Predictors of benefits from frontline chemoimmunotherapy in stage IV non-small-cell lung cancer: a meta-analysis

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) have dramatically expanded the therapeutic landscape of non-small-cell lung cancer (NSCLC). In a previous study, gender, smoking history, and PD-L1 status were found to influence the efficacy of single-agent ICI in NSCLC. This meta-analysis evaluated the clinical and molecular factors that could predict a benefit from adding ICIs to first-line chemotherapy in metastatic NSCLC.

Patients and Methods: The pooled hazard ratio (HR) of progression-free survival (PFS) and overall survival (OS) among the selected subgroups were analyzed using the random effects model. The correlation between PD-L1 expression and outcome was analyzed by meta-regression.

Results: Seven phase III randomized controlled trials comparing chemo-immunotherapy (CIT) with chemotherapy in untreated stage 4 NSCLC were included. CIT evenly improved PFS irrespective of age, gender, histology, smoking history, and performance status. Among patients with baseline hepatic metastasis treated with Atezolizumab-containing CIT, PFS improvement was only detected with the addition of Bevacizumab. Whereas patients with EGFR/ALK-driven cancer exhibited greater PFS with the addition of ICI to a Bevacizumab (BEV)-based regimen, the derived benefit was no longer statistically significant among those treated with non-BEV-based regimens. Although the superior PFS conferred by CIT was noticeable across all PD-L1 expression subgroups, this benefit correlated with PD-L1 level and was more pronounced in the “PD-L1 high” cohort. Except for patients harboring EGFR/ALK aberrations or squamous histology, CIT consistently improved OS across the other selected subgroups.

Conclusions: The survival advantage associated with first-line CIT in metastatic NSCLC was observed in different patient populations, including those for which single-agent ICI has marginal therapeutic benefit. Our findings support the role of chemotherapy with or without VEGF blockade as enhancers of ICI activity in NSCLC.

Background

Lung cancer remains the leading cause of cancer-related mortality in the US.¹ The successful incorporation of immune checkpoint inhibitors (ICIs) has revolutionized the treatment landscape of non-small-cell lung cancer (NSCLC). When used as single agents, PD1/PD-L1 inhibitors were proven superior to docetaxel in NSCLC patients that failed platinum-based chemotherapy.²–⁵ Nevertheless, the treatment approach shifted dramatically when a combination regimen that integrated a PD1 inhibitor with platinum-doublet chemotherapy in chemo-naïve patients showed substantial superiority in overall survival (OS) relative to conventional chemotherapy. Currently, the combinations of platinum-Pemetrexed with Pembrolizumab or Carboplatin-Paclitaxel-Bevacizumab (BEV) with Atezolizumab have received FDA approval as frontline therapies for metastatic lung adenocarcinoma.⁶,⁷ Similarly, Pembrolizumab was FDA approved for use in combination with Carboplatin and taxane for squamous histology.⁸ In this context, establishing reliable markers of clinical benefit to chemo-immunotherapy (CIT) is valuable to select the subset of patients that derives the most advantage from this therapy. As importantly, identifying subjects for whom the addition of PD1/PD-L1 inhibitor to chemotherapy is less likely to be effective will underscore the unmet need to enhance immunotherapy in that particular cohort of patients, and possibly offer an opportunity to improve outcome. In a previous study, gender, smoking history, and PD-L1 status were found to influence the efficacy of single-agent ICI in NSCLC.⁸ In addition, a growing body of evidence indicates that ICI monotherapy is not effective in the presence of EGFR mutation including the cases with elevated PD-L1 expression.¹⁰ However, it is not yet known whether these predictive factors are applicable to patients treated with ICI in combination with chemotherapy. Currently, there is uncertainty about who should be recommended chemoimmunotherapy consisting of platinum-based chemotherapy plus an ICI as first-line treatment of metastatic NSCLC. By assessing the comparative efficacy of
chemo-immunotherapy among different selected subgroups, this meta-analysis explored the demographic, pathological and molecular factors that are indicative of clinical benefit from the addition of ICI to conventional chemotherapy in treatment-naïve metastatic NSCLC.

