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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.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Single-agent PD-(L)1 blockade (IO) or in combination with platinum-doublet chemotherapy (Chemotherapy-IO) has each demonstrated superior survival compared with chemotherapy alone in patients with advanced non-small cell lung cancer with PD-L1≥1%, however, these regimens have never been compared prospectively, and limited studies are available to guide treatment selection.

WHAT THIS STUDY ADDS

⇒ Relative to IO alone, Chemotherapy-IO increased the probability of initial response in patients with PD-L1≥1% and ≥50%, however, overall survival was similar. In subgroup analysis, never-smokers derived a survival benefit from Chemotherapy-IO compared with IO alone. No genomic factors conferred differential survival benefit to Chemotherapy-IO or IO.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study sheds light on the comparative effectiveness of Chemotherapy-IO and IO in the first-line setting across all relevant PD-L1 subgroups and integrating genomic analyses, which may help guide treatment selection and future clinical trial design.

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

(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.

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 *KRAS*-mutant 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 included[14 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 χ^2 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] gtsummary (V.1.6.0),[25] survival (V.3.3.1) and survminer (V.0.4.9) packages.[26]

Table 1 Baseline characteristics

Characteristic	Overall, N=866*	Chemo/IO, N=395*	IO, N=471*	P value†
Site				0.072
DFCI	476 (55%)	204 (52%)	272 (58%)	
MSK	390 (45%)	191 (48%)	199 (42%)	
Age	68 (60, 75)	67 (59, 72)	69 (61, 76)	**<0.001**
Sex				0.2
Female	489 (56%)	214 (54%)	275 (58%)	
Male	377 (44%)	181 (46%)	196 (42%)	
ECOG				0.5
<2	716 (85%)	320 (86%)	396 (84%)	
≥2	126 (15%)	52 (14%)	74 (16%)	
Unknown	24	23	1	
Pack years	28 (11, 45)	25 (8, 42)	30 (15, 45)	**0.016**
Unknown	41	26	15	
Smoking status				**<0.001**
Current/former	764 (89%)	331 (84%)	433 (92%)	
Never	99 (11%)	62 (16%)	37 (7.9%)	
Unknown	3	2	1	
Baseline liver metastases	110 (13%)	43 (11%)	67 (15%)	0.13
Unknown	15	5	10	
Baseline brain metastases	220 (26%)	89 (23%)	131 (29%)	0.064
Unknown	21	8	13	
PD-L1 status				**<0.001**
PD-L1≥50%	515 (59%)	117 (30%)	398 (85%)	
PD-L1 1–49	351 (41%)	278 (70%)	73 (15%)	
% PD-L1	60 (10, 85)	20 (5, 60)	80 (50, 90)	**<0.001**
Unknown	10	10	0	
Harmonized TMB score	0.09 (–0.68, 0.65)	–0.05 (–0.73, 0.55)	0.09 (–0.50, 0.68)	**0.013**
Unknown	294	133	161	

Bold values represent statisitically significant p-values.
*n (%); median (IQR).
†Pearson's χ^2 test; Wilcoxon rank sum test.
DFCI, Dana-Farber Cancer Institute; ECOG, Eastern Cooperative Oncology Group; MSK, Memorial Sloan Kettering; TMB, tumor mutational burden.

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).[17] 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*, *KEAP1*, *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

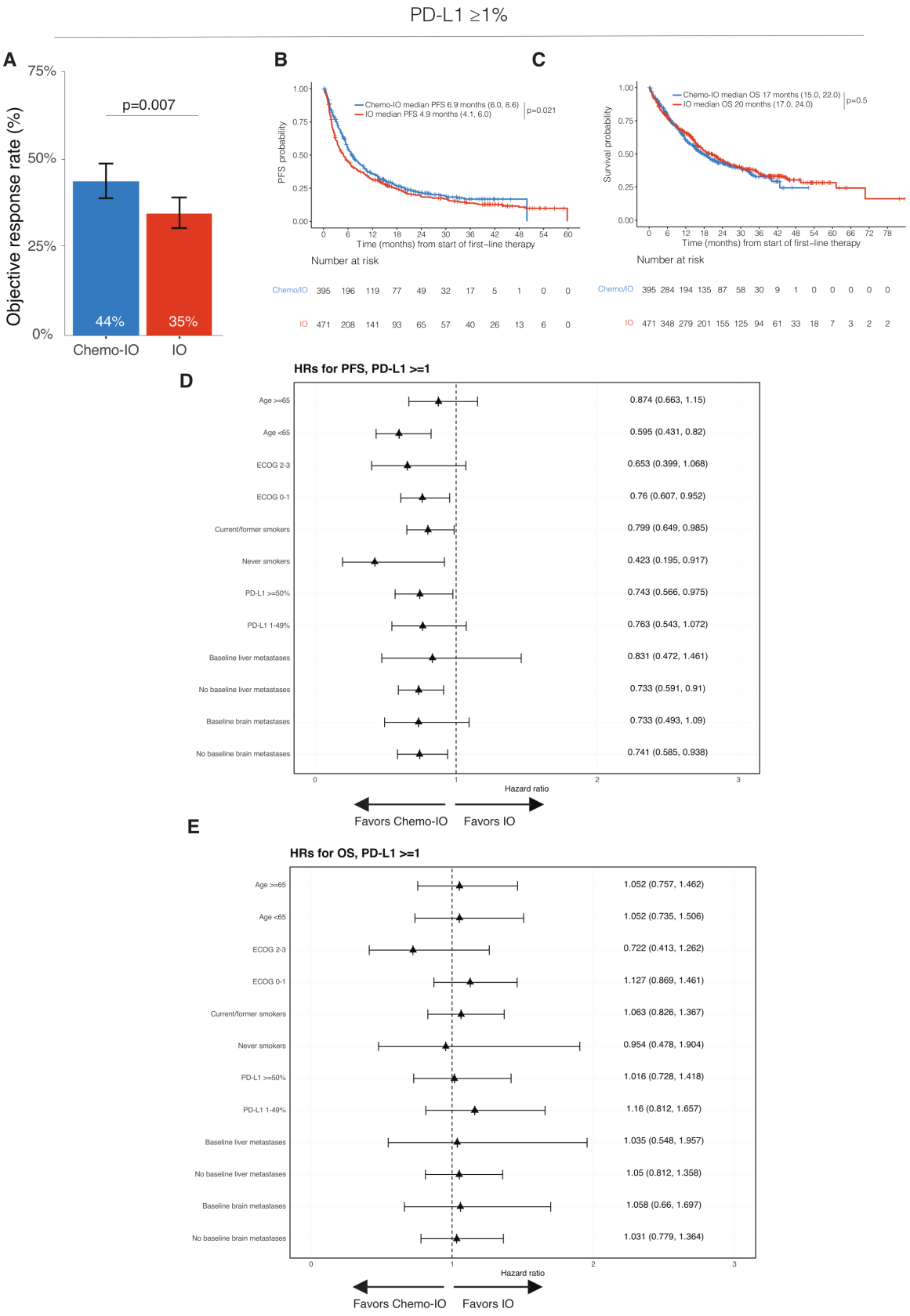

Figure 1 Comparative effectiveness of chemotherapy plus PD-(L)1 blockade (Chemotherapy-IO) versus single-agent PD-(L)1 blockade (IO) in patients with PD-L1≥1%. (A) Objective response rate, (B) progression-free survival (PFS), and (C) overall survival (OS) among patients with tumor PD-L1≥1% who received 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.

