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ORIGINAL ARTICLE

Real-world comparison of pembrolizumab alone and combined with chemotherapy in metastatic lung adenocarcinoma patients with PD-L1 expression ≥50%

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Objectives: The frontline treatment of metastatic lung adenocarcinoma with high Programmed death-ligand 1 (PD-L1) expression (≥50%) includes immune checkpoint inhibitors (ICIs) either as monotherapy or combined with chemotherapy. The added benefit of chemotherapy in this context lacks direct comparison in head-to-head trials. We aimed to compare these two ICI treatment modalities both overall and within relevant patient subgroups in a real-world setting.

Materials and methods: This retrospective, nationwide study included 410 individuals diagnosed in Norway during 2017 to 2021 with stage IV non-small-cell lung adenocarcinoma, PD-L1 expression ≥50%, and treated first line with the ICI pembrolizumab, either as monotherapy ($n = 317$) or in combination with platinum-based chemotherapy ($n = 93$). We analyzed early (6-month) and overall (3-year) risk of death after treatment initiation using Cox regression, adjusted for and stratified by sex, age, stage, PD-L1 expression, performance status, and education.

Results: Patients treated with combination therapy had a higher median overall survival compared with monotherapy (22.6 months versus 14.2 months), and reduced risk of overall death, although not statistically significant after adjustment [hazard ratio (HR) 0.74, 95% confidence interval (CI) 0.54-1.00]. However, the risk of early death was significantly lower in patients receiving combination therapy, even after adjustment (HR 0.41, 95% CI 0.23-0.76). Across most subgroups, patients receiving combination therapy had comparable or superior survival outcomes relative to those receiving monotherapy. Particularly noteworthy were the observed benefits from combination therapy over monotherapy among females, individuals with stage IVB disease, and those with PD-L1 expression exceeding 75%.

Conclusion: Our real-world study demonstrates that combination therapy with ICI and chemotherapy provides superior early survival benefits over monotherapy in PD-L1-high patients. Additionally, certain subgroups showed enhanced overall survival. These findings challenge current treatment practices and underscore the need for further validation to optimize patient selection for monotherapy versus combination therapy, in particular to reassess the role of PD-L1 in treatment decisions.

Key words: non-small-cell lung cancer, immunotherapy, pembrolizumab, immune checkpoint inhibitors, overall survival, chemotherapy

INTRODUCTION

Immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein 1 receptor (PD-1), or its ligand (PD-L1) have transformed the management of advanced non-small-cell lung cancer (NSCLC) without targetable mutations and is now the frontline treatment.[1] ICIs can be administered either as monotherapy or in combination with chemotherapy. Evidence from randomized controlled trials indicates that patients with high (≥50%) expression levels of PD-L1 on tumor cells benefit from ICIs alone,[2-5] while patients with low (<50%) PD-L1 expression benefit more from ICIs in combination with chemotherapy.[6-8] Consequently, clinical guidelines support combination therapy for patients with low PD-L1 expression and monotherapy for patients with high PD-L1 expression. However, the potential added benefit of combination

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therapy for those with high PD-L1 expression remains uncertain, and has not been directly compared with monotherapy in randomized controlled trials.[3]

Recent cross-trial comparisons and observational studies comparing ICI monotherapy and combination therapy in patients with advanced NSCLC with high PD-L1 expression reveal comparable long-term benefits between monotherapy and combination therapy, but a higher proportion of patients undergoing monotherapy experience early disease progression.[9-13] This has resulted in modification of the clinical guidelines for patients with high PD-L1 expression to include combination therapy for patients with a more threatening disease and good chemotherapy tolerance, and monotherapy in most other cases.[14] However, there is a lack of knowledge about the effectiveness of this practice in a real-world clinical setting, and further refinement of patient selection criteria is needed to identify patients that are of higher risk of progression during monotherapy, and thus could benefit from a more intensified regimen with chemotherapy.[5]

Subgroup analyses from both observational and clinical studies suggest that female sex, high tumor burden, and nonsmoking status may be associated with poorer response to ICI monotherapy and that patients with these characteristics may derive a greater benefit from combination therapy.[12,13,15-17] However, the extent of this research is limited, and more validation is needed to understand the added benefit of chemotherapy in different subpopulations. Additionally, there is a lack of studies examining the benefit of adding chemotherapy to ICIs in patients with even higher PD-L1 expression ($\geq$75%).