Materials and methods

Literature review

A systematic literature search was conducted in the PubMed and Embase databases, from their respective inception dates through August 2019. The following keywords were used in our bibliographic search: (“stage IV” or “advanced” or “metastatic”) AND (“lung cancer” or “non-small-cell lung cancer” or “lung carcinoma” or “non-small-cell lung carcinoma” or “NSCLC”) AND (“front line” or “first line” or “treatment naïve” or “untreated”) AND (“chemoimmunotherapy” or “Nivolumab” or “Pembrolizumab” or “Atezolizumab” or “Avelumab” or “Durvalumab”). Abstracts and original papers in peer-reviewed journals were considered.

Study selection and data extraction

The inclusion criteria were phase III randomized controlled trials comparing chemotherapy when used alone or combined with PD1/PD-L1 inhibitors in previously untreated stage 4 non-small cell lung cancer patients, and in whom the hazard ratio (HR) for progression-free survival (PFS) and overall survival (OS) by subgroups of age, gender, smoking history, performance status (PS), histology, presence of hepatic metastasis, EGFR mutation, ALK translocation, and PD-L1 expression. When HRs and/or the corresponding confidence intervals were not numerically provided in the text, they were manually extracted and calculated by plotting on a forest plot with a logarithmic scale. Results were presented as forest plots with square representing the size effect in each particular study and diamond representing the pooled size effect of the subgroup. The heterogeneity between studies was estimated by Q-test and the I² statistics, and considered to indicate high level of heterogeneity when I² is greater than 50%. The Egger test was performed to calculate the publication bias, which was presented by a funnel plot. The correlation between PD-L1 expression and outcome was analyzed by meta-regression. A P-value below 0.05 was considered statistically significant.

Comprehensive meta-analysis software (version 3.3.070, New Jersey USA) was used to perform statistical analyses. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used for the conduction of this meta-analysis.

Results

Study selection

Our initial literature search strategy yielded 1108 citations (882 from Embase and 226 from PubMed). Following the exclusion of studies that did not meet the inclusion criteria, seven trials comparing CIT vs. chemotherapy alone were included (summarized in Table 1).

Characteristics of the eligible studies

The baseline characteristics of these studies are reported in Table 1. All the studies were well designed randomized controlled phase III trials. Four studies enrolled patients with non-squamous NSCLC, two trials enrolled those with squamous NSCLC, and one trial accepted patients with either cell type. Among these studies, four were published in peer-reviewed journals and three were presented in major professional meetings only. Three trials investigated PD1 blocking agents (one with Nivolumab and two with Pembrolizumab), whereas four trials investigated Atezolizumab, a PD-L1 blocking antibody.

Chemo-immunotherapy offers an advantage in PFS compared with chemotherapy alone

The pooled analysis of all seven studies revealed that combination CIT yielded substantial reduction in the risk of disease progression when compared with platinum-based chemotherapy alone. This result corresponded to an HR of 0.65 (95% CI: 0.57–0.75; p < .01) (Figure 1). Significant heterogeneity between studies was identified (I² 75.73; P-value <0.0001). The 1-tailed P-value of the Egger test was 0.14, with no asymmetry in the funnel plot, indicating an absence of significant publication bias (Supplement 1).

We examined PFS HR of CIT relatively to chemotherapy as stratified by several clinical variables, including age, sex, and ECOG PS. Compared with chemotherapy, CIT invariably improved PFS, regardless of age. The HR was 0.60 (95% CI: 0.52–0.69) for the younger patient group (<65 years) and 0.64 (95% CI: 0.58–0.72) for the older patient group (≥65 years) (Figure 2). Of note, for trials that stratified enrollees into three age subgroups (<65, 65–74, and ≥75 years), the last two subgroups were combined in this analysis. As opposed to what we previously observed with single-agent ICI, CIT...
Table 1. Baseline characteristics and outcome of the eligible clinical trials comparing chemotherapy with CIT in metastatic NSCLC.

