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Efficacy of immune checkpoint inhibitors in the first line therapy of non-squamous non-small cell lung cancer: A systematic review and network meta-analysis

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ABSTRACT

Aim: By 2026, several PD-1/PD-L1 antibodies were approved by FDA, EMA and non-EU Eastern European countries for the first-line therapy in advanced non-squamous non-small cell lung cancer (nsNSCLC) without EGFR mutations or ALK alterations. This study aimed to compare overall (OS) and progression-free (PFS) survival among anti-PD-1/PD-L1-containing regimens and to evaluate the immunotherapy effect modification due to PD-L1 expression.

Methods: A systematic search in MEDLINE and Embase on December 23, 2025 identified 15 Phase III randomized clinical trials involving adults with advanced nsNSCLC treated with therapies containing prespecified anti-PD-1/PD-L1 agents. Bayesian multilevel network meta-regressions with M-splines were estimated for OS and PFS, incorporating covariates for PD-L1 expression (TPS $<1\%$ versus $\geq 1\%$) and its interaction with the treatment class (anti-PD-1/PD-L1-based regimens versus chemotherapy ± bevacizumab).

Results: Regardless of PD-L1 expression, treatments with the highest probability of being the best (SUCRA) by OS are prolgolimab + chemotherapy, pembrolizumab + chemotherapy and cemiplimab + chemotherapy (SUCRA 0.80–0.94), by PFS — nivolumab + bevacizumab + chemotherapy and atezolizumab + bevacizumab + chemotherapy (SUCRA 0.91–0.96). The hazard ratio for the interaction between PD-L1-negative status and anti-PD-1/PD-L1-containing therapy was 1.09 (95% CrI, 0.95–1.25) for OS and 1.41 (95% CrI, 1.16–1.71) for PFS.

Conclusion: For advanced nsNSCLC patients, irrespective of PD-L1 expression, prolgolimab, pembrolizumab or cemiplimab, each combined with chemotherapy, are most efficacious by OS; nivolumab or atezolizumab combined with bevacizumab and chemotherapy demonstrate the highest PFS. PD-L1 expression does not modify the effect of examined immunotherapy options on OS, though the opposite is true for PFS.

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1. Introduction

The first-line therapy determines the success of the treatment strategy in adults with non-squamous non-small cell lung cancer (nsNSCLC). The first step and a standard of care fur such patients is identification of the driver mutations following by prescription of the targeted therapy. In patients without driver mutations, immune checkpoint inhibitors (ICIs) are highly efficacious and are included in all leading treatment guidelines. Since 2015, the FDA approved five PD-1/PD-L1 antibodies (nivolumab, pembrolizumab, cemiplimab, atezolizumab, and durvalumab) in the first-line settings for adults with advanced nsNSCLC. Recently, other anti-PD-1/PD-L1 agents have been registered in this indication, including tislelizumab (in 2024) and sugemalimab (in 2025) in the European Union, prolgolimab (in 2023) and camrelizumab (in 2025) in the Russian Federation.

Although progression-free survival and overall survival were substantially improved by adding PD-1/PD-L1 inhibitors to chemotherapy in nsNSCLC, the unmet need in highly effective non-toxic treatment options still exists. Moreover, real-world data analysis shows that the effectiveness of anti-PD-1/PD-L1-containig regimens can be different in routine practice and clinical studies (Knetki-Wróblewska et al. 2024; Moiseenko et al., 2025). Due to the numerous options approved in advanced nsNSCLC, sometimes having the same priority in the clinical guidelines, clinicians are uncertain about which of the proposed treatment regimens is optimal. Currently there is no sufficient evidence on comparative efficacy and effectiveness of different anti-PD-1/PD-L1 agents, including newly emerged ones and their combinations with chemotherapy, bevacizumab and/or CTLA-4 antibodies.

Tumor and microenvironmental cell expression of PD-L1 is primarily considered as a biomarker predictor of response to ICIs. However, the results on its association with efficacy outcomes in nsNSCLC treated with chemoimmunotherapy are contradictory (Desai and Peters, 2023).

Previous meta-analyses often failed to account for the heterogeneity of included studies by NSCLC histology, as well as for new anti-PD-1/PD-L1 drugs, and had limited power in the subgroup analyses by PD-L1 expression (Aggarwal et al., 2023; Dafni et al., 2019; Gemelli et al., 2025; Girard et al., 2025; Herbst et al., 2021; Liang et al., 2020; Lu et al., 2023; O'Byrne et al., 2023; Peng et al., 2021; Shao et al., 2022).

We evaluated multilevel network meta-regressions (ML NMR) to compare overall (OS) and progression-free (PFS) survival across anti-PD-1/PD-L1 therapies approved by December 23, 2025 in the USA, the EU and the non-EU Eastern European countries in patients with advanced nsNSCLC without EGFR mutations or ALK alterations depending on the status of PD-L1 expression.

2. Materials and methods

2.1. Search strategy, study selection and data extraction

Systematic literature review (SLR) was performed to identify Phase II-IV randomized clinical trials (RCTs) on adults with unresectable and/or metastatic (advanced) NSCLC treated with ICIs approved for the first-line treatment in the USA, the EU or the non-EU Eastern European countries reporting OS and/or PFS. The database search was conducted in MEDLINE and Embase on March 12, 2024 based on PROSPERO protocol (CRD42024521004) which included the following anti-PD-1/PD-L1 agents: atezolizumab (ATEZO), cemiplimab (CEMI), durvalumab (DURVA), nivolumab (NIVO), pembrolizumab (PEMBRO), prolgolimab (PROLGO) and tislelizumab (TISLE) administered in monotherapy or in combination with anti-CTLA4 agents (ipilimumab (IPI) or tremelimumab (TREME)), bevacizumab (BEVA) and/or chemotherapy (CHEMO). The search was updated on December 23, 2025 to include additional treatments with sugemalimab (SUGE) and camrelizumab (CAMRE) which were approved in the region after the original SLR.

Studies were eligible irrespective of publication date. Only publications in English were included. Original and updated search strategies are provided in Supplementary Methods S1.

Search results and reference lists of relevant reviews and articles were imported into EndNote X9.2. Two reviewers (N.A.S. and L.A.A.) independently screened titles and abstracts and assessed full texts for eligibility; a third expert (T.D.G.) resolved disagreements. If a trial included patients irrespective of NSCLC histology or EGFR mutations or ALK rearrangements and survival curves for the subgroup with nsNSCLC without these alterations were published, it was included, otherwise – not included into our analysis. Trials recruited only patients with high PD-L1 expression were excluded.

Risk of bias was assessed by the Cochrane RoB 2 tool independently by two experts (N.A.S. and L.A.A), a third researcher (T.D.G) resolved disagreements.