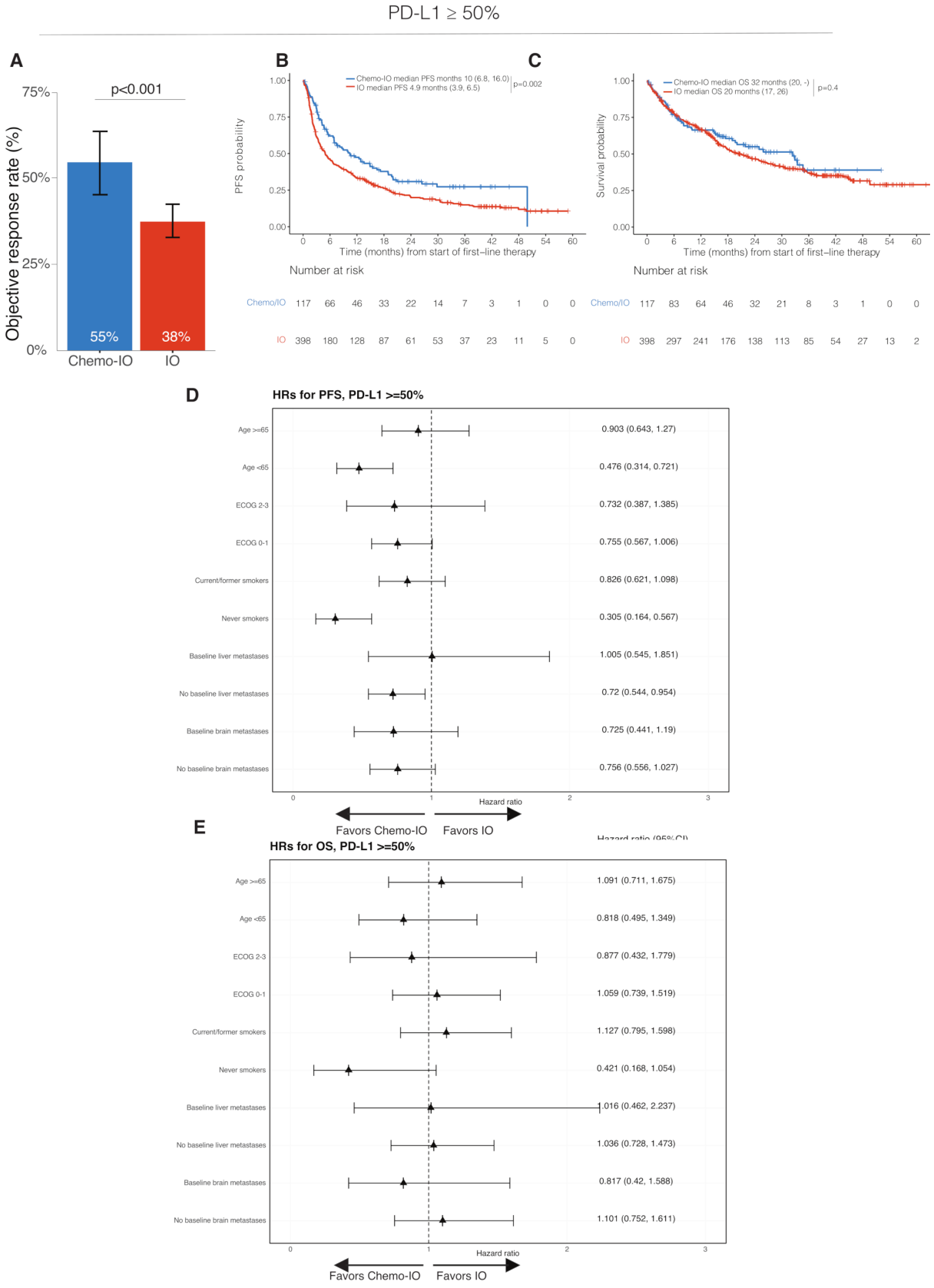

Figure 2 Comparative effectiveness of chemotherapy plus PD-(L)1 blockade (Chemotherapy-IO) versus single-agent PD-(L)1 blockade (IO) in patients with PD-L1≥50%. (A) Objective response rate (ORR), (B) progression-free survival (PFS) and (C) overall survival (OS) among patients with tumor PD-L1≥50% who 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-agen anti-PD(L)-1 blockade.