| Authors (year) | Study name | Study design/Stratification criteria | Histology | Study arm (N) | Control Arm (N) | PFS (months) | OS (months); HR (95% CI) |
|----------------|------------|-------------------------------------|-----------|--------------|----------------|--------------|--------------------------|
| Gandhi L et al. (NEJM 2018) | Keynote-189 | Double-blind phase III, stratified by PD-L1 expression, choice of platinum and smoking history | Non-squamous, EGFR/ALK wild-type | Platinum-Pemetrexed-Pembrolizumab (410) | Platinum-Pemetrexed (206) | 8.8 vs. 4.9; 0.52 (0.43–0.64) | Unreached vs. 11.3; 0.49 (0.38–0.64) |
| Garassino M et al (AACR 2019) | Keynote-407 | Double-blind phase III, stratified by PD-L1 expression, choice of taxane and geographic region | Squamous | Carboplatin-taxane-Pembrolizumab (278) | Carboplatin-Taxane (Paclitaxel or Nab-Paclitaxel) (281) | 6.4 vs. 4.8; 0.56 (0.45–0.70) | 15.9 vs. 11.3; 0.64 (0.49–0.85) |
| Paz-Ares L et al. (NEJM 2018) | Keynote-130 | Open-label, phase III, stratified by gender, presence of liver metastasis at baseline and PD-L1 expression | Non-squamous | Carboplatin-Nab-Paclitaxel-Atezolizumab (483) | Carboplatin-Nab-Paclitaxel (240) | 7.0 vs. 5.6; 0.65 (0.54–0.77) | 18.1 vs. 13.9; 0.80 (0.65–0.99) |
| Cappuzzo F et al. (ESMO 2018) | IMpower131 | Open-label phase III, stratified by gender, smoking status, performance status and chemotherapy regimen | Non-squamous | Carboplatin-taxane-Atezolizumab (343) | Carboplatin-taxane-Paclitaxel or Nab-Paclitaxel (340) | 6.3 vs. 5.6; 0.71 (0.60–0.85) | 14.0 vs. 13.9; 0.96 (0.78–1.18) |
| Jotte R et al. (ASCO 2018) | IMpower132 | Open-label phase III, stratified by gender, presence of liver metastasis at baseline and PD-L1 expression | Squamous | Carboplatin-Pemetrexed-Atezolizumab (292) | Carboplatin-Pemetrexed (286) | 7.6 vs. 5.2; 0.60 (0.49–0.72) | 18.1 vs. 13.6; 0.81 (0.64–1.03) |
| Papadimitrakopoulou V et al. (WCLC 2018) | IMpower150 | Open-label phase III, stratified by gender, presence of liver metastasis at baseline and PD-L1 expression | Non-squamous, EGFR/ALK wild-type | Carboplatin-Paclitaxel-Atezolizumab ± Bevacizumab (ABC or AC)(400 and 402 respectively) | Carboplatin-Paclitaxel-Bevacizumab (BPC)(400) | 8.1 vs. 7.3; 0.67 (0.50–0.84) | 19.8 vs. 14.9; 0.76 (0.63–0.93) |
| Socinski M et al. (ASCO 2016) | Checkmate 227 | Open-label phase III, stratified by histology | NSCLC (squamous and non-squamous), EGFR/ALK wild-type, PD-L1 < 1% | Histology-based chemotherapy plus Nivolumab (177) | Histology-based chemotherapy (186) | 9.2 vs. 7.3; 0.67 (0.50–0.84) | N/A |
evenly improved PFS in both genders, with an HR of 0.57 (95% CI 0.48–0.68) in females and 0.64 (95% CI 0.59–0.70) in males. There were no statistically significant differences between these two groups (P-value NS) (Figure 3). ECOG PS did not affect the PFS improvement associated with CIT with both PS 0 and 1 equally deriving benefit from the treatment (PS0 HR = 0.58, 95% CI: 0.51–0.67 vs. PS1 HR = 0.64, 95% CI: 0.59–0.70; difference P-value NS) (Supplement 2).

When used as monotherapy, we have previously shown that ICI is superior to chemotherapy among those with prior tobacco exposure. We observed the opposite in never-smokers. In contrast, the addition of ICI to chemotherapy equally and significantly reduced the risk of disease progression independently of their smoking exposure status (ever-smoker HR = 0.62, 95% CI 0.57–0.67 vs. never-smoker HR = 0.63, 95% CI 0.50–0.81; difference P-value NS) (Supplement 2).

Five included trials provided the HR for PFS according to the presence of hepatic metastasis at the time of enrollment. CIT resulted in statistically longer PFS independently of the presence of liver metastasis. For individuals with liver metastasis, the HR was 0.68 (95% CI: 0.53–0.87), and for those without liver metastasis, the HR was 0.63 (95% CI: 0.53–0.75). The difference between these two subgroups was not statistically significant (Figure 5). The combination carboplatin, Pemetrexed, and pembrolizumab improved PFS irrespective of the presence of liver metastasis. Interestingly, when the analysis was restricted to Atezolizumab-containing regimens in patients with baseline hepatic metastasis and non-squamous histology, the PFS advantage offered by CIT was significant only with the addition of Bevacizumab (HR = 0.41, 95%CI 0.26–0.62) as compared to an HR of 0.84 (95% CI 0.65–1.08) when Bevacizumab was not part of the treatment regimen, with p-value of the difference <0.001 (Supplement 12).

