Efficacy of PD-(L)1 blockade monotherapy compared with PD-(L)1 blockade plus chemotherapy in first-line PD-L1-positive advanced lung adenocarcinomas: a cohort study

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ABSTRACT

Background Single-agent PD-(L)1 blockade (IO) alone or in combination with chemotherapy (Chemotherapy-IO) is approved first-line therapies in patients with advanced lung adenocarcinomas (LUADs) with PD-L1 expression ≥1%. These regimens have not been compared prospectively. The primary objective was to compare first-line efficacies of single-agent IO to Chemotherapy-IO in patients with advanced LUADs. Secondary objectives were to explore if clinical, pathological, and genomic features were associated with differential response to Chemotherapy-IO versus IO.

Methods This was a multicenter retrospective cohort study. Inclusion criteria were patients with advanced LUADs with tumor PD-L1 ≥1% treated with first-line Chemotherapy-IO or IO. To compare the first-line efficacies of single-agent IO to Chemotherapy-IO, we conducted inverse probability weighted Cox proportional hazards models using estimated propensity scores.

Results The cohort analyzed included 866 patients. Relative to IO, Chemotherapy-IO was associated with improved objective response rate (ORR) (44% vs 35%, p=0.007) and progression-free survival (PFS) in patients with tumor PD-L1≥1% (HR 0.84, 95% CI 0.72 to 0.97, p=0.021) or PD-L1≥50% (ORR 55% vs 38%, p<0.001; PFS HR 0.68, 95% CI 0.53 to 0.87, p=0.002). Using propensity-adjusted analyses, only never-smokers in the PD-L1≥50% subgroup derived a differential survival benefit from Chemotherapy-IO vs IO (p=0.013). Among patients with very high tumor PD-L1 expression (≥90%), there were no differences in outcome between treatment groups. No genomic factors conferred differential survival benefit to Chemotherapy-IO versus IO.

Conclusions While the addition of chemotherapy to PD-(L)1 blockade increases the probability of initial response, never-smokers with tumor PD-L1≥50% comprise the only population identified that derived an apparent survival benefit with treatment intensification.

INTRODUCTION

Drugs that inhibit PD-1 or PD-L1 (PD-(L)1 blockade) have transformed the treatment landscape for patients with advanced non-small cell lung cancer (NSCLC) without targetable driver mutations. In 2023, there are several US Food and Drug Administration-approved first-line PD-(L)1 blockade regimens alone (IO) or in combination with platinum-doublet chemotherapy.
staining as previously described.13 For genomic analysis, the percentage of tumor cells with membranous or cytoplasmic staining in all patients included in the study and reported for analysis (online supplemental figure S1).

Prior studies have identified clinical and genomic factors associated with efficacy of PD-(L)1 blockade. Eastern Cooperative Oncology Group (ECOG) performance status, smoking history, PD-L1 expression, and tumor mutational burden (TMB) influence clinical activity and outcomes.8–10 NSCLCs harboring mutations in STK11 and/or KEAP1 have worse outcomes to PD-(L)1 blockade, particularly among KRASmutant NSCLCs.11 In these cases, addition of chemotherapy might overcome IO resistance.11 Conversely, other factors such as poor performance status may limit tolerability of chemotherapy and negate potential additive anti-cancer activity of combination therapy.12

We posited that clinical, pathologic, and molecular analyses of a real-world patient population could identify patient subpopulations that might differentially benefit from IO versus Chemotherapy-IO in the first-line setting. In order to address biases and differences in baseline characteristics between the IO and Chemotherapy-IO groups, we performed propensity-adjusted analyses in 866 patient cases of lung adenocarcinoma (LUAD) without EGFR or ALK-sensitizing alterations treated with IO or Chemotherapy-IO at two institutions.

**METHODS**

**Patients**

After institutional review board approval, patients with advanced LUAD from Memorial Sloan Kettering Cancer Center (MSK) and Dana-Farber Cancer Institute (DFCI) between 2011 and 2020 were assessed in this retrospective analysis. Only patients with advanced LUAD treated in the first-line with IO or Chemotherapy-IO were eligible for analysis (online supplemental figure S1).