Real-world studies are integral to supporting evidence-based medicine and can determine the effectiveness of clinical approaches in general and, particularly, in patient subgroups underrepresented in clinical trials.[18] This real-world nationwide study utilized data from a large registry linkage based on patients diagnosed with metastatic non-small-cell adenocarcinoma and registered in the Cancer Registry of Norway. Our study aimed to compare the survival among patients treated with the ICI pembrolizumab as a single agent versus in combination with platinum-based chemotherapy. Furthermore, we aimed to identify potential variations in treatment response among patient subgroups when comparing these two treatment options.

METHODS

Data sources

Individual-level data from four population-based registries were used in this study: the Cancer Registry of Norway (CRN)—including the quality registry for lung cancer, the radiation database, and the INSPIRE database[19,20]; the Norwegian Patient Registry (NPR); the Norwegian Prescription Database (NorPD); and Statistics Norway. Data were linked using the unique personal identification number assigned to all Norwegian residents.

The CRN provided information about patient and clinical characteristics related to incident cancer diagnoses and has 99% completeness for lung cancer cases due to mandatory reporting.[21] Detailed information on systemic anticancer treatment was obtained from the INSPIRE database, and covered nearly 90% of patients treated in Norway during 2019.[19] Additional information on systemic anticancer treatment was obtained from the NPR.[22] The NorPD provided details on dispensed prescription drugs, including targeted treatment. Information about education and income was obtained from Statistics Norway.

Variables

Information at diagnosis included age (years), sex, histology (adenocarcinoma), and clinical stage (IVA and IVB) based on the TNM 8th edition[23] Stage IVA included any T and N and either M1a (intrathoracic metastasis) or M1b (single extrathoracic metastasis in a single organ). Stage IVB included any T and N and M1c (multiple extrathoracic metastasis). We also included information on Eastern Cooperative Oncology Group performance status at diagnosis (ECOG PS) (0, 1, 2), PD-L1 expression level (50%-74% and $\geq$75%), mutation status [epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) rearrangements], vital status including date of death or emigration, and information on radiotherapy (intention to treat, region codes). Palliative radiation was defined based on this intention-to-treat information registered in the radiation information system by the oncologist. It did not count when defining treatment lines. Radiation to the brain was defined based on specific region codes. Patients were classified as having a recent history of an 'autoimmune disease' or 'chronic obstructive pulmonary disease' (COPD) if registered with an ICD-10 or an ICPC2 code for the respective diagnosis in NPR or NorPD up to 2 years before initiating ICI (Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2025.105073). Education was dichotomized based on the highest obtained educational level (less than college/university or college/university), and income was categorized into three groups based on household income the year before diagnosis (low: bottom 30%, intermediate: middle 40%, or high: top 30%).

Study population

This retrospective cohort study comprised all individuals diagnosed with and treated for a stage IV lung cancer (C34) with adenocarcinoma histology in Norway during 2017 to 2021. Additional inclusion criteria were a PD-L1 expression $\geq$50% and receiving first-line treatment with pembrolizumab (either as monotherapy or in combination with chemotherapy) during 2017 to 2021. First-line treatment was defined as the first systemic anticancer treatment after a diagnosis with metastatic disease (stage IV). First-line treatments of interest were pembrolizumab as monotherapy or in combination with chemotherapy (combination therapy). Patients were defined to have been treated with pembrolizumab combination therapy if they received chemotherapy within $\pm$6 days of their first dose of pembrolizumab.

Exclusion criteria included patients with targetable mutations and were determined based on known EGFR mutations or ALK rearrangements, or information about receiving targeted treatment. We also excluded individuals with an ECOG >2 at the time of diagnosis, those who commenced first-line treatment >3 months (>91 days) after diagnosis, those with curatively intended treatment, those with unspecified stage IV disease and those missing information on education (Figure 1).

Statistical analyses

Baseline patient and clinical characteristics were presented using descriptive statistics. Medians with interquartile range (IQR) were reported for continuous variables. Frequencies with percentages were presented otherwise.

The primary outcome was overall survival (OS). Patients were followed from initiation of first pembrolizumab treatment until death from any cause. Follow-up time was censored for patients at time of emigration or at the end of the study period (30 June 2023). In addition, we investigated the early risk of death by quantifying survival differences between treatment modalities within the first 6 months after treatment initiation. Median follow-up time was calculated using the reverse Kaplan—Meier estimator[24]; it was 49.9 months for those receiving monotherapy and 34.4 months for patients receiving pembrolizumab in combination with chemotherapy.