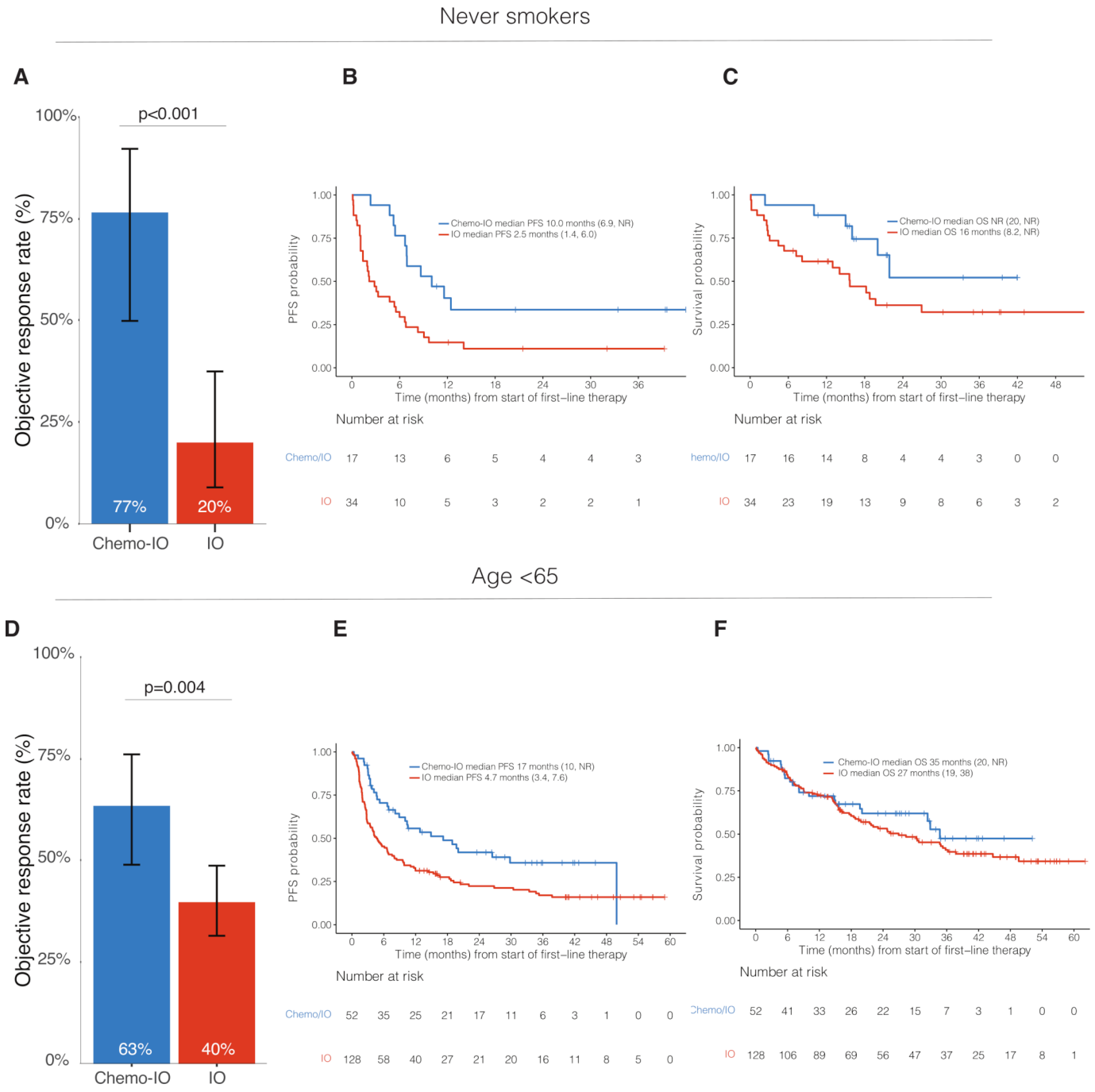

Figure 3 Comparative effectiveness of chemotherapy plus PD-(L)1 blockade (Chemotherapy-IO) versus single-agent PD-(L)1 blockade (IO) in patients with PD-L1≥50% in subgroups of interest. (A) Objective response rate, (B) progression-free survival (PFS), and (C) overall survival (OS) between Chemotherapy-IO 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-agen anti-PD(L)-1 blockade.

(figure 4D), also consistent with the treatment interaction model for PFS (p=0.003) (online supplemental table S16), however, this was not significant for the unadjusted OS analysis (figure 4E) or in the treatment interaction model for OS (online supplemental table S17).

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.

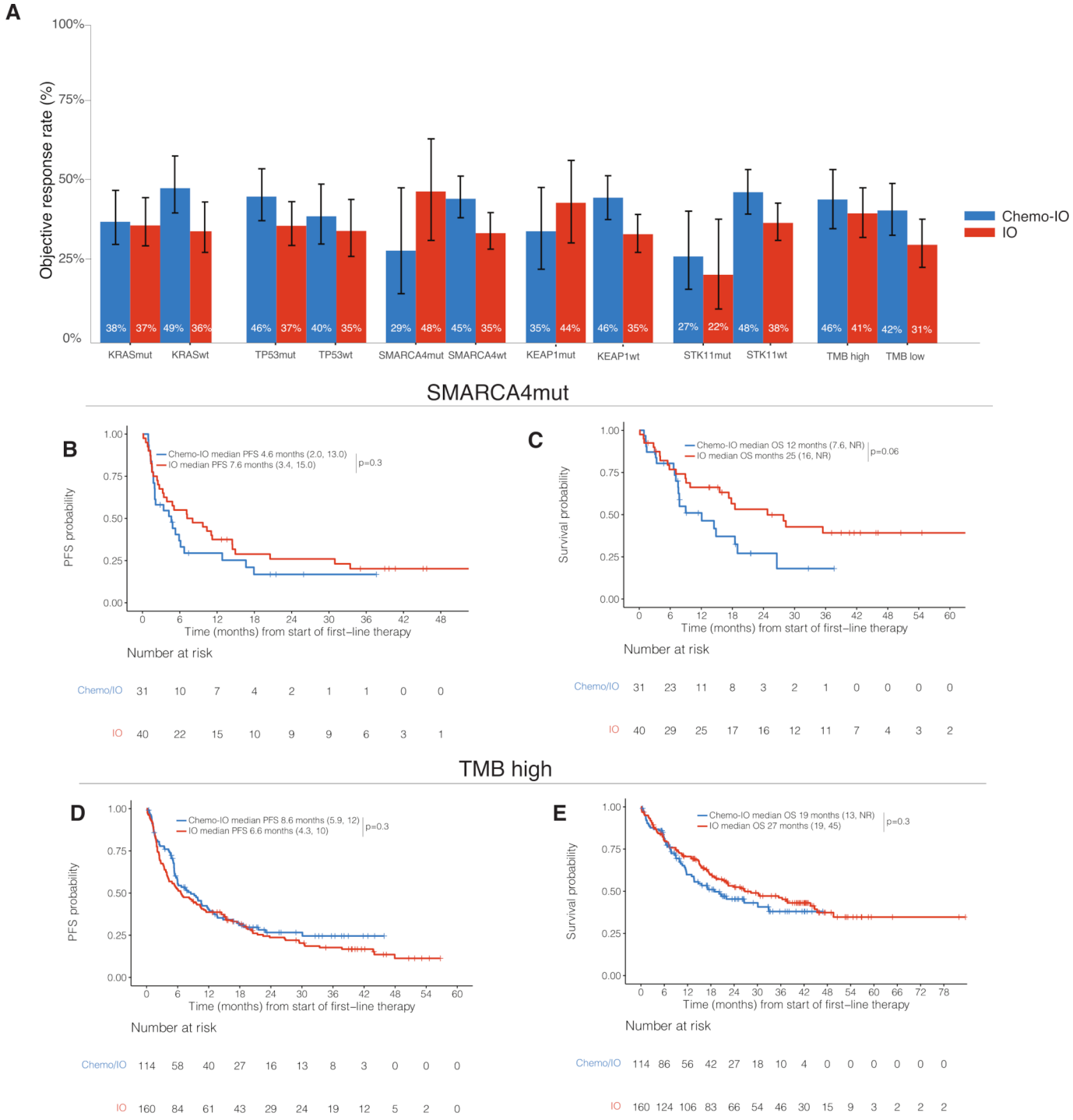

Figure 4 Comparative effectiveness of chemotherapy plus PD-(L)1 blockade (Chemotherapy-IO) versus single-agent PD-(L)1 blockade (IO) in the genomic analysis cohort (PD-L1≥1%). (A) Objective response rate (ORR) among genomic subgroups of interest (*KRAS*, *TP53*, *SMARCA4*, *KEAP1*, *STK11, TMB)*. (B) Progression-free survival (PFS) and (C) overall survival (OS) of chemotherapy-IO versus IO in patients with *SMARCA4* mutations. (D) PFS and (E) OS for the TMB high groups. Median survival times presented with CIs in brackets. Median survival times presented with CIs in brackets. Error bars in ORR plots represent 95% CI. Mut; mutated; IO, single-agen anti-PD(L)-1 blockade; TMB, tumor mutational burden; WT, wild type.

Our analyses found that the addition of chemotherapy increases the probability of initial response in a heterogenous 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 28]

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.[11] 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.[29] 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[30 31] but improved response to IO.[17] 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.[32 33] However, here, we found that even when accounting for TMB in a propensity adjusted model, smoking status remained a distinct predictive factor. Smoking history is a readily available biomarker that could be of value in determining regimen selection. Our analysis suggests that Chemotherapy-IO should be strongly considered for never-smokers even in the presence of high TMB and/or PD-L1 expression. Further work is needed to identify the underlying biological basis for this pattern. It is possible that the advantage observed for Chemotherapy-IO in the never-smoker population (PD-L1≥50%), despite adjustment for TMB, might represent a subset of LUAD which although it tests genomically negative for drivers such as EGFR or ALK, may in fact, be a group of patients whose cancer has yet unidentified drivers, for which existing data suggests inferior IO response. For example, several studies have identified oncogenic fusions using RNA sequencing for patients without a driver alteration identified through targeted NGS methods.