PD-L1 expression (tumor proportion score) was evaluated in all patients included in the study and reported as the percentage of tumor cells with membranous staining as previously described.13 For genomic analyses, only patients with genomic sequencing by MSK-IMPACT (MSK) or OncoPanel (DFCI) NGS panels were included14 15 (online supplemental methods). TMB was harmonized for comparison as previously published (online supplemental methods).16 Patients with tumors with PD-L1<1% or harboring sensitizing EGFR or ALK alterations were excluded (defined by EGFR exon 19 deletions or exon 21 L858R mutations). Pre-planned analyses in PD-L1 1%–49% and ≥50% subgroups were conducted to align with current first-line treatment guidelines.17 The primary outcomes were objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

**Statistical analysis**

Descriptive statistics were used to describe the analysis population by treatment group (Chemotherapy-IO vs IO). Differences in baseline characteristics by group were evaluated using the Wilcoxon rank sum test, Fisher’s exact test, or Pearson’s chi² test as appropriate.

Patients who did not experience progression or death by the data lock date (October 21, 2021) were censored at date of last assessment. Investigator-assessed ORR was defined as the rate of partial response + complete response. Real-world investigator-assessed PFS was assessed from the date the patient began therapy to the date of progression as previously described.18–20 OS was calculated from treatment start date until date of death or last assessment. Kaplan-Meier curves and log-rank test statistics were computed to compare PFS and OS between groups.

We conducted propensity score modeling for treatment group assignment using a logistic regression model with the following potential prognostic factors as categorical variables: age (≥65 vs <65), ECOG performance status (scores 2–3 vs scores 0–1), smoking status (current/former smokers vs never-smokers), PD-L1 tumor proportion score percentage (PD-L1 ≥50% vs PD-L1 1%–49%), and presence of liver or brain metastases at baseline. To account for the potential difference in treatment assignment, we conducted inverse probability weighted (IPW) Cox proportional hazards models using the estimated propensity scores. Three sets of IPW Cox models were explored. The first model (main effects model) contained treatment group along with clinical categorical variables (age, ECOG, smoking status, PD-L1 %, baseline liver metastases and baseline brain metastases) to examine the overall treatment effects on PFS and OS. The second model (treatment interaction model) further included interactions between treatment group and clinical variables to examine treatment effect modifications, to identify subgroups for differential benefit of Chemotherapy-IO versus IO. The third model was restricted to patients with genomic data available, building off our second model (treatment interaction model, genomics analysis cohort) with the additions of the following categorical variables: harmonized TMB score (see online supplemental methods) and five gene mutations (KRAS, TP53, KEAP1, STK11, and SMARCA4), as well as their interactions with treatment group. The five gene mutations were selected as they have previously been associated with IO outcomes in lung cancer.21–23 For each clinical subgroup of interest, we calculated the HR for treatment group (Chemotherapy-IO vs IO) adjusting for all clinical covariates included in the propensity score IPW Cox proportional hazards model and visualized these results using forest plots.

Analyses were conducted using R V.4.1.1 with the tidyverse (V.1.3.1),24 ggtsummary (V.1.6.0),25 survival (V.3.3.1) and survminer (V.0.4.9) packages.26

(Chemotherapy-IO), all of which demonstrated clinical benefit compared with chemotherapy.1–7 The increased breadth of treatment options in newly diagnosed advanced lung cancer and lack of published head-to-head trials makes regimen selection challenging. It is unclear if certain populations might derive similar or greater clinical benefit from IO monotherapy than Chemotherapy-IO and might thereby avoid the potential toxicities of chemotherapy.