Unadjusted OS was estimated using the Kaplan—Meier method and compared across treatment modalities using the log-rank test. To address confounding by indication, we additionally applied multivariate Cox regression to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the risk of death from any cause associated with monotherapy relative to combination therapy. These models were adjusted for age at diagnosis, sex, PD-L1 expression, ECOG, distant metastases, and education (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105073). HRs reflected average effects over time. Moreover, we investigated potential variations in treatment response among the clinical factors used for adjustment. *P* values for interaction effects between treatment and subgroup variables were also evaluated using Cox regression. All statistical analyses were carried out using Stata version 18.0.

RESULTS

Patient characteristics

A total of 410 patients received pembrolizumab as first-line treatment, either as monotherapy ($n = 317$) or in combination with chemotherapy ($n = 93$). Compared with patients receiving monotherapy, patients receiving combination therapy were younger at diagnosis (median 66 years versus 69 years), less likely to have poor PS (ECOG 2, 11% versus 25%), and less likely to receive brain radiation during their treatment course (11% versus 22%) (Table 1). The distribution of sex, PD-L1 expression level, COPD, autoimmune disease, and stage was similar for patients in both treatment groups.

Survival among all included patients

Median OS was 22.6 months for patients treated with pembrolizumab in combination with chemotherapy and 14.2 months for patients treated with monotherapy (Figure 2A, Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105073). Patients receiving combination therapy showed a lower risk of death from any cause compared with patients receiving monotherapy ($P_{\text{log-rank}} = 0.016$), and this trend was no longer statistically significant after adjustment (HR 0.74, 95% CI 0.54-1.00, $P = 0.051$; Figure 3A).

Thirteen percent (12/93) of patients treated with combination therapy and 32% (102/317) of patients treated with monotherapy died within the first 6 months after treatment initiation. Patients receiving combination therapy had a significantly lower risk of death within 6 months than patients receiving monotherapy before ($P_{\text{log-rank}} = 0.0004$) and after adjustment (HR 0.41, 95% CI 0.23-0.76, $P = 0.004$; Figure 3B).

Survival among subgroups of patients

Results for the subgroup analyses for sex, PD-L1 expression, age, ECOG PS, and stage are presented in Figure 2 (unadjusted), Figure 3 (adjusted), and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105073. In the unadjusted analyses (Figure 2A-F and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105073), we observed significantly better OS for patients treated with combination therapy over monotherapy in females (median OS 35 months versus 15 months; $P_{\text{logrank}} = 0.017$), patients with high (≥75%) PD-L1 expression (median OS >36 months versus 18 months; $P_{\text{logrank}} = 0.015$) and those with stage IVB disease (median OS 30 months versus 9 months; $P_{\text{logrank}} = 0.007$).

In the adjusted analyses, both males and females treated with combination therapy had a decreased risk of death within 6 months of treatment start compared with those treated with monotherapy (males: HR 0.44, 95% CI 0.20-0.99, $P = 0.046$; females: HR 0.39, 95% CI 0.15-0.98, $P = 0.045$). In addition, females showed a trend towards reduced risk of death overall, although not statistically significant (HR 0.65, 95% CI 0.42-1.01, $P = 0.057$).

Patients with high PD-L1 expression (≥75%) showed more favorable outcomes from combination therapy than monotherapy and this was more pronounced when considering the risk of early death (HR 0.31, 95% CI 0.12-0.78, $P = 0.012$) than overall (HR 0.66, 95% CI 0.43-1.02, $P = 0.061$). The subgroup of patients with stage IVB disease (high metastatic burden) experienced a significantly reduced risk of early death (HR 0.33, 95% CI 0.15-0.71, $P = 0.005$) and overall death (HR 0.60, 95% CI 0.40-0.89, $P = 0.012$) when treated with combination therapy over monotherapy.