The increased response rate and PFS benefit generally observed with Chemotherapy-IO suggests that therapeutic escalation could have an important role in aggressive or extensive disease. Here, the addition of chemotherapy could help provide more immediate symptom relief. Further, these patients may not otherwise have the opportunity to receive salvage chemotherapy after progression on immunotherapy. In this scenario, initial disease control with chemotherapy could create a window of disease control to enable the more gradual effects of IO to become operant. Notably, however, in the setting of brain or liver metastases, we did not find any clinical benefit from the addition of chemotherapy to IO, consistent with prior analysis.[18] In this setting, it is unclear if the added toxicity that comes with chemotherapy may abrogate the potential clinical benefits. Further investigation is also needed to understand the precise impact of volume of disease on patient outcomes.

Our study is a retrospective analysis with the associated limitations, but we sought to minimize inherent bias by including two large institutions and by applying robust propensity-matching methodology. The modest sample size of the PD-L1 1%–49% subgroup, especially within the patients who received single-agent IO limited the power of the analysis for this subpopulation. Despite these limitations, our study is the first to comprehensively study the comparative effectiveness of Chemotherapy-IO across all relevant PD-L1 subgroups, integrating TMB and genomic analyses for the first time.

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-(L)1 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-(L)1 with and without chemotherapy (NCT03793179, NCT04547504).

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Figure S1 **Cohort assembly.** A total of N=3769 patients treated with either Chemotherapy-IO or IO treated between 1/10/17 and 9/8/20. Chemotherapy-IO; Combination PD(L)-1 blockade and platinum chemotherapy. IO; single agent PD(L)-1 blockade.

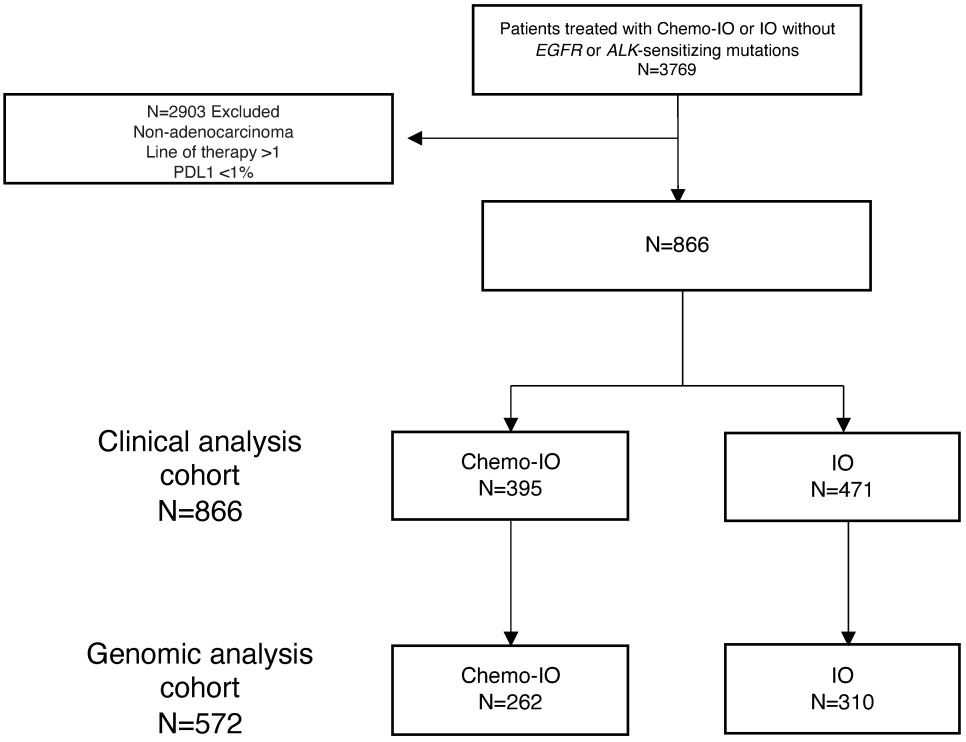
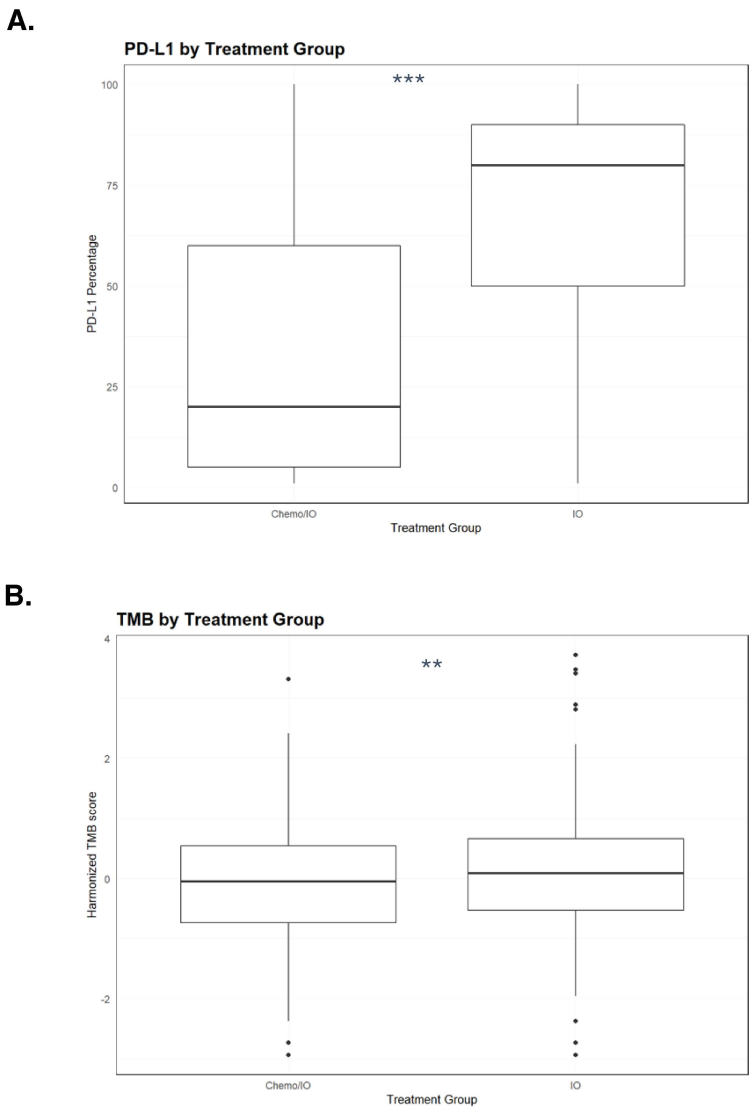
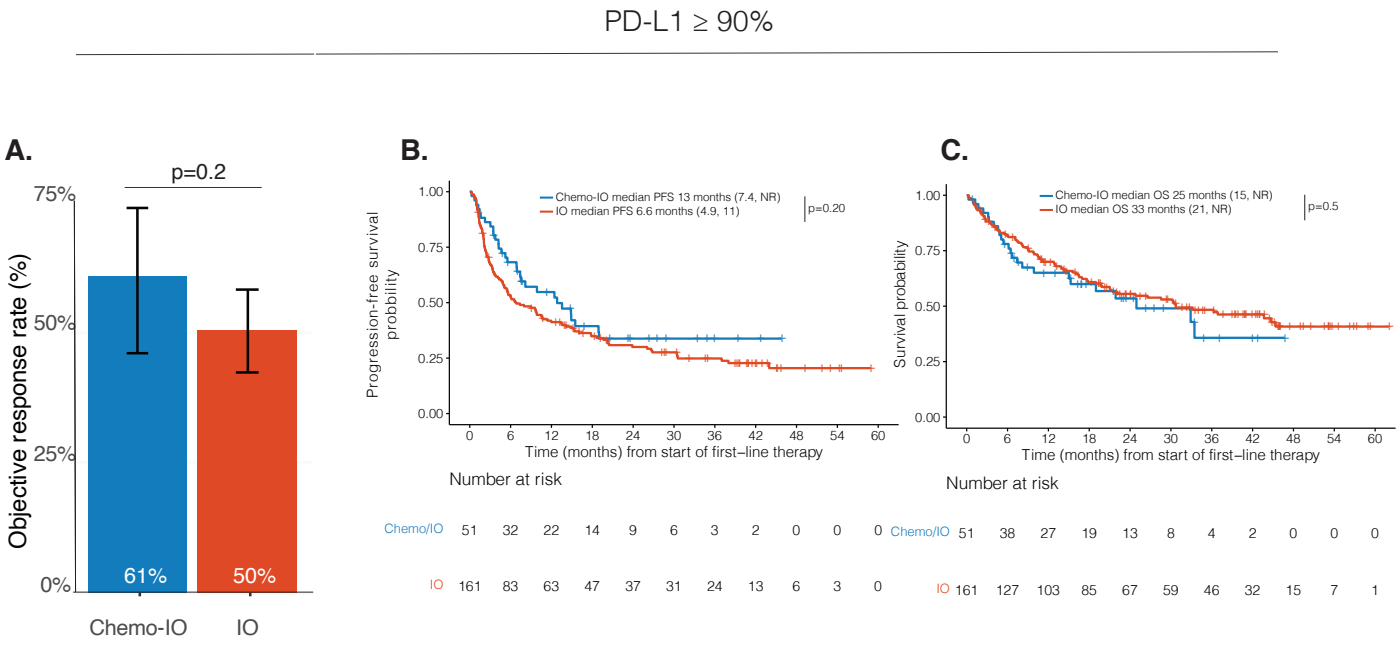