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RESULTS

Patient characteristics

Among all patients with advanced LUAD treated with Chemotherapy-IO or IO without a targetable driver alteration in EGFR or ALK, 866 patients met criteria for inclusion (online supplemental figure S1). Median follow-up for the clinical analysis cohort was 23 months (IQR: 12–38); 395 (45%) patients were treated with Chemotherapy-IO and 471 (55%) were treated with IO (table 1). Relative to the Chemotherapy-IO group, patients in the IO group were slightly older (median age 69 vs 67, p<0.001) with a more frequent and heavier smoking history (median pack years 30 vs 25 p=0.016) (table 1). PD-L1 high expression (≥50%) was enriched within the IO group relative to the Chemotherapy-IO group (85% vs 30% with PD-L1 high, p<0.001) (online supplemental figure S2A). Median harmonized TMB score (0.09 vs −0.05, p=0.013) was also significantly higher in the IO group (online supplemental figure S2B). Other baseline clinical factors such as ECOG performance status and sex were similarly distributed between the Chemotherapy-IO and IO groups (table 1). According to the propensity model, in the overall population (PD-L1 ≥1%), current/former smokers (OR 0.43, 95% CI 0.25 to 0.72, p=0.001), and those with tumor PD-L1 ≥50% (OR 0.07, 95% CI 0.05 to 0.10, p<0.001) were more likely to receive IO than Chemotherapy-IO (online supplemental table S1). Similar analysis for the PD-L1 ≥50% and 1%–49%
subgroups are presented in online supplemental tables S2,3.

**Clinical outcomes**

Among 866 patients with PD-L1≥1%, Chemotherapy-IO was associated with improved ORR (44% vs 35%, p=0.007) (figure 1A) and improved PFS (median PFS 6.9 (95% CI 6.0 to 8.6) vs 4.9 months (95% CI 4.1 to 6.0), p=0.021) (figure 1B), consistent with the results from the main effects model (online supplemental table S4) and treatment interaction model (online supplemental table S5) for PFS. There was no difference in OS between the Chemotherapy-IO versus IO groups (median OS 17 months, (95% CI 15 to 22) vs 20 months (95% CI 17 to 24), p=0.50) (figure 1C), consistent with results from the main effects model (online supplemental table S6) and the treatment interaction model (online supplemental table S7). While some factors such as age <65 (HR 0.59, 95% CI 0.43 to 0.82), and never smoking status (HR 0.42, 95% CI 0.20 to 0.92) were associated with improved PFS in the Chemotherapy-IO group (figure 1D), these were not significant for OS (figure 1E). Consistent with this, these factors were no longer significant in the treatment interaction model for both PFS (online supplemental table S5) and OS (online supplemental table S7).

In sum, among patients with PD-L1≥1%, Chemotherapy-IO demonstrated a PFS benefit in a propensity score-adjusted analysis; however, there was no OS benefit associated with Chemotherapy-IO compared with IO monotherapy.

**Clinical outcomes by PD-L1 subgroup**

In the PD-L1≥50% subgroup in 515 patients, Chemotherapy-IO was associated with improved ORR (55% vs 38%, p=0.001) (figure 2A) and PFS (median PFS 10.0 (95% CI 6.9 to 16.0) vs 4.9 months (95% CI 3.9 to 6.5), p=0.002) (figure 2B), consistent with the main effects model (p=0.037) (online supplemental table S8) and treatment interaction model (HR 0.22, 95% CI 0.1 to 0.51, p<0.001) (online supplemental table S9). This PFS benefit favoring Chemotherapy-IO was most pronounced in never-smokers (HR 0.31, 95% CI 0.16, 0.57) and patients <65 years of age (HR 0.48, 95% CI 0.31 to 0.72) (figure 2D), consistent with the treatment interaction model for smoking (p=0.013), but not for age (p=0.7) (online supplemental table S9). There was no significant difference in OS between the Chemotherapy-IO versus IO groups (median OS 32 (95% CI: 20 to not reached (NR)) vs 20 months (95% CI 17 to 26), p=0.40) (figure 2C), consistent in the main effects model (online supplemental table S10) and treatment interaction model (online supplemental table S11). Never-smokers derived an OS benefit to Chemotherapy-IO (HR 2.81, 95% CI 1.04 to 7.6, p=0.042) (online supplemental table S11). Examining clinical outcomes in these subgroups in greater detail, ORR in never-smokers was higher with Chemotherapy-IO versus IO group (76% vs 21%, p=0.001, respectively) (figure 3A). Median PFS among never-smokers in the Chemotherapy-IO versus IO group was 10.0 months vs 2.5 months, respectively (figure 3B). ORR among patients <65 years of age in the Chemotherapy-IO versus IO groups was higher (63% vs 40%, respectively; p=0.004) (figure 3D). Median PFS among <65 years of age in the Chemotherapy-IO versus IO group was 17.0 months vs 4.7 months, respectively (figure 3E). Taken together, these results suggest that in the PD-L1≥50% subgroup, there was a PFS benefit in never-smokers and in younger adults, and OS benefit in never-smokers favoring Chemotherapy-IO compared with IO.