For selected trials, publication lists on clinicaltrials.gov and conference proceedings from European Lung Cancer Congress (ELCC), American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) were additionally screened for the most recent available Kaplan-Meier curves for OS and PFS.

Study and baseline patient characteristics for each included RCT were extracted into Microsoft Excel forms.

Kaplan-Meier curves were digitized using EngaugeDigitizer v.12.1, and individual patient data (IPD) were reconstructed using Guyot's algorithm (Guyot et al., 2012). The quality of approximation was controlled by comparing the milestone values and median survival evaluated on the restored IPD with the published ones. If Kaplan-Meier curves were available for all subgroups by PD-L1 expression, we restored IPD for each of them.

2.2. Statistical analysis

Proportionality of hazards for OS and PFS between each ICIs-containing arm and CHEMO±BEVA in every trial was preliminary evaluated through Grambsch-Therneau test (Grambsch and Therneau, 1994) and visual inspection of plots for the cumulative hazard ratios and Schoenfeld residuals, with priority given to the visual diagnostics.

We estimated Bayesian ML NMRs for OS and PFS with cubic M-splines for baseline hazard stratified by study. For each trial, seven internal knots were placed at evenly spaced quantiles of the observed event times, boundary knots – at zero and maximum observation time. Although a smaller number of internal knots is usually sufficient, we used a slightly larger number as a safety margin, since potential overfitting was mitigated by shrinkage from the random-walk prior (Phillippo et al., 2024).

All trials for which we had original IPD on both survival and PD-L1 expression or restored IPD in subgroups by PD-L1 expression were included at the individual level of the ML NMRs. All patients here were divided into PD-L1-negative (tumor proportion score (TPS) < 1 % or PD-L1 expression < 1 % in both tumor cells (TC) and tumor-infiltrating immune cells (IC)) and PD-L1-positive (otherwise). For the rest of studies, we used approximated IPD on survival and aggregate data on the proportion of PD-L1-negative patients in the corresponding arms.

Status of PD-L1 expression and its interaction with a treatment class (anti-PD-1/PD-L1-based regimens versus CHEMO±BEVA) entered the individual level of the basic specification of ML NMRs as covariates. If PD-L1 expression is an immunotherapy effect modifier, then its omission can cause non-proportionality of hazards at the marginal level, when population is a mix of PD-L1-negative and PD-L1-positive patients. Thus, by inclusion of the covariate for PD-L1 expression we removed this potential source of non-proportionality of hazards between treatments of different classes, assuming their proportionality within classes and subgroups of PD-L1-negative and PD-L1-positive patients.

We also tried specifications with a division into five treatment classes (ICIs without CHEMO and BEVA, ICIs+CHEMO, ICIs+BEVA+CHEMO, BEVA+CHEMO, CHEMO), using ten internal knots and modeling non-proportionality of hazards with stratification of spline coefficients by

treatment class. Model fits were compared using the LOOIC (leave-one-out cross-validation information criteria) (Vehtari et al., 2017).

Treatment effects were estimated with marginal hazard ratios (HRs) in the situation of proportional hazards or 3-year marginal cumulative hazard ratios (cHRs) otherwise. Three years was chosen as a clinically relevant time point for survival comparisons.

We used the following prior distributions for the model parameters: normal with mean 0 and standard deviation 100 for the intercept of the linear predictor and all regression coefficients (on the log-hazard scale), random walk prior distribution for the inverse softmax transformed spline coefficients, half-normal distribution with mean 0 and standard deviation 1 for the random walk standard deviation. Bayesian estimation used a Markov chain Monte-Carlo algorithm with 4 chains of 5000 iterations each, 2500 burn-in iterations. The convergence was estimated using the Gelman-Rubin statistics (Rhat) with a convergence threshold of 1.05 (Vehtari et al., 2021).

Due to the limited number of direct comparisons in both networks random-effects models had problems with convergence, so fixed-effects models were estimated.

Posterior results were presented by median posterior estimates with 95 % quantile credible intervals (CrIs): for survival – in the population of the reference study, i.e. based on its baseline hazard and with its proportion of PD-L1-negative patients, for marginal HRs and cHRs – just with its proportion of PD-L1-negative patients, as they do not depend on the baseline hazard.

In addition, results in subgroups of PD-L1-negative and PD-L1-positive patients were reported.

Treatments were ranked by SUCRA (surface under the cumulative ranking curve). In case of proportional hazards SUCRAs are independent of time and estimand (milestone survival, hazard or cumulative hazard), otherwise we assessed SUCRA for 3-year survival.

Analysis was done in R v.4.3.1. using the "multinma" package v.0.7.2. (Phillippo, 2024).

3. Results

3.1. Systematic literature search and characteristics of selected trials

Publication selection process for the combined original and updated search results is shown in the PRISMA diagram (Figure S1), Key excluded articles with the reason of exclusion are listed in Supplementary Results S1. 15 Phase III RCTs were included into the OS network (Borghaei et al., 2023; Brahmer et al., 2023; Carbone et al., 2025; Garassino et al., 2023; Laktionov et al., 2025; Lee et al., 2025; Ma et al., 2024; Makharadze et al., 2023; Nishio et al., 2021; Peters et al., 2025; Socinski et al., 2021; West et al., 2019; Zhou et al., 2025b, 2025a, 2024). 14 of these contributed to the PFS network (Borghaei et al., 2023; Carbone et al., 2025; Garassino et al., 2023; Johnson et al., 2023; Laktionov et al., 2025; Lee et al., 2025; Ma et al., 2024; Makharadze et al., 2023; Nishio et al., 2021; West et al., 2019, 2022; Zhou et al., 2025b, 2025a, 2024). The OS and PFS networks comprised 17 and 15 unique treatment options, respectively, of which 15 and 13 included ICIs. CHEMO and BEVA+CHEMO were used for connectivity in both of them (Fig. 1).

The included RCTs with their key characteristics and publications from which data were extracted are listed in Table S1. All trials except DOMAJOR, EMPOWER-Lung 3, GEMSTONE-302, IMpower151, KEYNOTE-189 and TASUKI-52 were open-label. In all arms with CHEMO, platinum-based doublet therapy was used. According to the RoB2 tool, all studies had low risk of bias overall and across each domain (Table S2), so methodological between-trial heterogeneity was assessed as low and sensitivity analyses to exclusion of trials according to design issues were not performed.