Figure S2



Median PD-L1 and harmonized tumor mutational burden (TMB) between chemotherapy plus PD-(L)1 blockade (Chemotherapy-IO) vs single-agent PD-(L)1 blockade (IO) groups.
A. Box plots of tumor PD-L1 expression and B. Median TMB between Chemotherapy-IO and IO. ***p<0.001

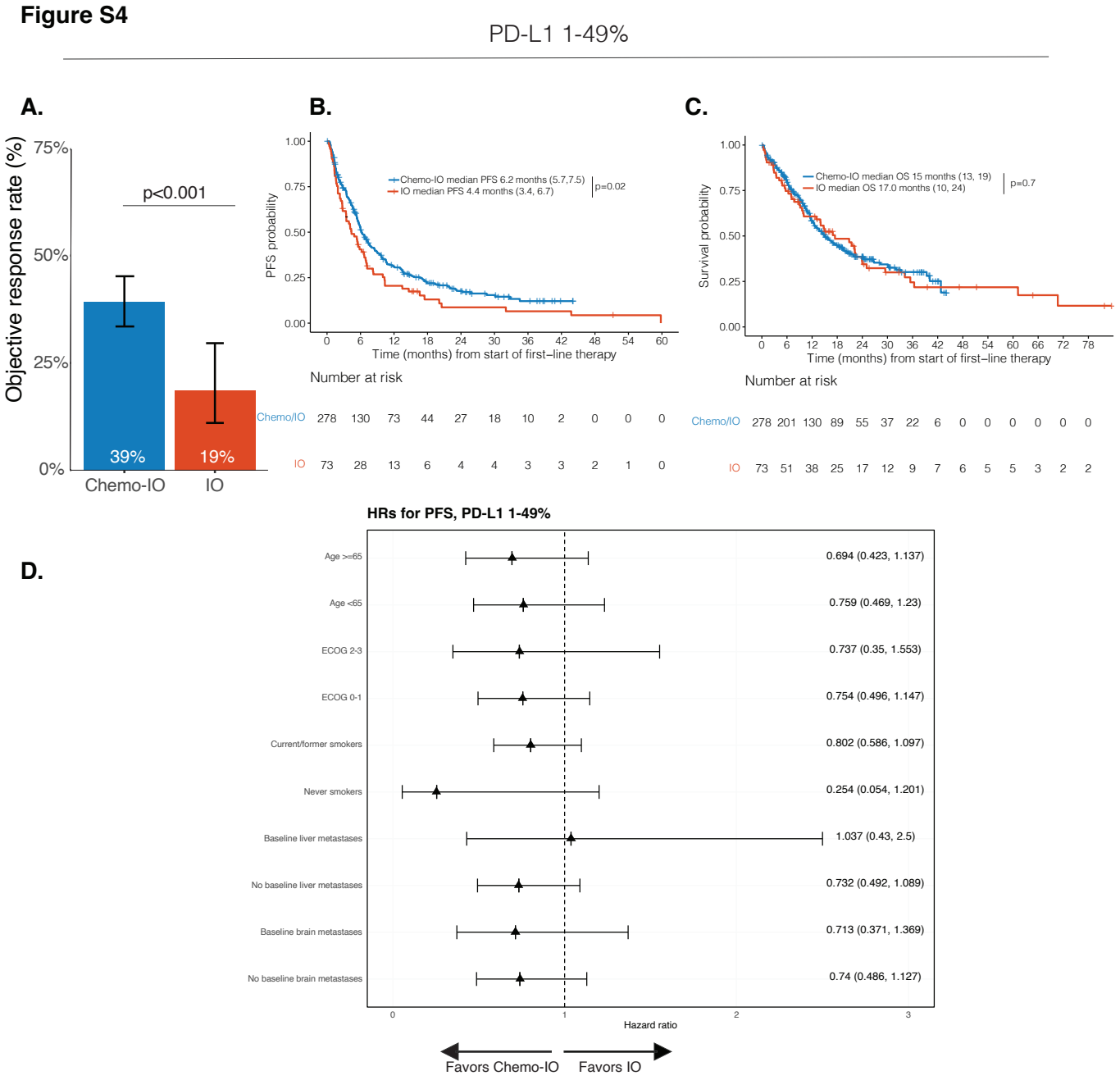
Figure S3



Outcomes to chemotherapy plus PD-(L)1 blockade (Chemotherapy-IO) vs single-agent PD-(L)1 blockade (IO) among patients with PD-L1 >90%.

A. Objective response rate, B. Progression-free survival and C. Overall survival. Chemotherapy-IO and IO. Chemotherapy-IO; Combination PD(L)-1 blockade and platinum chemotherapy. IO; single agent PD(L)-1 blockade.

Figure S4



Comparative effectiveness of chemotherapy plus PD-(L)1 blockade (Chemotherapy-IO) vs single-agent PD-(L)1 blockade (IO) in patients with PD-L1 1-49%.