Likewise, a significantly prolonged PFS was equally demonstrated with CIT in both histologic subtypes, with an HR = 0.68 (95% CI: 0.50–0.94) for squamous and HR = 0.65 (95% CI: 0.55–0.77) for non-squamous lung cancer (difference P-value NS) (Supplement 3).

We then evaluated the influence of molecular aberrations in EGFR or ALK genes on PFS outcome in non-squamous lung cancers. We found that treatment with CIT led to longer PFS, regardless of EGFR or ALK status (HR = 0.63, 95% CI: 0.43–0.94 for EGFR/ALK genetic aberration vs. HR = 0.60, 95% CI: 0.55–0.66 for EGFR/ALK wild-type, P-value NS) (Figure 6). Both IMPower150 and IMPower130 studies described this PFS outcome in patients harboring EGFR or ALK aberrations. In the former, patients with an EGFR mutation or ALK translocation exhibited remarkable PFS improvement with the addition of ICI to a BEV-based regimen (HR = 0.59; 95% CI: 0.37–0.94).

**Figure 1.** Forest plots of hazard ratios comparing PFS and OS between patients treated with chemotherapy or CIT.
Intriguingly, there was no clear PFS superiority in the latter study, in which patients were treated with non-BEV-based regimens (HR = 0.75; 95% CI: 0.36–1.54).

We examined whether PD-L1 expression was predictive for improved PFS with CIT treatment. CIT significantly prolonged PFS across all PD-L1 expression cohorts. However, the benefit magnitude was greater for PD-L1-expressing patients (HR = 0.75; 95% CI: 0.64–0.88 in PD-L1-negative patients vs. HR = 0.56; 95% CI: 0.48–0.65 in PD-L1 positive patients, difference P = .01). We then conducted the analysis according to three PD-L1 expression cohorts: Low (PD-L1 < 1% or IC0/TC0), intermediate (PD-L1 1–49% or IC1/2 or TC1/2), and high (PD-L1 ≥ 50% or IC3 or TC3). Using the meta-regression model, we noticed a linear correlation between efficacy and PD-L1 level. Hence, patients with the highest PD-L1 expression achieved the optimal PFS benefit when ICI was added to frontline chemotherapy (test of the model P-value<0.001; goodness-of-fit P-value = 0.013) (Figure 7).

Data heterogeneity was detected for the following tested subgroups: squamous and non-squamous cell type, liver and non liver metastasis, age <65, PDL1 negative and positive subgroups.

Publication bias was observed with the following cohorts: ever-smoker, absence of baseline liver metastasis and PD-L1 negative.

### Chemo-immunotherapy offers an advantage in OS compared with chemotherapy alone

The pooled analysis of six studies demonstrated a significant reduction in the risk of death with the addition of checkpoint inhibitor to platinum-doublet chemotherapy in the frontline setting (HR: 0.75, 95% CI: 0.65–0.88, P < .01) (Figure 1). Heterogeneity of OS data between studies was detected (I^2 = 68.46, P = .004). Egger test revealed the presence of publication bias (1-sided P-value = 0.039).

Except for patients with EGFR/ALK abnormalities, squamous histology, CIT yielded a significant amelioration of OS across the other selected subgroups: age, gender, smoking status, ECOG PS, PD-L1 expression and hepatic metastasis (Table 2, Supplements 4–11). Three trials addressed the impact of CIT on OS based upon the presence of liver involvement, all pertaining to patients with Non-squamous histology. In Keynote-189, the combination pembrolizumab, platinum, and Pemetrexed reduced the risk of death irrespective of the presence or absence of liver metastasis. Conversely, in Atezolizumab-based CIT, the improved overall survival was noted for patients with liver metastasis only when Bevacizumab was added (HR 0.52, 95% CI 0.33–0.82). In patients treated with non-BEV-containing Atezolizumab-based CIT, no OS benefit was observed in those with liver metastasis (HR 0.94, 95%CI 0.68–1.29), with p-value of the

