated by attributing disease-related events to treatment, since standard-dose nivolumab trials in pretreated disease reported grade 3–4 treatment-related events of about 7 to 13%: 7% in CheckMate 017, 10% in CheckMate 057 and 13.1% in CheckMate 141[31],[32],[33]. Against that explanation, the DELII chemotherapy arm (60.8%) recorded a rate close to the docetaxel arms of CheckMate 017 and 057 (55% and 54%), so over-attribution would have to affect the nivolumab arm more than the chemotherapy arm to account for the gap. No evidence suggests that 20 mg is more toxic than 240 mg. The true rate of serious events at low dose is unknown, and the DELII safety population and attribution rule should be confirmed from the full report.

The case for a randomised dose comparison

Pharmacology predicts that 20 to 40 mg saturates peripheral PD-1, and the observational response rate sits in the range reported for standard dose. Neither establishes equivalence: tumour receptor occupancy, antibody clearance in cachectic patients and the frequency of dosing may matter more than peak occupancy. Retrospective comparisons will not resolve this, because affordability selects patients. The obvious design is a randomised non-inferiority trial of nivolumab 20 mg every 2 weeks, the regimen with randomised support from DELII, against 240 mg every 2 weeks, with overall survival as the endpoint. Extending the interval is not advisable without trough data. Gandhi 2024 measured first-dose kinetics only: half-life (about 11 to 12 days) and clearance were similar after 40 mg and 3 mg/kg, and peak concentration after 40 mg was 9.06 µg/mL against 47.3 µg/mL, but no trough concentrations were reported[22]. NVALT-30 shows that dose-reduction trials of checkpoint inhibitors are feasible[34].

Limitations and the direction of bias

Evidence base. The search was targeted, not systematic. Missing cohorts are most likely small Indian retrospective series.

Selection. Patients offered low-dose nivolumab on compassionate grounds had exhausted standard options and were often frail; the direction of this bias is unknown.

Dose intensity. Three cohorts did not report how many patients received each dose, so their intensity is a range.

Overlapping cohorts. Kumar 2025 (treatment started up to February 2020) and Gandhi 2024 (enrolment 2019 to 2021) both come from Tata Memorial Hospital, so some patients may appear in both; removing Gandhi 2024 changed the primary estimate from 13.9% to 14.4% (Table 3).

Single reviewer. Screening, extraction and appraisal were done once and must be repeated independently.

Implications

For clinicians where standard dose is unaffordable, two randomised trials support low-dose nivolumab in pretreated solid tumours, chiefly head and neck cancer: alone in place of a taxane, or added to metronomic chemotherapy. For trialists, the dose question is open and testable. For journals, low-dose

cohorts should report responders against all treated patients, the dose actually delivered and adverse events with an explicit attribution rule.

Appendix A. Extraction sheet**Table A1. Every count used in the analyses**

Study	Respo nders	Treat ed	Evalu able	Grade ≥ 3 events / N	Definition
Joris 2022	4	18	18	1/18	irAE (polyarthrititis)
Gauduchon 2026	11	53	53	2/53	irAE (preprint)
Mishra 2025	29	104	73	21/104	All-cause
Tiwari 2024	12	46	42	NR	—
Trikha 2024	7	30	30	0/30	irAE
Kumar 2025	9	54	50	6/54	All-cause (hyponatraemia)
Gandhi 2024	1	11	9	0/11	irAE
Yoo 2018	3	18	18	NR	—
Chen 2022	4	78	78	0/78	AE as reported¶
Schwarze 2022 (adjuvant, safety only)	—	21	—	1/21	TRAE
Comparative (low dose vs standard dose, all treated)					
Yoo 2018 (solid tumours)	3 vs 4	18 vs 29	—	—	Objective response
Gandhi 2024 (solid tumours)	1 vs 2	11 vs 14	—	—	Objective response
Trikha 2024§ (solid tumours)	7 vs 12	30 vs 35	—	—	Objective response
Fedorova 2025* (classical Hodgkin lymphoma)	42 vs 43	62 vs 62	—	—	Objective response
CMC Vellore 2026* (classical Hodgkin lymphoma)	12 vs 15	20 vs 25	—	—	Objective response
Randomised trials					
DELII 2026	—	250 vs 250	—	42.5% vs 60.8%	Treatment-related, as reported
Patil 2023	—	151	—	NR	—

Appendix B. Reports not used**Table B1. Reports assessed and not used in the solid-tumour analysis**

Report	Reason
Patel 2024[35]	Response table has no stable-disease category; "partial response" cannot be separated from disease control
Dhanawat 2024[36]	Immunotherapy combined with chemotherapy; survival only, no response by dose
Devabhaktuni 2023[37]	55% received chemotherapy; two reports disagree on response counts
Zhao 2021[38]	Low dose defined as below a median of 2.15 mg/kg, which overlaps the approved range
Low 2021; To 2022; Chang 2022; Souza 2024	Pembrolizumab or mixed agents at about 50% dose intensity; Table S1
Lepik 2020[39]	Contained within Fedorova 2025; Hodgkin sensitivity analysis only

Appendix C. Supplementary tables**Table S1. Pembrolizumab and mixed-agent comparisons (not pooled, not in any figure)**

Study	Low dose	Standard dose	RR (95% CI)	Note
Low 2021, monotherapy	15/33	3/13	1.97 (0.68 to 5.69)	Pembrolizumab 100 mg vs 200 mg, first line[40]
Low 2021, with chemotherapy	6/13	14/29	0.96 (0.48 to 1.92)	First line with chemotherapy
To 2022	5/36	15/28	0.26 (0.11 to 0.63)	Low-dose arm had more combination and later-line use[41]
Souza 2024 (mixed agents)	16/42	6/17	1.08 (0.51 to 2.29)	Mostly pembrolizumab; 9 nivolumab[42]
Chang 2022[43]	—	—	OS HR 1.19 (0.88 to 1.61)	IPTW-adjusted; reported as 0.84 standard vs low, inverted

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