Patients with a low performance status (ECOG PS 0-1) had significantly lower risks of both early death (HR 0.33,

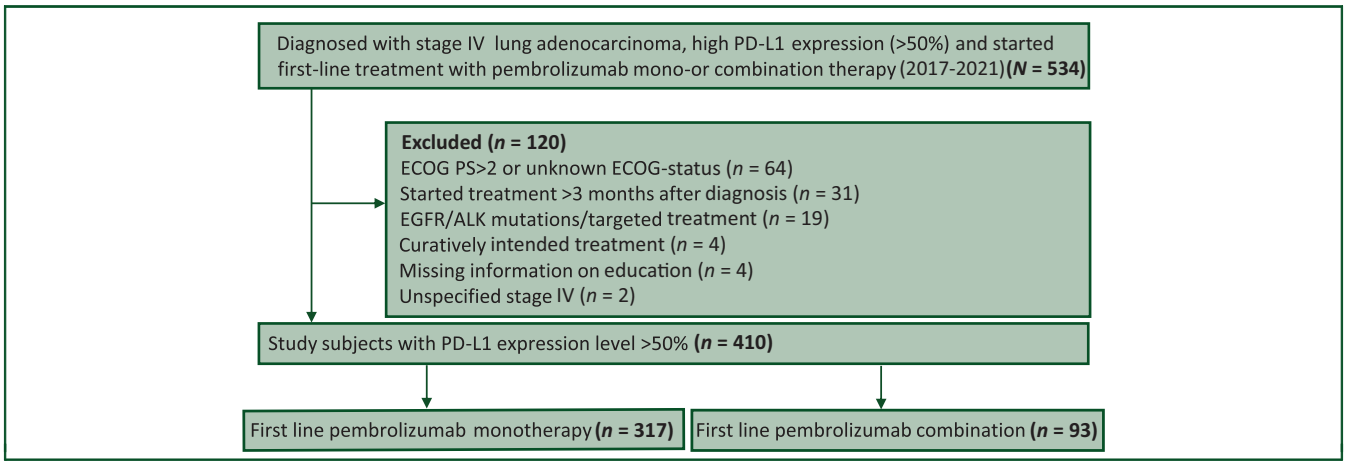

Figure 1. Flowchart of patients included in this study. Exclusion criteria were applied sequentially.

95% CI 0.16-0.70, $P = 0.004$) and overall death (HR 0.70, 95% CI 0.50-0.98, $P = 0.039$) with combination therapy (Figure 2). No significant outcome differences were observed between monotherapy and combination therapy in patients with higher performance status (ECOG PS 2). For patients <75 years, combination therapy reduced the risk of early death (HR 0.47, 95% CI 0.25-0.91, $P = 0.024$), but was not significant for overall death (HR 0.76, 95% CI 0.54-1.08, $P = 0.123$. For the elder patients (>75 years), we observed similar trends, but no significant outcome difference. We note that there was no statistically significant differential treatment effects detected for any of the included subgroups for overall survival ($P_{interaction}$ >0.1 for all models; Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105073).

DISCUSSION

This retrospective real-world study compared the effectiveness of ICI pembrolizumab as monotherapy versus in combination with chemotherapy in patients with advanced lung adenocarcinoma and high PD-L1 expression (≥50% of tumor cells). Our findings revealed that patients receiving combination therapy in first line had better OS within the first 6 months after treatment start compared with those treated with monotherapy. In our study, most subgroups receiving combination therapy showed comparable or better outcomes than patients receiving monotherapy, with potential treatment advantages for specific subgroups including females, individuals with stage IVB disease, and individuals with PD-L1 expression above 75%.

Overall effect

Most cross-trial comparisons and observational studies to date, comparing monotherapy and combination therapy in NSCLC patients with high PD-L1 expression, indicate an initial benefit associated with combination treatment over monotherapy.[9-13] Consistent with these findings, our study also observed a significant initial benefit, shown as lower rates of early deaths (within 6 months), for patients receiving combination therapy compared with monotherapy after controlling for potential confounders such as sex, age, metastatic burden, PD-L1 status, and ECOG PS.

Additionally, we observed a trend indicating that combination therapy might be better than monotherapy in terms of OS. A pooled analysis of 12 randomized trials demonstrated a similar trend in favor of combination therapy in OS; however, like our findings, the OS benefit was not statistically significant, and appeared to be weaker compared with the benefit in progression-free survival.[11] This suggests that the favorable OS may be driven by the instant benefit of adding chemotherapy. Shah et al. observed an early survival advantage for combination therapy (versus ICI monotherapy) during the first 6-12 months after treatment start, after which the survival curves leveled out and eventually crossed.[25]

Despite, the huge success of ICIs, demonstrating clear survival benefits and improved long-term survival rates over conventional chemotherapy, several trial results reveal that patients receiving single agent ICIs are at higher risk of death during the first 3-6 months after treatment start compared with those in the chemotherapy control arm. Thus, adding chemotherapy to the ICI regimen may contribute to delay the disease progression in a subset of patients not initially responding to ICIs as monotherapy.[4,7] Furthermore, initial disease control may also allow for the more gradual effects of ICI to become apparent, and thus explain the trend of prolonged OS among those that receive combination therapy.[26]