A. Objective response rate, B. Progression-free survival (PFS), and C. Overall survival (OS) among Chemotherapy-IO vs IO groups. D. Hazard ratio for covariates associated with PFS, note that too few events were present in this subgroup for OS analysis.
ECOG; Eastern Cooperative Oncology Group performance status. Median survival times presented with confidence intervals in brackets. HR; hazard ratio. 95%CI; 95% confidence intervals.

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Supplemental Methods

Genomic sequencing – Memorial Sloan Kettering Cancer Center (MSK)

Biopsies from patients treated at MSK underwent next-generation sequencing (NGS) using the MSK-IMPACT platform as previously described[34]. Briefly, DNA was extracted from tumors and patient-matched blood samples. Bar-coded libraries were generated and sequenced for targeted all exons and select introns of a custom gene panel of 341 (version1), 410 (version 2), or 468 (version 3) genes. Samples were run through a custom pipeline to identify somatic alterations, including mutations and copy number alterations. Tumor mutational burden was calculated as previously described[35].

Genomic sequencing – Dana-Farber Cancer Institute (DFCI)

Targeted exome NGS (Profile) was carried out using the validated OncoPanel assay in the Center for Cancer Genome Discovery at the DFCI for 277 (POPv1), 302 (POPv2), or 447 (POPv3) cancer-associated genes. Variants were filtered to remove potential germline variants as previously published and annotated using Oncotractor as previously described. To remove additional germline noise, variants that were annotated as benign/likely benign in ClinVar or were present at a population maximum allele frequency of < 0.1% were excluded. Variants were retained in either case if they were annotated as confirmed somatic in at least two samples in COSMIC as previously described[36].

Harmonization of Tumor Mutation Burden

Tumor mutational burden was calculated at MSK and at DFCI as previously described. To address differences in sequencing methodologies, we performed harmonization of TMB as previously done[15]. TMB distributions were harmonized by applying a normal transformation followed by standardization to z-scores, which enables integration of datasets derived from different sequencing panels[15].

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Table S1: PD-L1≥1%: Propensity score analysis for Chemo-IO vs. IO determining likelihood of receiving Chemo-IO vs. IO

Propensity score analysis for Chemo + IO vs. IO			
Characteristic	**OR**[1]	**95% CI**[1]	**p-value**
>=65 vs. <65	0.78	0.55, 1.11	0.2
ECOG 2-3 vs. 0-1	0.91	0.57, 1.46	0.7
Current/Former Smoker vs. Never Smoker	0.43	0.25, 0.72	**0.001**
PD-L1 >=50 vs. 1-49	0.07	0.05, 0.10	**<0.001**
Baseline liver metastases	0.74	0.44, 1.22	0.2
Baseline brain metastases	0.87	0.59, 1.28	0.5
[1] OR = Odds Ratio, CI = Confidence Interval			

Table S2: PD-L1≥50%: Propensity score analysis for Chemo-IO vs. IO determining likelihood of receiving Chemo-IO vs. IO

PD-L1 >= 50: Propensity score analysis for Chemo + IO vs. IO			
Characteristic	**OR**[1]	**95% CI**[1]	**p-value**
>=65 vs. <65	0.57	0.37, 0.89	**0.012**
ECOG 2-3 vs. 0-1	0.92	0.49, 1.65	0.8
Current/Former Smoker vs. Never Smoker	0.52	0.28, 0.99	**0.041**
Baseline liver metastases	0.78	0.39, 1.46	0.5
Baseline brain metastases	0.86	0.52, 1.39	0.5
[1] OR = Odds Ratio, CI = Confidence Interval			

Table S3: PD-L1 1-49%: Propensity score analysis for Chemo-IO vs. IO determining likelihood of receiving Chemo-IO vs. IO

PD-L1 1-49: Propensity score analysis for Chemo + IO vs. IO			
Characteristic	**OR**[1]	**95% CI**[1]	**p-value**
>=65 vs. <65	1.33	0.76, 2.35	0.3
ECOG 2-3 vs. 0-1	0.90	0.43, 2.05	0.8
Current/Former Smoker vs. Never Smoker	0.23	0.05, 0.66	**0.017**
Baseline liver metastases	0.75	0.35, 1.73	0.5
Baseline brain metastases	0.98	0.52, 1.91	>0.9
[1] OR = Odds Ratio, CI = Confidence Interval			

Table S4: PD-L1≥1%: Propensity-adjusted Cox model for PFS – Main effects model

Propensity-adjusted Cox model for PFS - Main effects model			
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**
Chemo + IO vs. IO	0.75	0.61, 0.92	**0.006**
>=65 vs. <65	1.29	1.06, 1.58	**0.012**
ECOG (2-3 vs. 0-1)	1.45	1.10, 1.92	**0.008**
Current/Former Smoker vs. Never Smoker	0.86	0.62, 1.21	0.4
PD-L1 >=50 vs. 1-49	0.73	0.60, 0.90	**0.003**
Baseline liver metastases	1.58	1.16, 2.13	**0.003**
Baseline brain metastases	1.02	0.82, 1.28	0.8
[1] HR = Hazard Ratio, CI = Confidence Interval			

Table S5: PD-L1 ≥1%: Propensity-adjusted Cox model for PFS – Treatment interaction model

Propensity-adjusted Cox model for PFS			
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**
Chemo + IO vs. IO	0.36	0.15, 0.88	**0.025**
>=65 vs. <65	1.09	0.83, 1.43	0.6
ECOG (2-3 vs. 0-1)	1.54	1.13, 2.10	**0.006**
Current/Former Smoker vs. Never Smoker	0.62	0.32, 1.20	0.2
PD-L1 >=50 vs. 1-49	0.77	0.56, 1.04	0.090
Baseline liver metastases	1.55	1.08, 2.24	**0.019**
Baseline brain metastases	0.98	0.73, 1.31	0.9
Chemo + IO vs. IO * >=65 vs. <65	1.45	0.96, 2.18	0.075
Chemo + IO vs. IO * ECOG (2-3 vs. 0-1)	0.85	0.48, 1.50	0.6
Chemo + IO vs. IO * Current/Former Smoker vs. Never Smoker	1.84	0.88, 3.83	0.10
Chemo + IO vs. IO * PD-L1 >=50 vs. 1-49	0.93	0.62, 1.41	0.7
Chemo + IO vs. IO * Baseline liver metastases	1.08	0.59, 1.99	0.8
Chemo + IO vs. IO * Baseline brain metastases	1.08	0.68, 1.70	0.7
[1] HR = Hazard Ratio, CI = Confidence Interval			

Table S6: PD-L1 ≥1%: Propensity-adjusted Cox model for OS - Main effects model

Propensity-adjusted Cox model for OS - Main effects model			
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**
Chemo + IO vs. IO	1.06	0.83, 1.35	0.6
>=65 vs. <65	1.43	1.13, 1.82	**0.003**
ECOG (2-3 vs. 0-1)	1.96	1.41, 2.73	**<0.001**
Current/Former Smoker vs. Never Smoker	1.35	0.94, 1.95	0.11
PD-L1 >=50 vs. 1-49	0.80	0.63, 1.01	0.060
Baseline liver metastases	1.47	1.04, 2.09	**0.029**
Baseline brain metastases	0.96	0.73, 1.26	0.7
[1] HR = Hazard Ratio, CI = Confidence Interval			

Table S7: PD-L1 ≥1%: Propensity-adjusted Cox model for OS – Treatment interaction model