There were no published data on PFS for CheckMate 227 Part 1. For the remaining studies the latest available data on OS and PFS were obtained from the same publication, except for IMpower150 for which PFS was reported for the later cut-off than OS, and POSEIDON for which the reverse was true. IPD for both survival and patient characteristics for the RCT DOMAJOR were provided to us by the study Sponsor. IPD on OS in CameL, CheckMate 227 Part 1, CheckMate 9LA, IMpower150, KEYNOTE-189 and TASUKI-52, as well as on PFS in CameL, CheckMate 9LA, KEYNOTE-189 and TASUKI-52, were restored in subgroups by PD-L1 expression. Therefore, along with IPD in DOMAJOR, they were used

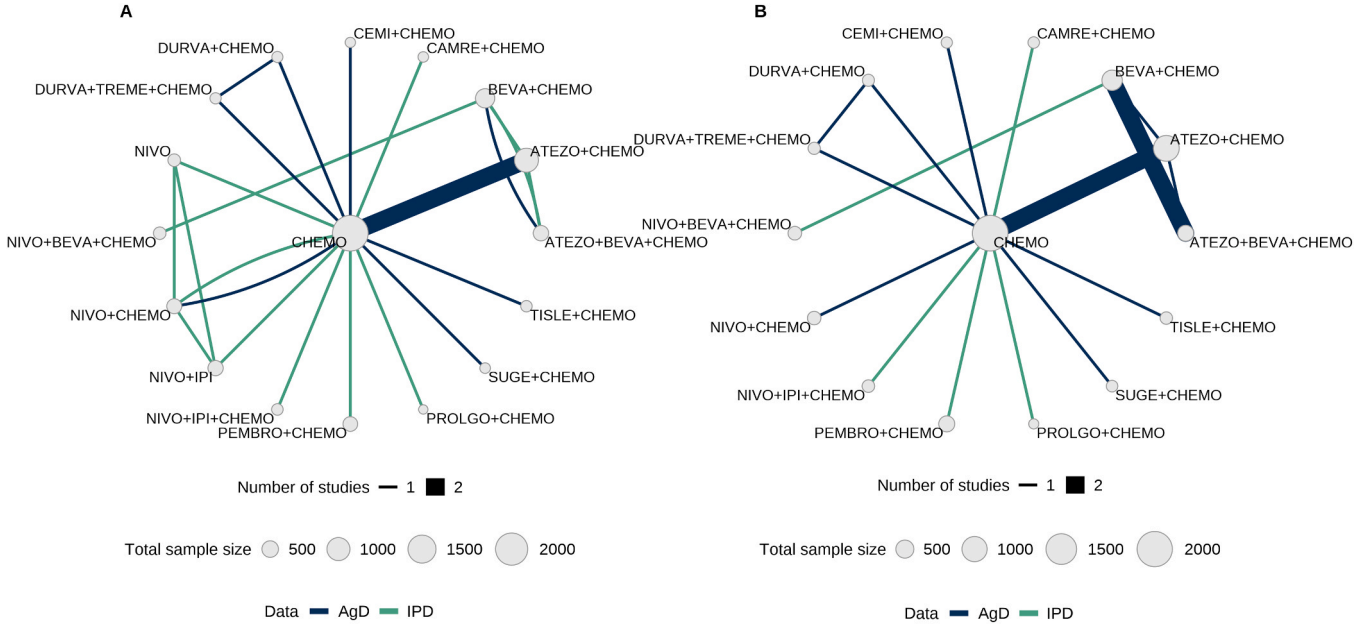

Fig. 1. Network diagrams for overall (A) and progression-free (B) survival. AgD: aggregate data for covariates (PD-L1 expression). IPD: individual patient data for covariates (PD-L1 expression). ATEZO: atezolizumab. BEVA: bevacizumab. CAMRE: camrelizumab. CEMI: cemiplimab. CHEMO: chemotherapy. DURVA: durvalumab. IPI: ipilimumab. NIVO: nivolumab. PEMBRO: pembrolizumab. PROLGO: prolgolimab. SUGE: sugemalimab. TISLE tislelizumab. TREME: tremelimumab.

at the individual level of the corresponding ML NMRs. For remaining trials, we used IPD on survival restored for the whole arm population and proportion of PD-L1-negative patients in each arm at the aggregate level of the model. In Nishio et al. (2021) Kaplan-Meier curves by PD-L1 expression were published, but PD-L1 expression was not evaluable in 40 % of patients. Thus, IMpower132 was included only at the aggregate level, with the assumption that the proportion of PD-L1-negative patients among evaluable and not evaluable populations is the same. In CameL, CheckMate 227 Part2, CheckMate 9LA, IMpower150, KEYNOTE-189 and POSEIDON the proportion of patients with missing PD-L1 expression was negligible (<1–9 %), in the rest of trials it was zero. In TASUKI-52 individuals with indeterminate expression (number not reported) were combined with PD-L1-negative patients.

In total, the OS and PFS networks contain data on 8006 and 6631 patients with 5692 and 5149 events, respectively. Baseline patient characteristics are presented in Table S3 (Borghaei et al., 2023; Brahmer et al. 2023; Garassino et al., 2023; Gogishvili et al., 2022; Laktionov et al., 2025; Lee et al., 2025; Lu et al., 2021; Nishio et al., 2021; Peters et al., 2025; Reck et al., 2021; Socinski et al., 2021; West et al., 2019; Zhou et al., 2025b, 2025a, 2021). CheckMate 227 Part 1, CheckMate 227 Part 2, CheckMate 9LA, EMPOWER-Lung 3, GEMSTONE-302 and POSEIDON included patients with both squamous and non-squamous NSCLC (with proportion of the latter varied from 57 % to 72 %); for nsNSCLC strata, data on survival were available in all of them, while baseline characteristics were reported only for CheckMate 227 Part 2 and POSEIDON. Therefore, for EMPOWER-Lung 3 and GEMSTONE-302, for which survival curves in subgroups by PD-L1 expression in patients with nsNSCLC were not published, we assumed that the proportion of PD-L1-negative patients in the nsNSCLC subgroup was the same as in the whole corresponding trial arm population.

Kaplan-Meier curves for OS and PFS obtained from the original IPD (for DOMAJOR) or restored IPD (for the rest of studies) are shown in Figures S2-S5, the number of events and median survival estimated from them, along with the proportion of PD-L1-negative patients used or assumed in our analysis are reported in Tables S4-S5. Maximum follow-up exceeded 5 years in five trials in the OS network (CameL, CheckMate 227 Part 1, CheckMate 9LA, KEYNOTE-189, POSEIDON) and three trials in the PFS network (CameL, CheckMate 9LA, KEYNOTE-189). In four (CheckMate 227 Part 2, EMPOWER-Lung 3, IMpower130, Impower151) and five (EMPOWER-Lung 3, IMpower130, IMpower132, IMpower151, POSEIDON) studies, respectively, it was less than 3 years. Median OS and PFS were reached in all included studies and arms. Progression was registered according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.