Patient subgroups

In a heterogenous real-world patient population (as was included in this study), patients will have variable sensitivity to both ICI and chemotherapy. Thus, combining the two drugs could potentially increase the probability of response to treatment, however, with an increased risk of side effects.[27] Identifying specific patient subpopulations that can particularly benefit from the combination regimen is therefore crucial. Our study highlighted potential variations in treatment response among patient subgroups when comparing monotherapy and combination therapy.

Table 1. Patient characteristics for patients treated with pembrolizumab as monotherapy versus in combination with chemotherapy

	Monotherapy, *n* (%)	Combination, *n* (%)
	N = 317	*N* = 93
Age at diagnosis, median (interquartile range)	69 (63-75)	66 (61-72)
Age at diagnosis, categories		
<65 years	105 (33.1)	36 (38.7)
65-74 years	127 (40.1)	45 (48.4)
≥75 years	85 (26.8)	12 (12.9)
Sex		
Female	170 (53.6)	51 (54.8)
Male	147 (46.4)	42 (45.2)
ECOG PS		
ECOG 0	80 (25.2)	36 (38.7)
ECOG 1	159 (50.2)	47 (50.5)
ECOG 2	78 (24.6)	10 (10.8)
Autoimmune disease		
No	272 (85.8)	77 (82.8)
Yes	45 (14.2)	16 (17.2)
COPD		
No	238 (75.1)	72 (77.4)
Yes	79 (24.9)	21 (22.6)
Stage		
IVA	135 (42.6)	40 (43.0)
IVB	182 (57.4)	53 (57.0)
PD-L1 expression		
50%-74%	118 (37.2)	39 (41.9)
≥75%	199 (62.8)	54 (58.1)
Palliative radiation		
No	194 (61.2)	60 (64.5)
Yes	123 (38.8)	33 (35.5)
Palliative radiation, brain metastasis		
No	249 (78.5)	83 (89.2)
Yes	68 (21.5)	10 (10.8)
Household income		
Low	128 (40.4)	29 (31.2)
Intermediate	134 (42.3)	47 (50.5)
High	52 (16.4)	17 (18.3)
Unknown	3 (0.9)	0 (0.0)
Highest obtained education		
Less than college/university	262 (82.6)	76 (81.7)
College/university	55 (17.4)	17 (18.3)

COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, Programmed death-ligand 1.

Tumor burden. Previous studies indicate that baseline tumor burden can influence treatment response and outcomes to ICI monotherapy in advanced NSCLC.[28,29] Faehling et al. showed that patients with high tumor burden benefited less from ICI monotherapy (relative to chemotherapy) than those with a lower tumor burden.[30] As a measure of tumor burden, we investigated the extent of metastatic lesions and observed that patients with multiple distant metastases (stage IVB) receiving monotherapy had poorer survival than patients with local or singular metastatic disease (stage IVA). Conversely, in patients receiving combination therapy, there was no difference in survival between patients with IVA and IVB disease. This finding aligns with results from *post hoc* analyses of the Keynote-189 trial, which indicated comparable survival outcomes for patients receiving combination therapy regardless of tumor burden.[31] Thus, for patients with high metastatic burden (stage IVB), our results support that combination therapy was superior to monotherapy.

Sex. Although, in our study, both sexes benefited from combination treatment relative to monotherapy, females seemed to derive a larger survival benefit than males, particularly with respect to OS. A meta-analysis by Conforti et al. has suggested that females derive a larger benefit from the addition of chemotherapy to ICI treatment than males,[32] and findings from exploratory subgroup analyses in a multicenter cohort have suggested the same.[15] We have previously shown that females and males have similar outcomes when treated with pembrolizumab as monotherapy, but males have poorer prognosis when treated with chemotherapy.[33] Indeed, males might be less sensitive to chemotherapy than females,[34,35] which might partly explain why adding chemotherapy to ICI was less beneficial for males. We note, however, that males in our study experienced an initial benefit from combination therapy relative to monotherapy of a similar magnitude as females.