Next, since very high PD-L1% (≥90%) has previously been associated with improved outcomes to IO,27 we explored this group in our dataset. Among patients with very high tumor PD-L1 expression (≥90%, N=212) there was no difference in ORR (p=0.2) (online supplemental figure S3A), PFS (p=0.2) (online supplemental figure S3B) or OS (p=0.5) (online supplemental figure S3B) between the Chemotherapy-IO or IO groups. Lastly, in the PD-L1 1%–49% subgroup (N=351 patients), while Chemotherapy-IO was associated with improved ORR (39% vs 19%, p=0.001) (online supplemental figure S4A) and PFS (median PFS 6.2 (95% CI 5.7 to 7.5) vs 4.4 months (95% CI 3.4 to 6.7), p=0.02) (online supplemental figure S4B) compared with IO, this was not significant for OS (median OS 15 (95% CI 13 to 19) vs 17 months (95% CI 13 to 24), p=0.8) (online supplemental figure S4C), or in the adjusted analyses (online supplemental tables S12-S14) in any subgroup examined.

**Differential genomic biomarkers of response to Chemotherapy-IO versus IO**

There were 572 patients with tumor PD-L1≥1% who were treated with Chemotherapy-IO (N=262) or IO (N=310) and underwent genomic sequencing (online supplemental figure S1, genomic analysis cohort). Median follow-up for the genomic analysis cohort was 24 months (IQR: 13–40). Patient baseline characteristics for the genomic analysis cohort were similar to the clinical analysis cohort (online supplemental table S15). ORR in Chemotherapy-IO and IO within different mutation subgroups of interest in KRAS, TP53, SMARCA4, KEAPI, STK11, or TMB are shown in figure 4A. Notably, in patients with SMARCA4 mutations, ORR was higher for those treated with IO alone (48% vs 29%), with a non-significant trend for improved PFS (7.6 vs 4.6 months, p=0.3) (figure 4B) as well as a non-significant trend for improved OS (25 vs 12 months, p=0.06) (figure 4C) favoring IO alone in patients with SMARCA4 mutations. In adjusted analyses, for patients with SMARCA4 mutations, the PFS benefit favoring IO alone was significant in the treatment interaction model (p=0.011) (online supplemental table S16), but not for OS (online supplemental table S17). No other specific mutations were significant in the treatment interaction model for PFS (online supplemental table S16) or OS (online supplemental table S17). For TMB, we observed a non-significant trend for improved PFS among patients with high median TMB favoring Chemotherapy-IO.
Figure 1  Comparative effectiveness of chemotherapy plus PD-(L)1 blockade (Chemotherapy-IO) versus single-agent PD-(L)1 blockade (IO) in patients with PD-L1 ≥1%. (A) Objective response rate, (B) progression-free survival (PFS), and (C) overall survival (OS) among patients with tumor PD-L1 ≥1% who received first-line Chemotherapy-IO (N=395) vs IO (N=471). (D) PFS and (E) OS analysis for Chemotherapy-IO versus IO adjusting for covariates of interest among different subgroups. Median survival times presented with CIs in brackets. Error bars in ORR plots represent 95% CI. ECOG, Eastern Cooperative Oncology Group; IO, single-agen anti-PD(L)-1 blockade.
Figure 2  Comparative effectiveness of chemotherapy plus PD-(L)1 blockade (Chemotherapy-IO) versus single-agent PD-(L)1 blockade (IO) in patients with PD-L1≥50%. (A) Objective response rate (ORR), (B) progression-free survival (PFS) and (C) overall survival (OS) among patients with tumor PD-L1≥50% who received first-line Chemotherapy-IO (N=117) vs IO (N=398). (D) PFS and (E) OS analysis for Chemotherapy-IO versus IO adjusting for covariates of interest among different subgroups. Median survival times presented with CIs in brackets. Error bars in ORR plots represent 95% CI. ECOG, Eastern Cooperative Oncology Group; IO, single-agent anti-PD(L)-1 blockade.