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**Table 2.** Forest plots of hazard ratios comparing PFS between patients treated with chemotherapy or CIT according to age. * 65–74 years-old, **≥75 years-old.
| Study name  | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|------------|--------------|-------------|-------------|---------|---------|
| Keynote-189| 0.40         | 0.29        | 0.54        | -5.79   | 0.00    |
| Keynote-407| 0.49         | 0.30        | 0.81        | -2.82   | 0.00    |
| IMpower130 | 0.59         | 0.45        | 0.78        | -3.76   | 0.00    |
| IMpower131 | 0.66         | 0.45        | 0.97        | -2.12   | 0.03    |
| IMpower132 | 0.51         | 0.36        | 0.71        | -3.90   | 0.00    |
| IMpower150 | 0.73         | 0.55        | 0.97        | -2.17   | 0.03    |
| CheckMate 227 | 0.70   | 0.44        | 1.11        | -1.51   | 0.13    |

**Figure 3.** Forest plots of hazard ratios comparing PFS between patients treated with chemotherapy or CIT according to gender.

| Study name  | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|------------|--------------|-------------|-------------|---------|---------|
| Keynote-189| 0.54         | 0.43        | 0.66        | -5.71   | 0.00    |
| IMpower130 | 0.64         | 0.53        | 0.77        | -4.68   | 0.00    |
| IMpower131 | 0.70         | 0.59        | 0.83        | -4.10   | 0.00    |
| IMpower132 | 0.61         | 0.50        | 0.74        | -4.94   | 0.00    |
| IMpower150 | 0.58         | 0.48        | 0.70        | -5.66   | 0.00    |
| CheckMate 227 | 0.64   | 0.59        | 0.70        | -10.73  | 0.00    |

**Figure 4.** Forest plots of hazard ratios comparing PFS between patients treated with chemotherapy or CIT according to tobacco exposure history.
The difference between Bevacizumab and non-Bevacizumab containing regimen equal to 0.04 (Supplement 12). Improved OS after CIT treatment was statistically significant in the EGFR/ALK wild-type cohort (HR = 0.71; 95%CI 0.57–0.88). In patients harboring EGFR/ALK aberration, the OS superiority was relevant numerically but not statistically (HR = 0.67; 95%CI 0.39–1.17). When we analyzed the data by histology, OS amelioration with CIT was remarkable in non-squamous NSCLC (HR 0.74; 95%CI 0.62–0.88). CIT failed to significantly increase OS in squamous subtype (HR = 0.79, 95%CI

**Figure 5.** Forest plots of hazard ratios comparing PFS between patients treated with chemotherapy or CIT according to the presence of baseline liver metastasis.

| Study name    | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---------------|--------------|-------------|-------------|---------|---------|
| Keynote-189   | 0.52         | 0.34        | 0.81        | -2.94   | 0.00    |
| Impower130    | 0.93         | 0.59        | 1.47        | -0.31   | 0.76    |
| Impower131    | 0.77         | 0.54        | 1.10        | -1.44   | 0.15    |
| Impower132    | 0.77         | 0.47        | 1.25        | -1.05   | 0.29    |
| Impower150(ABCP) | 0.41     | 0.26        | 0.62        | -4.10   | 0.00    |
| Impower150(ACP) | 0.81     | 0.55        | 1.21        | -1.03   | 0.30    |
|               | 0.68         | 0.53        | 0.87        | -3.10   | 0.00    |

**Figure 6.** Forest plots of hazard ratios comparing PFS between patients treated with chemotherapy or CIT according to the presence of EGFR mutation or ALK translocation.

| Study name    | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---------------|--------------|-------------|-------------|---------|---------|
| Keynote-189   | 0.48         | 0.39        | 0.59        | -6.95   | 0.00    |
| Impower130    | 0.59         | 0.49        | 0.71        | -5.58   | 0.00    |
| Impower131    | 0.68         | 0.56        | 0.82        | -3.96   | 0.00    |
| Impower132    | 0.56         | 0.46        | 0.69        | -5.61   | 0.00    |
| Impower150(ABCP) | 0.61     | 0.52        | 0.73        | -5.70   | 0.00    |
| Impower150(ACP) | 0.90     | 0.77        | 1.06        | -1.29   | 0.20    |
|               | 0.63         | 0.53        | 0.75        | -5.13   | 0.00    |
 Indeed, only two trials provided the OS HR in squamous lung cancers: IMpower131 and Keynote-407. When compared with platinum-doublet regimens, CIT was associated with better OS in Keynote-407, but equal OS in IMpower131.