Propensity-adjusted Cox model for OS			
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**
Chemo + IO vs. IO	1.01	0.43, 2.40	>0.9
>=65 vs. <65	1.40	1.03, 1.90	**0.033**
ECOG (2-3 vs. 0-1)	2.27	1.54, 3.35	**<0.001**
Current/Former Smoker vs. Never Smoker	1.30	0.70, 2.43	0.4
PD-L1 >=50 vs. 1-49	0.83	0.60, 1.16	0.3
Baseline liver metastases	1.37	0.91, 2.07	0.13
Baseline brain metastases	0.88	0.63, 1.24	0.5
Chemo + IO vs. IO * >=65 vs. <65	1.06	0.65, 1.72	0.8
Chemo + IO vs. IO * ECOG (2-3 vs. 0-1)	0.74	0.37, 1.45	0.4
Chemo + IO vs. IO * Current/Former Smoker vs. Never Smoker	1.06	0.50, 2.24	0.9
Chemo + IO vs. IO * PD-L1 >=50 vs. 1-49	0.91	0.57, 1.47	0.7
Chemo + IO vs. IO * Baseline liver metastases	1.15	0.56, 2.35	0.7
Chemo + IO vs. IO * Baseline brain metastases	1.19	0.69, 2.05	0.5
[1] HR = Hazard Ratio, CI = Confidence Interval			

Table S8: PD-L1 ≥50%: Propensity-adjusted Cox model for PFS - Main effects model

Propensity-adjusted Cox model for PFS (PD-L1 >=50 subgroup) - Main effects model			
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**
Chemo + IO vs. IO	0.75	0.57, 0.98	**0.037**
>=65 vs. <65	1.35	1.04, 1.76	**0.024**
ECOG (2-3 vs. 0-1)	1.37	0.92, 2.03	0.12
Current/Former Smoker vs. Never Smoker	0.92	0.64, 1.33	0.7
Baseline liver metastases	1.66	1.14, 2.41	**0.008**
Baseline brain metastases	0.95	0.71, 1.26	0.7
[1] HR = Hazard Ratio, CI = Confidence Interval			

Table S9: PD-L1 ≥50%: Propensity-adjusted Cox model for PFS – Treatment interaction model

Propensity-adjusted Cox model for PFS			
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**
Chemo + IO vs. IO	0.22	0.10, 0.51	**<0.001**
>=65 vs. <65	1.04	0.81, 1.35	0.7
ECOG (2-3 vs. 0-1)	1.38	0.99, 1.92	0.058
Current/Former Smoker vs. Never Smoker	0.58	0.38, 0.89	**0.013**
Baseline liver metastases	1.50	1.07, 2.10	**0.019**
Baseline brain metastases	0.97	0.75, 1.25	0.8
Chemo + IO vs. IO * >=65 vs. <65	1.77	1.04, 3.03	**0.036**
Chemo + IO vs. IO * ECOG (2-3 vs. 0-1)	0.89	0.37, 2.15	0.8
Chemo + IO vs. IO * Current/Former Smoker vs. Never Smoker	2.54	1.24, 5.24	**0.011**
Chemo + IO vs. IO * Baseline liver metastases	1.31	0.60, 2.88	0.5
Chemo + IO vs. IO * Baseline brain metastases	0.91	0.50, 1.66	0.8
[1] HR = Hazard Ratio, CI = Confidence Interval			

Table S10: PD-L1 ≥50%: Propensity-adjusted Cox model for OS - Main effects model

Propensity-adjusted Cox model for OS (PD-L1 >=50 subgroup) - Main effects model			
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**
Chemo + IO vs. IO	1.02	0.73, 1.43	>0.9
>=65 vs. <65	1.51	1.10, 2.07	**0.011**
ECOG (2-3 vs. 0-1)	1.97	1.25, 3.10	**0.003**
Current/Former Smoker vs. Never Smoker	1.28	0.80, 2.03	0.3
Baseline liver metastases	1.67	1.08, 2.57	**0.020**
Baseline brain metastases	0.88	0.61, 1.26	0.5
[1] HR = Hazard Ratio, CI = Confidence Interval			

Table S11: PD-L1 ≥50%: Propensity-adjusted Cox model for OS – Treatment interaction model

Propensity-adjusted Cox model for OS			
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**
Chemo + IO vs. IO	0.37	0.12, 1.13	0.081
>=65 vs. <65	1.36	1.02, 1.82	**0.037**
ECOG (2-3 vs. 0-1)	2.05	1.41, 2.98	**<0.001**
Current/Former Smoker vs. Never Smoker	0.82	0.52, 1.27	0.4
Baseline liver metastases	1.67	1.21, 2.31	**0.002**
Baseline brain metastases	0.97	0.72, 1.30	0.8
Chemo + IO vs. IO * >=65 vs. <65	1.30	0.67, 2.51	0.4
Chemo + IO vs. IO * ECOG (2-3 vs. 0-1)	0.87	0.32, 2.35	0.8
Chemo + IO vs. IO * Current/Former Smoker vs. Never Smoker	2.81	1.04, 7.58	**0.042**
Chemo + IO vs. IO * Baseline liver metastases	0.99	0.36, 2.67	>0.9
Chemo + IO vs. IO * Baseline brain metastases	0.78	0.36, 1.70	0.5
[1] HR = Hazard Ratio, CI = Confidence Interval			

Table S12: PD-L1 1-49%: Propensity-adjusted Cox model for PFS - Main effects model

Propensity-adjusted Cox model for PFS (PD-L1 1-49 subgroup) - Main effects model			
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**
Chemo + IO vs. IO	0.74	0.51, 1.07	0.11
>=65 vs. <65	1.32	0.94, 1.85	0.11
ECOG (2-3 vs. 0-1)	1.59	1.09, 2.32	**0.017**
Current/Former Smoker vs. Never Smoker	0.73	0.34, 1.55	0.4
Baseline liver metastases	1.38	0.83, 2.30	0.2
Baseline brain metastases	1.28	0.89, 1.86	0.2
[1] HR = Hazard Ratio, CI = Confidence Interval			

Table S13: PD-L1 1-49%: Propensity-adjusted Cox model for PFS – Treatment interaction model

Propensity-adjusted Cox model for PFS			
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**
Chemo + IO vs. IO	0.43	0.08, 2.31	0.3
>=65 vs. <65	1.48	0.73, 3.00	0.3
ECOG (2-3 vs. 0-1)	1.86	0.87, 3.99	0.11
Current/Former Smoker vs. Never Smoker	0.44	0.08, 2.52	0.4
Baseline liver metastases	1.54	0.59, 4.02	0.4
Baseline brain metastases	1.34	0.66, 2.73	0.4
Chemo + IO vs. IO * >=65 vs. <65	0.86	0.40, 1.85	0.7
Chemo + IO vs. IO * ECOG (2-3 vs. 0-1)	0.77	0.34, 1.78	0.5
Chemo + IO vs. IO * Current/Former Smoker vs. Never Smoker	2.19	0.37, 12.8	0.4
Chemo + IO vs. IO * Baseline liver metastases	0.87	0.31, 2.44	0.8
Chemo + IO vs. IO * Baseline brain metastases	1.01	0.46, 2.20	>0.9
[1] HR = Hazard Ratio, CI = Confidence Interval			

Table S14: PD-L1 1-49%: Propensity-adjusted Cox model for OS - Main effects model