Preliminary diagnostics showed only minor deviations from proportionality of hazards in KEYNOTE-189 and RATIONALE-304 in the OS network and IMpower150 (ATEZO+CHEMO versus BEVA+CHEMO) in the PFS network (Figures S6-S9).

In CheckMate 227 Part 1, NIVO+CHEMO was administered only to PD-L1-negative patients, and NIVO monotherapy only to PD-L1-positive patients. On the trial level, the proportion of PD-L1-negative patients varied from 30 % (EMPOWER-Lung 3) to 52 % (IMpower130), of high PD-L1 expressors ranged from 13 % (IMpower132) to 35 % (CheckMate 227 Part 1). Similar variation was observed for other baseline characteristics (Table S3).We considered clinical between-trial heterogeneity as moderate. We were unable to account for it with random treatment effects because estimation did not converge due to the small number of direct comparisons in our networks. Between-trial differences in PD-L1 expression were adjusted by incorporating the covariate for it into ML NMRs. We did not include other covariates because IPD for them were available from only one study, and using aggregate data for these covariates for the other studies would have forced us to use aggregate data for the proportion of PD-L1-negative patients as well, resulting in less accurate estimates.

3.2. ML NMR results

3.2.1. Posterior survival estimates

Using five treatment classes (instead of two), ten internal knots (instead of seven), and stratifying spline coefficients by treatment class within each study did not improve the fit of OS and PFS models: these specifications produced significantly higher LOOIC and were therefore rejected. In the final specification we used seven internal knots, stratified spline coefficients only by trial, and included an interaction between PD-L1 expression status and a binary treatment-class variable (anti-PD-1/PD-L1-containing regimens versus CHEMO±BEVA). In the PD-L1-negative and PD-L1-positive subgroups hazards for any pair of therapies were modeled as proportional; therefore, results for treatment comparisons in these subgroups are reported with marginal HRs (time-invariant). For the combined population (both PD-L1-negative and PD-L1-positive patients), hazards were modeled as non-proportional for pairs of options from different classes; accordingly, results for treatment comparisons in such populations are presented with marginal 3-year cHRs.

Posterior OS and PFS estimates in the original study populations, predicted by the final model specifications, along with Kaplan-Meier curves, are shown in Figures S11-S12. Visually, models fit available data quite well.

Unless otherwise stated, all further calculations implying survival estimates were done with the baseline hazard for the DOMAJOR study and 40 % for proportion of PD-L1-negative patients observed in it – this population will be indicated as a reference one. We chose DOMAJOR due to the availability of the original IPD for it. In addition, the percentage of PD-L1-negative patients in it was the same to their share in the whole OS and PFS networks (41 % and 42 %, respectively). Posterior OS and PFS distributions for each treatment option in this population are shown in Fig. 2. The choice of the reference study does not change rankings of the treatments (see Figures S13-S14).

Plots for dynamics of hazard rates on each treatment option in the reference population and time-dependent HRs in comparison to CHEMO are shown in Figures S15-S17. In population with 40 % of PD-L1-negative patients, marginal HRs of all anti-PD-1/PD-L1-containing options versus CHEMO±BEVA are almost constant in the OS network and slightly decreasing over time in the PFS network.

3.2.2. Effect modification due to PD-L1 expression status

PD-L1 expression is a prognostic factor for OS on both immunotherapy and CHEMO±BEVA and for PFS on the immunotherapy. For anti-PD-1/PD-L1-based regimens, the HR for PD-L1-negative versus PD-L1-positive status is 1.38 (95 % CrI, 1.25–1.53) for OS and 1.51 (95 % CrI, 1.31–1.73) for PFS. For CHEMO±BEVA, the corresponding HRs are 1.27 (95 % CrI, 1.14–1.41) and 1.07 (95 % CrI, 0.94–1.22). At the same time, PD-L1 expression is an effect modifier for PFS, but not for OS. Specifically, PD-L1-negative individuals gain less benefit from immunotherapy over CHEMO±BEVA than PD-L1-positive ones concerning lower hazard of PFS events (HR for the interaction term between expression status and treatment class is 1.41; 95 % CrI, 1.16–1.71), but almost the same reduction in the hazard of death (interaction HR 1.09; 95 % CrI, 0.95–1.25) (Fig. 3).

3.2.3. Treatment comparisons and rankings

3-year cHRs for each treatment in comparison to CHEMO along with 3-year survival and SUCRAs are given in Figs. 4–5, cumulative ranking curves and league tables for 3-year cHRs for all pairwise treatment comparisons are shown in Figures S17-S19. Posterior survival distributions, HRs in comparison to CHEMO and all pairwise HRs in subpopulations by PD-L1 status can be found in Figures S20-S25.

As PD-L1 expression does not modify the immunotherapy effect on OS, treatment rankings are almost identical in the population comprising 40 % of PD-L1-negative patients and in the PD-L1-negative and PD-L1-positive subgroups. This yields similar HRs and 3-year

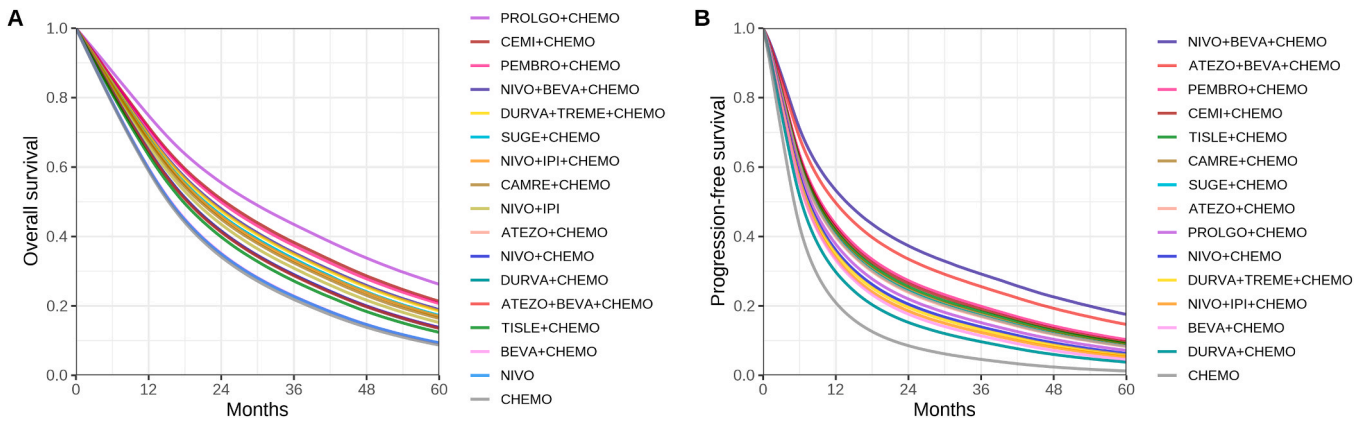

Fig. 2. Median posterior estimates of the overall (A) and progression-free (B) survival in the reference population. Notes. Treatment options in legends are listed in the descending order by survival probability at 60 months. For the reference population, the baseline hazard was set equal to that estimated for the DOMAJOR trial, and the proportion of PD-L1-negative patients was set at 40 %. ATEZO: atezolizumab. BEVA: bevacizumab. CAMRE: camrelizumab. CEMI: cemiplimab. CHEMO: chemotherapy. DURVA: durvalumab. IPI: ipilimumab. NIVO: nivolumab. PEMBRO: pembrolizumab. PROLGO: prolgolimab. SUGE: sugemalimab. TISLE tislelizumab. TREME: tremelimumab.