PD-L1 expression. PD-L1 expression correlates with increased response to ICI when administered as monotherapy, even at very high levels (>90%).[25,36,37] However, the predictive value of PD-L1 expression for combination therapy is less well studied. The Keynote-189 trial demonstrated improved survival with increasing PD-L1 expression up to 50%.[6] In our study, patients with PD-L1 expression ≥75% exhibited better survival outcomes compared with those with lower expression (50%-74%), for both monotherapy and combination therapy. Particularly noteworthy was that the addition of chemotherapy provided the greatest benefit for patients with PD-L1 expression levels above 75%. A study carried out by Elkrief et al. found that combination therapy was favorable over monotherapy up to a certain threshold, and showed no additional benefit of combination therapy for patients with very high PD-L1 expression (≥90%).[13] Conversely, another large cohort study indicated an initial advantage of combination therapy even for patients with PD-L1 expression ≥90%.[25] Thus, while the literature is conflicting on the optimal PD-L1 cut-off for adding chemotherapy, emerging evidence challenges the current clinical practice of using a 50% PD-L1 threshold to decide between monotherapy and combination therapy.[37] Our findings support that PD-L1 expression >50% and <50% may not be the best indicator for stratifying patients into monotherapy versus combination therapy, as patients derive beneficial effects of adding chemotherapy even at levels >75%.

Age and performance status. In this study, the number of elderly patients (aged ≥75 years) and those with poorer performance status (ECOG 2) undergoing combination therapy was limited, which made interpretation of results from these subgroups difficult. However, results pertaining to elderly patients did not seem to deviate from those for younger patients and both showed a trend favoring combination therapy over monotherapy. These results are supported by previous clinical trial results showing that ICI as monotherapy works similarly in elderly and younger patients, without excessive toxicities.[38,39] Likewise, in trial results of the