Propensity-adjusted Cox model for OS (PD-L1 1-49 subgroup) - Main effects model			
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**
Chemo + IO vs. IO	1.17	0.82, 1.68	0.4
>=65 vs. <65	1.36	0.95, 1.93	0.090
ECOG (2-3 vs. 0-1)	2.03	1.31, 3.15	**0.002**
Current/Former Smoker vs. Never Smoker	2.06	1.02, 4.17	**0.044**
Baseline liver metastases	1.18	0.68, 2.05	0.5
Baseline brain metastases	1.18	0.78, 1.78	0.4
[1] HR = Hazard Ratio, CI = Confidence Interval			

Table S15: Baseline characteristics for genomic analysis cohort

Characteristic	Overall, N = 572[1]	PD-L1 1-49, N = 240[1]	PD-L1 >=50, N = 332[1]	p-value[2]
Site				0.8
DFCI	315 (55%)	131 (55%)	184 (55%)	
MSK	257 (45%)	109 (45%)	148 (45%)	
Age	67 (60, 75)	65 (58, 73)	68 (60, 76)	**0.003**
Sex				0.6
Female	327 (57%)	134 (56%)	193 (58%)	
Male	245 (43%)	106 (44%)	139 (42%)	
ECOG				0.6
< 2	521 (93%)	211 (93%)	310 (94%)	
>= 2	38 (6.8%)	17 (7.5%)	21 (6.3%)	
Unknown	13	12	1	
Pack yrs	30 (12, 45)	26 (10, 42)	30 (14, 45)	0.3
Unknown	27	16	11	
Smoking Status				0.4
Current/Former	505 (88%)	208 (87%)	297 (89%)	
Never	66 (12%)	31 (13%)	35 (11%)	
Unknown	1	1	0	
Treatment group				**<0.001**
Chemo/IO	262 (46%)	194 (81%)	68 (20%)	
IO	310 (54%)	46 (19%)	264 (80%)	
Baseline liver metastases	77 (13%)	32 (13%)	45 (14%)	>0.9
Baseline brain metastases	162 (28%)	64 (27%)	98 (30%)	0.5
Unknown	2	2	0	
Harmonized TMB score	0.09 (-0.68, 0.65)	-0.04 (-0.73, 0.57)	0.09 (-0.53, 0.68)	0.2
SMARCA4	71 (12%)	37 (15%)	34 (10%)	**0.064**
STK11	92 (16%)	55 (23%)	37 (11%)	**<0.001**
KRAS	301 (53%)	130 (54%)	171 (52%)	0.5
KEAP1	116 (20%)	61 (25%)	55 (17%)	**0.009**
TP53	347 (61%)	135 (56%)	212 (64%)	**0.066**
[1] n (%); Median (IQR)				
[2] Pearson's Chi-squared test; Wilcoxon rank sum test				

Table S16: PD-L1 ≥1% Propensity-adjusted Cox model for PFS – Treatment interaction model

Propensity-adjusted Cox model for PFS			
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**
Chemo + IO vs. IO	0.22	0.06, 0.83	**0.025**
>=65 vs. <65	1.20	0.89, 1.63	0.2
ECOG (2-3 vs. 0-1)	1.70	0.90, 3.21	0.10
Current/Former Smoker vs. Never Smoker	0.67	0.24, 1.90	0.5
PD-L1 >=50 vs. 1-49	0.64	0.47, 0.89	**0.007**
Baseline liver metastases	1.16	0.73, 1.83	0.5
Baseline brain metastases	0.99	0.69, 1.42	>0.9
Harmonized TMB score	0.93	0.78, 1.11	0.4
SMARCA4	0.89	0.58, 1.36	0.6
STK11	1.73	1.16, 2.57	**0.007**
KRAS	1.07	0.77, 1.50	0.7
KEAP1	1.15	0.82, 1.60	0.4
TP53	1.22	0.87, 1.72	0.3
Chemo + IO vs. IO * >=65 vs. <65	1.25	0.78, 1.99	0.4
Chemo + IO vs. IO * ECOG (2-3 vs. 0-1)	1.07	0.44, 2.60	0.9
Chemo + IO vs. IO * Current/Former Smoker vs. Never Smoker	2.50	0.80, 7.84	0.11
Chemo + IO vs. IO * PD-L1 >=50 vs. 1-49	1.26	0.80, 2.00	0.3
Chemo + IO vs. IO * Baseline liver metastases	1.73	0.84, 3.54	0.14
Chemo + IO vs. IO * Baseline brain metastases	1.03	0.58, 1.83	>0.9
Chemo + IO vs. IO * Harmonized TMB score	0.67	0.52, 0.87	**0.003**
Chemo + IO vs. IO * SMARCA4	2.24	1.21, 4.16	**0.011**
Chemo + IO vs. IO * STK11	0.79	0.44, 1.41	0.4
Chemo + IO vs. IO * KRAS	0.87	0.50, 1.52	0.6
Chemo + IO vs. IO * KEAP1	1.21	0.68, 2.17	0.5
Chemo + IO vs. IO * TP53	0.93	0.54, 1.61	0.8
[1] HR = Hazard Ratio, CI = Confidence Interval			

Table S17: PD-L1 ≥1% Propensity-adjusted Cox model for OS – Treatment interaction model

Propensity-adjusted Cox model for OS			
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**
Chemo + IO vs. IO	0.67	0.19, 2.31	0.5
>=65 vs. <65	1.71	1.19, 2.46	**0.004**
ECOG (2-3 vs. 0-1)	1.96	1.05, 3.68	**0.035**
Current/Former Smoker vs. Never Smoker	1.59	0.61, 4.19	0.3
PD-L1 >=50 vs. 1-49	0.58	0.40, 0.85	**0.005**
Baseline liver metastases	1.15	0.69, 1.94	0.6
Baseline brain metastases	0.90	0.58, 1.38	0.6
Harmonized TMB score	0.76	0.62, 0.93	**0.009**
SMARCA4	1.04	0.56, 1.94	>0.9
STK11	1.40	0.78, 2.53	0.3
KRAS	1.14	0.77, 1.68	0.5
KEAP1	1.32	0.82, 2.13	0.3
TP53	1.30	0.85, 1.99	0.2
Chemo + IO vs. IO * >=65 vs. <65	0.92	0.53, 1.60	0.8
Chemo + IO vs. IO * ECOG (2-3 vs. 0-1)	0.99	0.39, 2.50	>0.9
Chemo + IO vs. IO * Current/Former Smoker vs. Never Smoker	1.29	0.40, 4.10	0.7
Chemo + IO vs. IO * PD-L1 >=50 vs. 1-49	1.90	1.10, 3.29	**0.022**
Chemo + IO vs. IO * Baseline liver metastases	1.62	0.73, 3.62	0.2
Chemo + IO vs. IO * Baseline brain metastases	1.37	0.71, 2.67	0.4
Chemo + IO vs. IO * Harmonized TMB score	0.89	0.66, 1.20	0.4
Chemo + IO vs. IO * SMARCA4	1.88	0.86, 4.07	0.11
Chemo + IO vs. IO * STK11	0.87	0.40, 1.91	0.7
Chemo + IO vs. IO * KRAS	0.70	0.37, 1.33	0.3
Chemo + IO vs. IO * KEAP1	1.42	0.71, 2.83	0.3
Chemo + IO vs. IO * TP53	0.86	0.44, 1.68	0.7