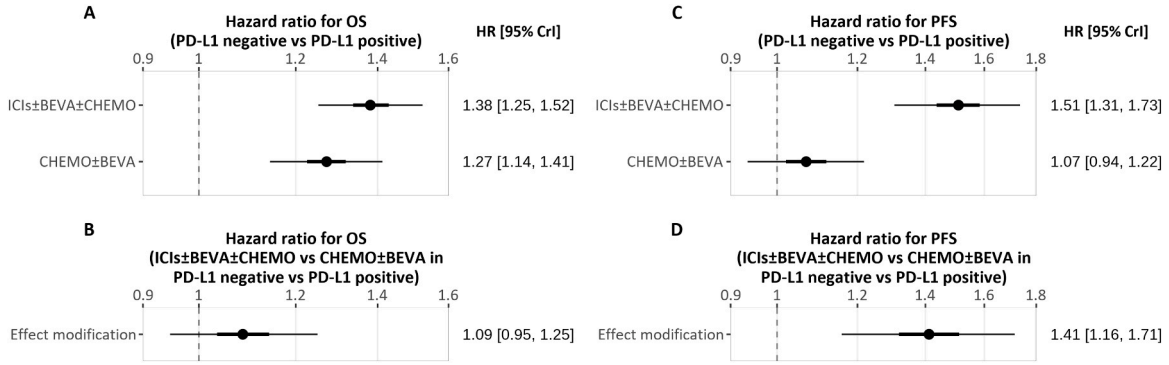

Fig. 3. Marginal hazard ratios for overall (A) and progression-free (C) survival for PD-L1-negative versus PD-L1-positive status and for treatment class effect modification due to PD-L1 expression for overall (B) and progression-free (D) survival. Notes. Median posterior estimates with 50 % (bold line) and 95 % (thin line) credible intervals are shown. OS: overall survival. PFS: progression-free survival. BEVA: bevacizumab. CHEMO: chemotherapy. ICIs: immune checkpoint inhibitors. HR: hazard ratio. CrI: credible interval.

cHRs for OS across these populations, with less uncertainty in the PD-L1-positive subgroup, as it predominated in our network. The highest-ranked treatment options by OS are PROLGO+CHEMO (in the population with 40 % of PD-L1-negative patients, 3-year cHR versus CHEMO 0.55, 95 % CrI, 0.40–0.74; SUCRA 0.94), PEMBRO+CHEMO (cHR 0.65, 95 % CrI, 0.54–0.78; SUCRA 0.81) and CEMI+CHEMO (cHR 0.63, 95 % CrI, 0.46–0.87; SUCRA 0.80). The credibility intervals for the hazard ratios of SUGE+CHEMO, CAMRE+CHEMO and combinations of anti-PD-L1 with anti-CTLA4 ±CHEMO overlap substantially with those for the three top options, so these regimens may have clinically comparable OS. The remaining four combinations of anti-PD-1/PD-L1 (ATEZO, NIVO, DURVA, TISLE) with CHEMO have a bit lower OS: their median 3-year cHRs versus CHEMO exceed 0.8.

The ranking by PFS is different. The top-ranked treatments here, irrespective of PD-L1 expression, are NIVO+BEVA+CHEMO (in the population with 40 % of PD-L1-negative patients, 3-year cHRs versus CHEMO 0.40, 95 % CrI, 0.30–0.54; SUCRA 0.96) and ATEZO+BEVA+CHEMO (cHR 0.44, 95 % CrI, 0.36–0.55; SUCRA 0.91). These regimens have more favorable PFS outcomes than all others. Immunotherapy effect modification by PD-L1 expression leads to marginal HRs for PFS for all anti-PD-1/PD-L1-containing options versus CHEMO±BEVA depending on the proportion of PD-L1-negative patients in the population. As a result, BEVA+CHEMO is comparable in PFS to anti-PD-1/PD-L1 +CHEMO for PD-L1-negative patients but is inferior to these combinations for PD-L1-positive patients. In contrast to OS, combinations of anti-PD-1/PD-L1 and CHEMO a bit outperform anti-CTLA-4-containing options by PFS, except for DURVA+CHEMO, which is at the bottom of treatment rankings by PFS.

4. Discussion

To compare OS and PFS between ICIs in the first-line therapy of adults with advanced nsNSCLC we conducted SLR and estimated Bayesian ML NMRs with a covariate for PD-L1 expression status and its effect modification shared between options of the same treatment class (anti-PD-1/PD-L1-based regimens or CHEMO±BEVA). We utilized IPD on survival with the mix of IPD and aggregate data for PD-L1 expression.

4.1. Main results

We demonstrated that, irrespective of PD-L1 expression, the top-ranked therapies by OS are three combinations of anti-PD-1 drugs (PROLGO, PEMBRO or CEMI) with CHEMO. The second-best options are SUGE+CHEMO, CAMRE+CHEMO, NIVO+BEVA+CHEMO and anti-PD-1/PD-L1 +anti-CTLA-4 ±CHEMO. The third group consists of the rest four combinations of anti-PD-1/PD-L1 (ATEZO, NIVO, DURVA, TISLE) with CHEMO and ATEZO+BEVA+CHEMO. NIVO monotherapy and CHEMO±BEVA complete the rating. Irrespective of PD-L1 expression, the most highly ranked therapies by PFS are combinations of BEVA, CHEMO and anti-PD-1/PD-L1 (NIVO or ATEZO), while all anti-PD-1/