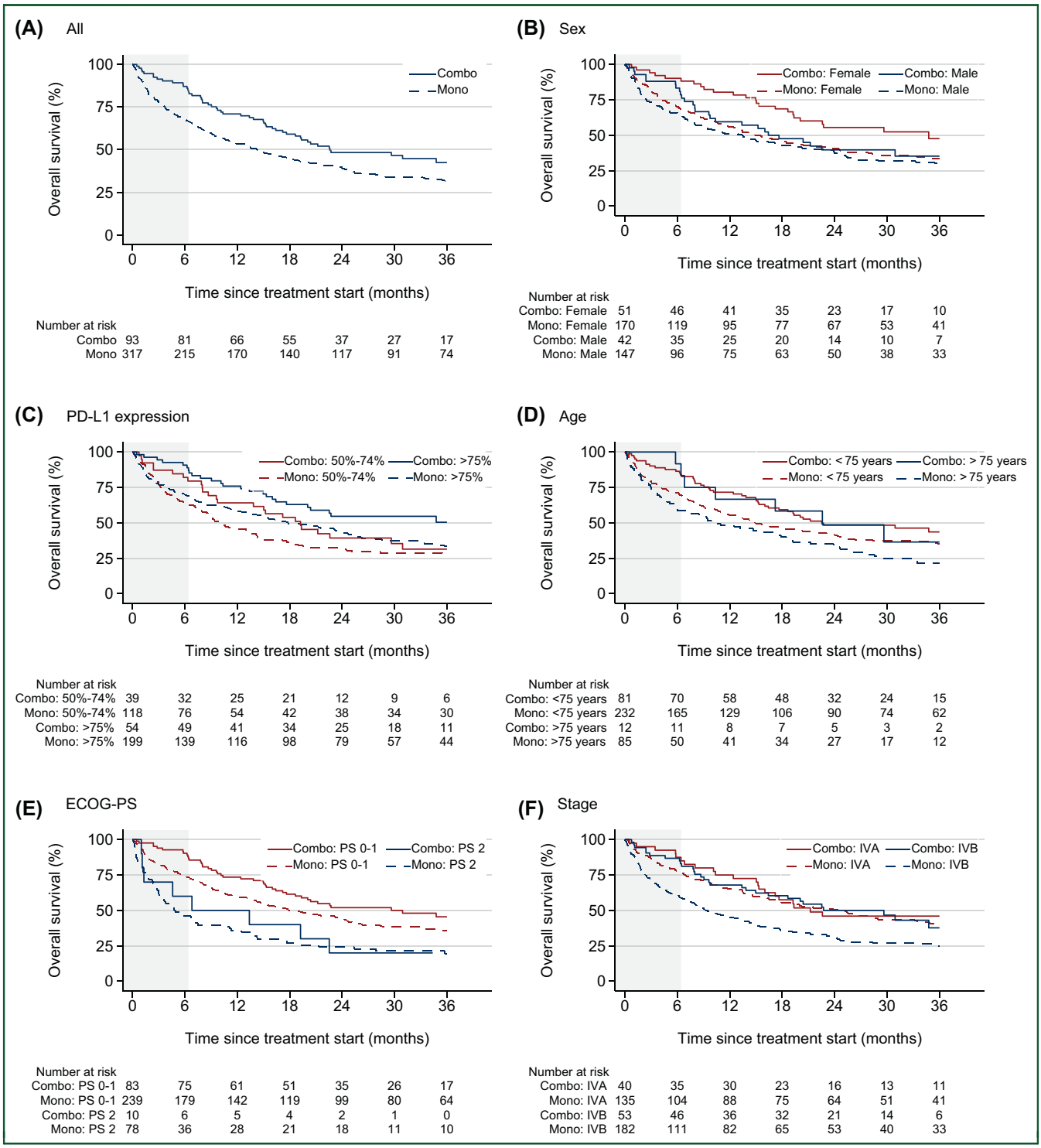

Figure 2. Kaplan–Meier curves stratified by treatment regimen: pembrolizumab in combination with chemotherapy (combo) versus monotherapy (mono). (A) Overall and stratified by (B) sex: male/female; (C) PD-L1 status: 50%-74%/75%; (D) age: <75 years or >75 years; (E) ECOG PS: 0-1/2; and (F) stage: IVA/IVB. ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, Programmed death-ligand 1.

ICI as combination therapy, the advantages of combination therapy over chemotherapy also extended to elderly patients.[40] Nonetheless, the direct benefit of combination therapy for the elderly (relative to monotherapy) is still unclear. An observational study comparing ICI monotherapy with combination therapy in patients ≥75 years revealed no discernible survival advantage with the addition of chemotherapy to ICI monotherapy in terms of OS. However, a closer examination of the Kaplan–Meier plots indicates an survival advantage among patients receiving combination therapy during the first months following treatment start,[41] suggesting that the elderly may also initially benefit from combination therapy.

For patients with poor performance status (ECOG 2), combination treatment was not associated with a lower risk of death compared with monotherapy in our study. It