OS heterogeneity was detected between studies in each of the following subgroups: age below 65 years, female gender, ever-smoker, never-smoker, positive PD-L1 expression, absence of EGFR/ALK aberrations, and squamous and non-squamous histology. Publication bias was observed with the following cohorts: ever-smoker, absence of baseline liver metastasis, PD-L1 negative and ECOG PS of 1.

**Discussion**

In this study, we conducted a meta-analysis of published data from 7 phase III randomized controlled trials with the aim of defining the subset of patients with metastatic non-small cell lung cancer (NSCLC) who would benefit in the first-line from the addition of ICI to chemotherapy. To fulfill this purpose, we compared the efficacy of chemotherapy alone or in combination with anti-PD1 or anti-PDL1 monoclonal antibody according to different clinical and molecular features. Through conducting a subgroup analysis of 7 landmark trials, we found that the PFS benefit added by CIT was not influenced by age, gender, histological cell type, history of tobacco use, smoking status, PS, EGFR/ALK mutation status, cell type, PD-L1 level and EGFR/ALK aberrations.

**Table 2.** Subgroup analysis comparing the PFS and OS in patients treated with chemotherapy or CIT.

| Cell type       | Study name            | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value | OS HR (95%CI) | Difference p-Value | Difference p-Value |
|-----------------|-----------------------|--------------|-------------|-------------|---------|---------|---------------|-------------------|-------------------|
| Negative        | Age                   | 0.68(0.58–0.78) | 0.59(0.55–0.80) | 0.62(0.57–0.81) | 0.63(0.50–0.81) | 0.63(0.50–0.81) | 0.63(0.50–0.81) | 0.63(0.50–0.81) | 0.63(0.50–0.81) |
|                 | Gender                | Female       | 0.57(0.48–0.68) | 0.59(0.53–0.70) | 0.62(0.57–0.87) | 0.63(0.50–0.81) | 0.63(0.50–0.81) | 0.63(0.50–0.81) | 0.63(0.50–0.81) |
|                 |                       | Male         | 0.64(0.59–0.70) | 0.70(0.55–0.89) | 0.70(0.65–0.87) | 0.70(0.65–0.87) | 0.70(0.65–0.87) | 0.70(0.65–0.87) | 0.70(0.65–0.87) |
|                 |                       | PS           | 0.58(0.51–0.67) | 0.72(0.62–0.83) | 0.74(0.63–0.89) | 0.74(0.63–0.89) | 0.74(0.63–0.89) | 0.74(0.63–0.89) | 0.74(0.63–0.89) |
|                 |                       | 1            | 0.64(0.59–0.70) | 0.72(0.62–0.83) | 0.74(0.63–0.89) | 0.74(0.63–0.89) | 0.74(0.63–0.89) | 0.74(0.63–0.89) | 0.74(0.63–0.89) |
|                 |                       | Never        | 0.63(0.50–0.81) | 0.70(0.55–0.89) | 0.70(0.65–0.87) | 0.70(0.65–0.87) | 0.70(0.65–0.87) | 0.70(0.65–0.87) | 0.70(0.65–0.87) |
|                 | Cell type             | Squamous     | 0.68(0.54–0.86) | 0.79(0.54–1.18) | 0.74(0.62–0.88) | 0.74(0.62–0.88) | 0.74(0.62–0.88) | 0.74(0.62–0.88) | 0.74(0.62–0.88) |
|                 |                       | Non-squamous | 0.65(0.55–0.77) | 0.74(0.62–0.88) | 0.74(0.62–0.88) | 0.74(0.62–0.88) | 0.74(0.62–0.88) | 0.74(0.62–0.88) | 0.74(0.62–0.88) |
|                 |                       | Mutant       | 0.63(0.43–0.94) | 0.67(0.39–1.17) | 0.70(0.57–0.88) | 0.70(0.57–0.88) | 0.70(0.57–0.88) | 0.70(0.57–0.88) | 0.70(0.57–0.88) |
|                 |                       | WT           | 0.60(0.55–0.66) | 0.71(0.57–0.88) | 0.71(0.57–0.88) | 0.71(0.57–0.88) | 0.71(0.57–0.88) | 0.71(0.57–0.88) | 0.71(0.57–0.88) |
|                 |                       | PD-L1        |               |              | 0.01       | 0.82(0.72–0.94) | 0.82(0.72–0.94) | 0.82(0.72–0.94) | 0.82(0.72–0.94) |