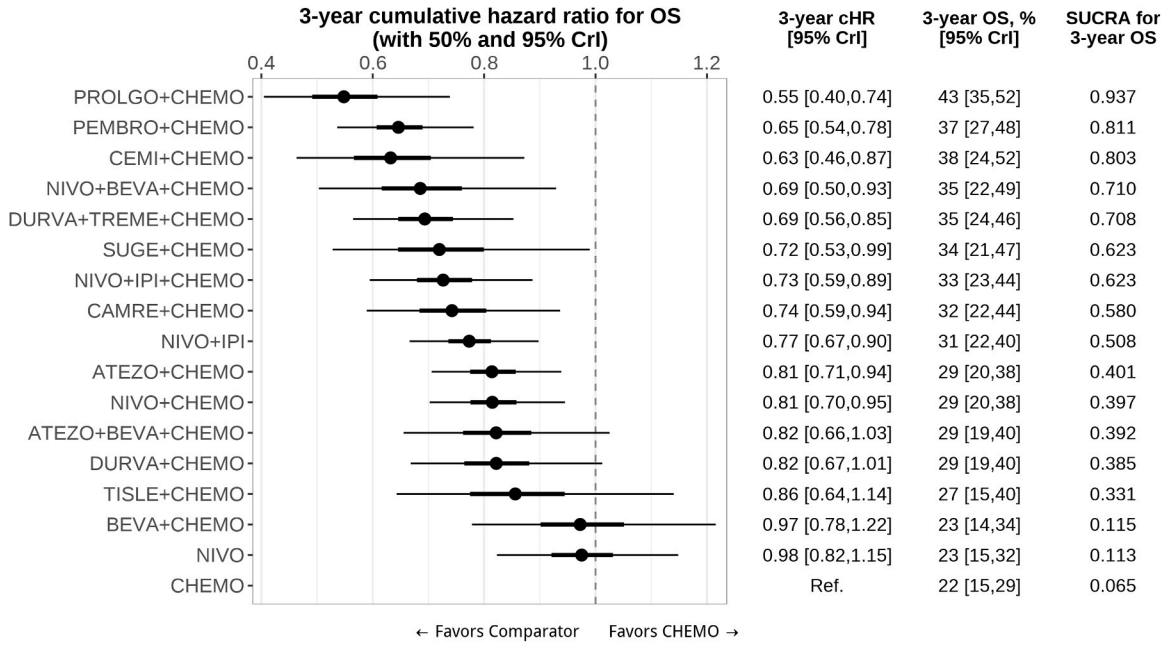

Fig. 4. Marginal 3-year cumulative hazard ratios for overall survival in comparison to chemotherapy in the reference population. Notes. Median posterior estimates with 50 % (bold line) and 95 % (thin line) credible intervals are shown. Treatment options are listed in the descending order by SUCRA value. For the reference population, the proportion of PD-L1-negative patients was set at 40 %. OS: overall survival. cHR: cumulative hazard ratio. CrI: credible interval. Ref.: reference group. ATEZO: atezolizumab. BEVA: bevacizumab. CAMRE: camrelizumab. CEMI: cemiplimab. CHEMO: chemotherapy. DURVA: durvalumab. IPI: ipilimumab. NIVO: nivolumab. PEMBRO: pembrolizumab. PROLGO: prolgolimab. SUGE: sugemalimab. TISLE tislelizumab. TREME: tremelimumab.

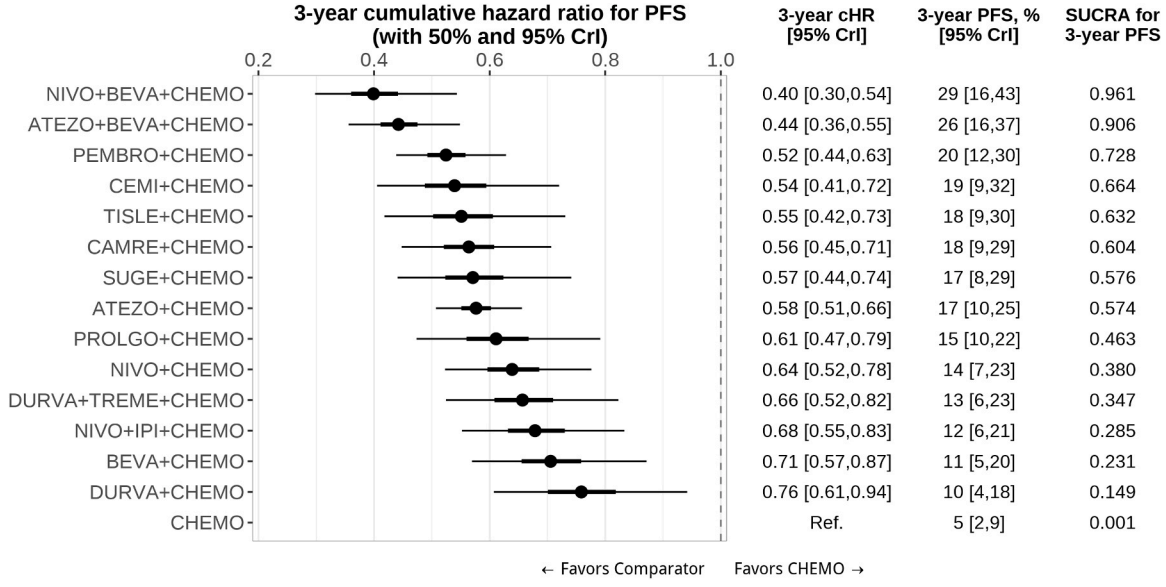

Fig. 5. Marginal 3-year cumulative hazard ratios for progression-free survival in comparison to chemotherapy in the reference population. Notes. Median posterior estimates with 50 % (bold line) and 95 % (thin line) credible intervals are shown. Treatment options are listed in the descending order by SUCRA value. For the reference population, the proportion of PD-L1-negative patients was set at 40 %. PFS: progression-free survival. cHR: cumulative hazard ratio. CrI: credible interval. Ref.: reference group. ATEZO: atezolizumab. BEVA: bevacizumab. CAMRE: camrelizumab. CEMI: cemiplimab. CHEMO: chemotherapy. DURVA: durvalumab. IPI: ipilimumab. NIVO: nivolumab. PEMBRO: pembrolizumab. PROLGO: prolgolimab. SUGE: sugemalimab. TISLE tislelizumab. TREME: tremelimumab.

PD-L1 +CHEMO options, except for DURVA+CHEMO, are more efficacious than combinations with anti-CTLA-4. It should be noted that treatment rankings by SUCRA are subject to the number of treatments in the network and does not reflect the effect sizes, so we would recommend to make clinical conclusions based on the credibility intervals for HRs, cHRs and differences in the milestone survival estimates in the target population.