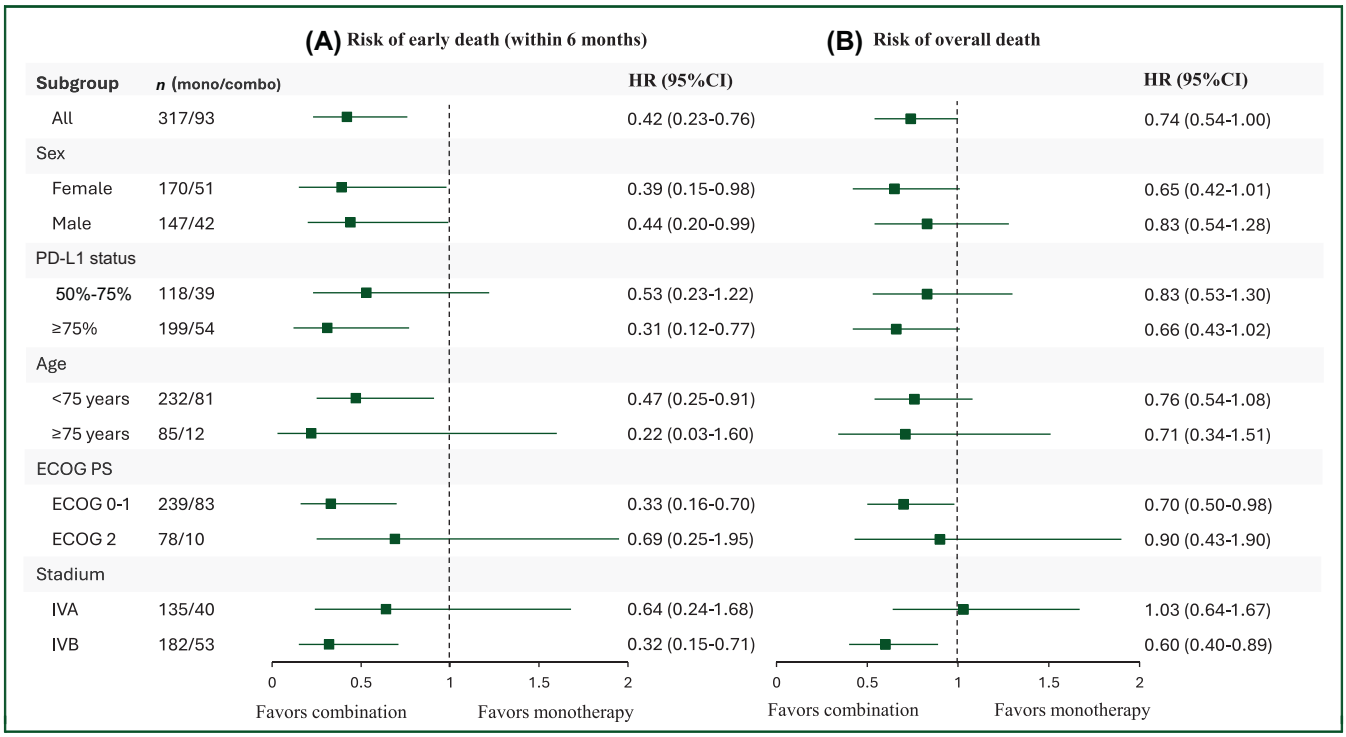

Figure 3. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs), stratified by subgroup, for the risk of (A) early death within 6 months from treatment start and (B) overall death for patients receiving combination therapy versus monotherapy. Monotherapy is the reference group.
ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, Programmed death-ligand-1.

should be noted, however, that there were few patients with ECOG 2 in the combination treatment group and these results should be interpreted with caution.

Strengths and limitations

Our real-world study offered the opportunity to compare survival for patients treated with mono- and combination therapy and investigate which patient subgroups may benefit most from combination therapy. Indeed, although several large, randomized trials provide support for the use of ICIs in lung cancer treatment, both alone and in combination with chemotherapy, no trials have directly compared the effects of monotherapy versus combination therapy. Additionally, it is important to re-evaluate results from clinical trials in a real-world setting, as the general population in clinical practice is more heterogeneous.[18] An important strength of this population-based study is therefore that nearly all patients treated in routine clinical care were included, instead of the selected patient groups studied in clinical trials—thus selection bias is negligible with our study design. However, an important limitation of the observational study design we used is that patients included in our study received monotherapy or combination therapy based on their largely unknown (to us) personal clinical scenario. As a result, patients in the combination therapy group tended to be younger, have less comorbidities and better PS. Although we adjusted for available factors that were likely to inform to the decision to treat with one regimen over the other (and were related to OS), we cannot rule out residual confounding by indication from unavailable clinical factors such as tumor aggressiveness, or smoking status. This applies for both the overall and subgroup analyses, nonetheless, E-values indicate that residual confounding is unlikely to be a major weakness of our study (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105073). Lastly, the subgroup analyses we carried out must be interpreted as exploratory in nature—some subgroups had few subjects, and caution is required when interpreting these results. Our estimates are nonetheless hypothesis generating and valuable for future meta-analyses.[42]

Conclusion

In a heterogenous real-world population, we observed that the benefit of ICI in combination with chemotherapy was associated with favorable OS outcomes within the first 6 months after treatment start compared with monotherapy. Specific subgroups, particularly those with high tumor burden (stage IVB) and females, also benefited in the long term from adding chemotherapy to the ICI regimen, suggesting that these patients should be considered for combination therapy. In addition, our findings challenge the current clinical practice of using PD-L1 (>50% and <50%) in guiding treatment decisions into monotherapy versus combination therapy, as patients with even higher PD-L1 expression (≥75%) can benefit from the addition of chemotherapy. Further validation is required from future studies.

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DISCLOSURE

OTB declares receiving grants or contracts from Amgen, AstraZeneca, Boehringer Ingelheim, GSK, Pfizer, Roche/Genentech, and Ultimovacs; receiving payment or honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Eli Lilly, Merck Sharp & Dohme (MSD), Novartis, Pfizer, Pierre Fabre, Roche, Sanofi Genzyme, and Takeda; and having consulting/advisory roles for Janssen, MSD, and Boehringer Ingelheim. The remaining authors declare no conflicts of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Use and reporting of de-identified data from the CRN was covered by the CRN's regulations of collection and treatment of health information. Use, linkage, and reporting of de-identified data from all other registries was approved by the regional ethics committee (2018/775/REK sør-øst B) and all involved registries. The study was carried out in accordance with the Declaration of Helsinki.

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