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Figure 3  Comparative effectiveness of chemotherapy plus PD-(L)1 blockade (Chemotherapy-Io) versus single-agent PD-(L)1 blockade (Io) in patients with PD-L1≥50% in subgroups of interest. (A) Objective response rate, (B) progression-free survival (PFS), and (C) overall survival (OS) between Chemotherapy-Io versus Io groups in never-smokers with tumor PD-L1≥50%. (D) Objective response rate, (E) PFS, and (F) OS between Chemotherapy-Io versus Io groups in patients <65 years of age with PD-L1≥50%. Median survival times presented with CIs in brackets. Error bars in ORR plots represent 95% CI. Io, single-agent anti-PD(L)-1 blockade.

Discussion and conclusion
We examined the efficacy of Io compared with treatment intensification with Chemotherapy-Io, in the context of key clinical and molecular features of LUAD. Within the PD-L1≥50% subgroup, we found the addition of chemotherapy to PD-(L)1 blockade led to improvements in ORR and PFS, but this only translated into an OS benefit in never-smokers. The only population that did not derive any initial benefit to Chemotherapy-Io over Io was the PD-L1 very high (≥90%) subgroup.
Our analyses found that the addition of chemotherapy increases the probability of initial response in a heterogeneous patient population with differential sensitivity to chemotherapy and immunotherapy, but long-term benefit appears largely driven by whether PD-(L)1 blockade generates durable antitumor immunity. The lack of OS benefit with Chemotherapy-IO compared with IO in our overall study population is also supported by recent clinical analyses of real-world and randomized controlled trials in patients with PD-L1≥50% non-squamous NSCLC.18,19

We initially hypothesized that distinct clinical and molecular characteristics previously associated with IO
resistance (eg, baseline liver metastases, STK11, and/or KEAP1 mutations) might distinguish patient populations that would benefit from treatment intensification with Chemotherapy-IO. Contrary to our hypothesis, we found that while factors such as liver metastases and STK11 mutations were associated with poor response overall, they did not confer superior long-term benefit from Chemotherapy-IO. Thus, treatment escalation with chemotherapy may not be sufficient or indicated solely based on these factors. Conversely, predictors of benefit from IO, such as very high PD-L1 (≥90%), may be a useful indicator of IO monotherapy appropriateness.

For this select group of patients, we found no difference in initial response between the Chemotherapy-IO or IO groups. Interestingly, our study also found that patients with SMARCA4 mutations experienced better response rates and PFS with IO compared with Chemotherapy-IO. The clinical implication of this observation is supported by prior studies, which have identified SMARCA4 mutation as a poor prognostic factor, potentially associated with resistance to chemotherapy. However, only 12% of patients had SMARCA4 mutations. More extensive molecular and gene expression analyses may be helpful in determining if specific genomic signatures benefit differentially from Chemotherapy-IO versus IO, but these analyses require much larger sample size for adequate power in the face of multiple hypothesis testing.

Never smoking status emerged as the primary factor associated with survival benefit favoring Chemotherapy-IO within the PD-L1≥50% subgroup. Prior studies have found a correlation between smoking history and increased TMB and that smoking history could be a potential clinical surrogate for TMB. However, we found that when accounting for smoking status in the PD-L1 expression adjusted model, smoking status remained a distinct predictive factor. Smoking history is a readily available biomarker that could be of value in determining if specific genomic signatures benefit differentially from Chemotherapy-IO versus IO, but these analyses require much larger sample size for adequate power in the face of multiple hypothesis testing.

In conclusion, we observed improvements in ORR and PFS associated with Chemotherapy-IO compared with IO, particularly in young, never-smokers. Never smoking status in the PD-L1≥50% subgroup was the only characteristic in which ORR and PFS improvement translated into a survival benefit. No genomic alterations favored OS with Chemotherapy-IO compared with IO. Our findings demonstrate that the addition of chemotherapy to PD-L1 blockade generally increases the probability of initial response but leads to improved survival only among never-smokers in the PD-L1≥50% subgroup. Our study highlights the critical nature of ongoing clinical trials prospectively evaluating the comparative effectiveness of anti-PD-L1 with and without chemotherapy (NCT03793179, NCT04547504).

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