In our analysis, several regimens with modest PFS achieved more favorable ranks by OS, and vice versa. An imperfect correlation between PFS and OS has previously been reported in advanced NSCLC (Goulart et al., 2024; Shameer et al., 2021). This discrepancy can be explained by several factors. On the one hand, OS, in contrast to PFS, does not reflect solely the success of the first-line therapy, but also depend on the efficacy of the following treatment regimens. On the other hand, the first-line therapy directly determines the risk of progression and the choice and to a certain extent efficacy of subsequent treatments. It has

been shown that the beneficial effect of ICIs can be realized even after progression determined by the traditional RECIST version 1.1 (Blumenthal et al., 2017; Gandara et al., 2018), which therefore can overestimate the frequency of progression and underestimate the time to it for options with a delayed response (Oxnard et al., 2012). In addition, based on the preclinical studies, which have shown that tumors acquire a more aggressive phenotype after exposure to BEVA (Ebos et al., 2009; Goldhirsch et al., 2009; Pàez-Ribes et al., 2009), we can hypothesize that the differences between OS and PFS rankings for BEVA-containing combinations may be associated with the reduced post-progression survival in comparison with ICIs not combined with BEVA. This hypothesis requires further investigation.

According to our results, positive PD-L1 expression is a favorable prognostic factor for OS both on immunotherapy and CHEMO±BEVA and for PFS on immunotherapy. This role of PD-L1 expression in advanced nsNSCLC has been previously investigated for ICIs (Arfè et al., 2020; Mino-Kenudson et al., 2022; Yu et al., 2016). Concerning its effect for OS with chemotherapy, it may reflect a benefit from higher PD-L1 expression during subsequent lines of treatment, as many patients receive ICIs after progression on CHEMO±BEVA in the first line (see Figure S10).

PD-L1 positivity modifies the effect of immunotherapy over chemotherapy on PFS, but not on OS. This means that, when treated with ICIs in comparison to CHEMO±BEVA, PD-L1-negative patients, on average, experience almost the same reduction in the hazard of death but a considerably smaller reduction in the hazard of PFS events than PD-L1-positive patients. Consequently, the ranks of treatments by OS are similar between these groups, whereas in the rankings by PFS the position of BEVA+CHEMO differs: in PD-L1-positive patients it occupies the bottom of the list, while in PD-L1 negative patients it is comparable by PFS to combinations of anti-PD-1/PD-L1 and CHEMO.

4.2. Comparison to other network meta-analyses

Previously, several network meta-analyses have evaluated survival with ICIs as first-line therapy for advanced NSCLC. However, not all of them are directly comparable to our study in terms of patient populations, investigated treatments, or methods of evidence synthesis.

Our analysis thoroughly reflects the first-line treatment options accepted in the USA, the EU and non-EU Eastern European countries at the time of our updated systematic literature search (December 23, 2025), as we included all regimens containing anti-PD-1/PD-L1 agents approved for advanced nsNSCLC and used the most recent OS and PFS data available for each selected trial. Several prior network meta-analyses combined trials in patients with non-squamous and squamous NSCLC (Aggarwal et al., 2023; Kim et al., 2018; Liang et al., 2020; Lu et al., 2023; Peng et al., 2021) without accounting for effect modification by histology (Mino-Kenudson et al., 2022). Other analyses restricted to nsNSCLC (Dafni et al., 2019; Gemelli et al., 2025; Girard et al., 2025; Herbst et al., 2021; O'Byrne et al., 2023; Shao et al., 2022) are therefore the most appropriate comparators for our work, although important differences remain: (Gemelli et al., 2025) limited their research to PD-L1-negative patients, while (Girard et al., 2025; Herbst et al., 2021) focused on high PD-L1 expressors. None of these analyses included PROLGO. All except (Dafni et al., 2019) included TISLE, but (Gemelli et al., 2025; Herbst et al., 2021; Shao et al., 2022) used earlier PFS data than we had, and (Gemelli et al., 2025; Shao et al., 2022) reported no OS data. Only (Gemelli et al., 2025) included DURVA and SUGE in their network, only (Gemelli et al., 2025; Shao et al., 2022) included CAMRE, (Gemelli et al., 2025; Girard et al., 2025) included CEMI but not any BEVA-containing combinations. Conversely, compared to (Gemelli et al., 2025; Herbst et al., 2021; Shao et al., 2022), we did not include sintilimab and to (Gemelli et al., 2025) we did not include toripalimab – as they were not approved in the regions specified at the time of our updated search.

Most authors of previous network meta-analyses synthesized published HRs (Dafni et al., 2019; Gemelli et al., 2025; Girard et al., 2025; Kim et al., 2018; Xu et al., 2023). Several researchers restored IPD and applied flexible survival models (fractional polynomials in (Herbst et al., 2021; O'Byrne et al., 2023), Royston-Parmar splines in (Shao et al., 2022)), using differences in restricted mean survival time or time-dependent HRs as estimands. These models require selection of hyperparameters (powers for fractional polynomials, number of knots and specification of the baseline hazard distribution for Royston-Parmar splines): choosing them by deviance information criteria can lead to overfitting to the observed data, while judging the adequacy of survival predictions beyond the follow-up period may be too subjective. In contrast, our synthesis using M-splines relied on less restrictive assumptions and on Bayesian regularization, applying shrinkage via a random-walk prior on the spline coefficients to control overfitting.

Another advantage of ML NMR in our study is that it enabled direct estimation of effect modification of ICIs by PD-L1 expression using data from all included trials, and allowed prediction of survival and treatment comparisons for populations with any specified proportion of PD-L1-negative patients. Previous syntheses depended on separate subgroup analyses of published results for PD-L1-negative and positive patients (Aggarwal et al., 2023; Dafni et al., 2019; Kim et al., 2018; Lu et al., 2023; O'Byrne et al., 2023; Shao et al., 2022; Xu et al., 2023), which reduces statistical power and at best produces naïve between-group comparisons of the relative immunotherapy effect. We identified only one prior example (Girard et al., 2025) that applied NMRs to published HRs with covariates for multiple effect modifiers; however, that work did not synthesize survival estimates or report the magnitude of modification effects. Relying on aggregate data alone also has a risk of ecological bias in covariate coefficients and interaction terms. By combining IPD with aggregate data on PD-L1 expression in an ML NMR framework, we were able to mitigate this bias.

Of the existing network meta-analyses, (Shao et al., 2022) is the most comparable to ours in terms of population, interventions and, to some extent, methodology. Moreover, the ranks for the overlapping therapies were broadly concordant between their results and ours.

4.3. Limitations

However, our approach has several limitations. Because the networks contained few direct comparisons, we could not model between-trial heterogeneity with random effects or additional covariates. Therefore, our results may underestimate the uncertainty. It is worth noting that (Dafni et al., 2019; Shao et al., 2022; O'Byrne et al., 2023) estimated fixed-effects models for the same reason, in (Aggarwal et al., 2023; Girard et al., 2025) fixed-effects models had either similar or better fit compared with random-effects models and were used for inferences.

The lack of closed loops also precluded formal assessment of inconsistency between direct and indirect evidence. IPD on PD-L1 expression were missing for 7/15 trials in the OS network and 5/14 in the PFS network, which reduced the precision of covariate and effect-modification estimates. Consequently, we were unable to estimate treatment-specific interactions with PD-L1 status and instead assumed a shared class effect modification. That assumption may be too strong, especially in the presence of intra-class heterogeneity (for example, when BEVA is added).

Network meta-analysis relies on the transitivity assumption: trials must be exchangeable with respect to the common comparator(s) so that indirect comparisons are valid. In our networks the dominant common comparator was chemotherapy, so transitivity implies not only comparable distributions of baseline effect modifiers across trials, but also comparable follow-up procedures and subsequent therapies – the latter being particularly important for interpreting OS results. Although chemotherapy arms differed in the proportion of patients receiving subsequent immunotherapy (Figure S10), observed OS in those arms was similar across the network (see Figure S4).

The evidence for CAMRE+CHEMO, SUGE+CHEMO and NIVO+BEVA+CHEMO comes from trials, which populations were 100 % Asians, due to geographical reasons (CameL and GEMSTONE-302 were conducted in China, TASUKI-52 – in Japan, South Korea and Taiwan); this limits the external validity of the corresponding estimates to non-Asian populations and warrants cautious interpretation.

Observation periods and sample sizes differed between studies. Overall, 3-year OS and PFS results in our analysis are informed by observed data from at least one trial, except for PFS on DURVA+-CHEMO, DURVA+TREME+CHEMO and NIVO+CHEMO, which are model projections beyond the available follow-up and should be interpreted with caution. This is reflected statistically in higher uncertainty, namely, in wider credibility intervals and lower SUCRA for these options. The same applies to treatments with relatively few events and to estimates for all options at their right tail of the observation period and beyond.

Longer follow-up and additional trials, including head-to-head comparisons, are needed for more certain conclusions and overcoming the identified limitations.

Finally, it is important to mention, that not every molecule included in the analysis is equally available in the US, EU or non-EU Eastern European countries due to the regulatory and reimbursement reasons. National clinical guidelines may not include all of these options, both because of limited availability and because several agents have only recently emerged in the markets. Nevertheless, our results suggest that PD-1/PD-L1 inhibitors identified as most efficacious among the compared options in our analysis often represent the standard of care for advanced nsNSCLC and are widely used in many countries. Given the dozens of new agents currently in development outside the US and EU, analyses like ours need to be reproduced and updated regularly to account for the most recent developments in the field.

5. Conclusion

Our analysis showed that for patients with advanced nsNSCLC, irrespective of PD-L1 expression, the highest-ranked first-line treatment options by OS are PROLGO+CHEMO, PEMBRO+CHEMO and CEMI+-CHEMO, by PFS — NIVO+BEVA+CHEMO and ATEZO+BEVA+CHEMO. Positive PD-L1 expression does not modify the effect of immunotherapy on OS but does modify its effect on PFS.

Critical view

Our review aimed to compare overall (OS) and progression-free (PFS) survival among anti-PD-1/PD-L1-containing treatment options in the first-line therapy for patients with advanced non-squamous NSCLC without EGFR mutations or ALK alterations. Although multiple therapies with immune checkpoint inhibitors are approved, their head-to-head randomized comparisons are lacking.

We conducted a systematic search on March 12, 2024 and updated it on December 23, 2025. In the final analysis, we included 15 Phase III randomized controlled trials in the OS network (8006 patients) and 14 in the PFS network (6631 patients), covering 17 and 15 unique treatment options, respectively. We fitted fixed-effects Bayesian multilevel network meta-regressions (ML NMR) for OS and PFS with a covariate for PD-L1 expression status (<1 % or ≥ 1 % by TPS or TC and IC) interacted with treatment class (anti-PD-1/PD-L1-based regimen versus CHEMO $\pm$BEVA), and trial-specific baseline hazards modelled with M-splines. We used individual patient data (IPD) for survival and a mix of IPD and aggregate data for the PD-L1 status.

Compared with previous meta-analyses, our study (1) is restricted to non-squamous NSCLC to avoid bias from mixing histology subgroups, which may differ in immunotherapy effect and in survival; (2) covers all anti-PD-1/PD-L1 agents approved in the USA, the EU and non-EU Eastern European countries at the moment of our updated systematic search (including agents absent in previous syntheses); (3) applies ML NMR – a recommended method to adjust for observed effect modifiers using the mix of IPD and aggregate data, allowing control over ecological bias and prediction of treatment effects for any specified distribution of effect modifiers; (4) directly estimates immunotherapy effect modification by PD-L1 status within a unified model.

Key contributions and clinical implications of our study are the following. Irrespective of PD-L1 expression, the highest OS was observed for chemotherapy combined with one of three anti-PD-1 agents (prolgolimab, pembrolizumab, cemiplimab), while PFS favored bevacizumab + chemotherapy combinations with one of anti-PD-L1 agents (nivolumab, atezolizumab). There is a partial dissociation between PFS and OS rankings, warning that PFS-based decisions may not translate into OS benefits. PD-L1 positivity modifies immunotherapy effect on PFS but not on OS – thus negative PD-L1 status alone should not preclude immunotherapy when OS benefit is the primary goal.

We transparently report important limitations: (1) sparse direct comparisons prevented modelling between-trial heterogeneity with random treatment effects and limited our ability to adjust for additional covariates; (2) shared class effect modification may mask intra-class heterogeneity, while the small number of direct comparisons limited estimation of treatment-specific interactions with PD-L1 status; (3) survival projections for some regimens extend beyond observed follow-up and therefore carry greater uncertainty.

Within the defined scope and data limits, our ML NMR provides a methodologically strengthened comparison of OS and PFS among the first-line anti-PD-1/PD-L1 regimens in EGFR-wild and ALK-negative advanced non-squamous NSCLC, refines the role of PD-L1 expression, and identifies priorities for head-to-head trials, IPD access, and longer follow-up.

CRediT authorship contribution statement

Mikhail Fedyanin: Conceptualization, Writing - Review & Editing. **Nikolai Zhukov**: Conceptualization, Writing - Review & Editing. **Fedor Moiseenko**: Conceptualization, Writing - Review & Editing. **Olga Mironenko**: Methodology, Software, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Visualization. **Kirill Sapozhnikov**: Methodology, Software, Formal analysis, Writing - Original Draft, Project administration. **Natalia Sableva**: Investigation, Data Curation, Writing - Original Draft. **Andrei Lazarev**: Software, Formal analysis, Investigation, Data Curation. **Daria Tolkacheva**: Conceptualization, Methodology, Investigation, Writing - Review & Editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2026.105216.

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