Figure 7. On upper and lower left: Forest plots of hazard ratios comparing PFS between patients treated with chemotherapy or CIT according to PD-L1 expression. *PD-L1 low (TC1/2 or IC1/2); **PD-L1 high (TC3 or IC3). On right: Graph demonstrating the relationship between PD-L1 expression and PFS HR on logarithmic scale. The graph displays the regression line between its corresponding confidence interval lines. A value of “1” on the x-axis corresponds to the group of patients with negative PD-L1 expression: PD-L1 < 1% or TC0&IC0 (TC and IC <1%). A value of “2” on the x-axis corresponds to the group of patients with low PD-L1 expression: PD-L1 1-49% or TC1/2 (TC ≥1% and <50%) or IC1/2 (IC ≥1% and <10%). A value of “3” on the x-axis corresponds to the group of patients with high PD-L1 expression: PD-L1 ≥ 50% or TC3 or IC3 (IC≥10%). TC: tumor cells; IC: tumor-infiltrating immune cells.

0.54–1.18). Indeed, only two trials provided the OS HR in squamous lung cancers: IMpower131 and Keynote-407. When compared with platinum-doublet regimens, CIT was associated with better OS in Keynote-407, but equal OS in IMpower131.
exposure or ECOG PS. The significant predictor of PFS benefit was PD-L1 expression.

Interestingly, the PFS superiority conferred by CIT was demonstrated in conditions considered traditionally to be weakly immunogenic, such as the lack of PD-L1 expression, female gender, and the absence of prior exposure to tobacco. This finding is in contrast with previous meta-analyses, which failed to reveal greater efficacy of single-agent ICI over chemotherapy among female patients and those with negative PD-L1 expression, and more importantly, demonstrated a relatively lower efficacy in never-smoker patients. These observations indicate that chemotherapy synergizes with ICI, even in the setting of less immunogenic tumor. The underlying mechanisms by which chemotherapy enhances antitumoral immunity are multiple and complex. By inducing cell death, cytotoxic chemotherapy promotes the release of cell antigens from dying cells and increases the antigen cross-presentation by dendritic cells. By inhibiting myeloid-derived suppressive cells and regulatory T-cells, chemotherapy modulates tumor microenvironment to overcome immune evasion. Finally, chemotherapy may cause increased tumor mutational burden by inducing DNA damage, leading to increased tumor immunogenicity.

When we narrowed down our analysis to individuals with EGFR/ALK-driven cancer with progressive disease following prior targeted therapy, we found that a favorable result was attained only among patients treated with Bevacizumab-including CIT. This observation provides insight on the potential of antagonizing VEGF in restoring an immunogenic microenvironment in oncogene-driven lung cancer.Reportedly, VEGF blockade may result in a less-immunosuppressive microenvironment. Moreover, VEGF is believed to mediate resistance to EGFR inhibitors. These explanations could have accounted for the positive effect observed when VEGF inhibitors are added to CIT in EGFR-mutant lung cancer patients who progressed on EGFR inhibitors. This intriguing observation carries several caveats, as it stems from a post-hoc, unplanned analysis, and only 2 studies allowed the enrollment of patients with EGFR/ALK aberrations. As such, further large prospective trials are needed to elucidate the possible impact of VEGF neutralization on potentiating CIT efficacy among patients harboring actionable molecular abnormalities who have disease progression on targeted therapy.

In parallel, mounting evidence suggests that the presence of liver metastasis is a hallmark of modest therapeutic efficacy of single-agent ICI in lung cancer. This observation is linked to diminished tumor infiltration by CD8-positive T-cells in hepatic metastases. In our analysis, we observed that CIT yielded a greater survival independently of the presence or absence of liver metastasis. However, among patients with baseline hepatic metastasis treated with Atezolizumab-based CIT, the survival advantage was only noticeable when Bevacizumab was included in their treatment regimen. Understanding whether this phenomenon is VEGF-mediated or owing to population’s difference merits to be investigated more in depth.

The predictive role of PD-L1 expression in the era of CIT is not well defined. In a previous meta-analysis, the absence of PD-L1 expression was associated with no ICI superiority over chemotherapy when used as monotherapy in NSCLC. In this meta-analysis, we showed that PD-L1 expression influenced the likelihood of disease progression or death with CIT. Although patients with no PD-L1 expression still benefit from CIT, the PD-L1 level correlated directly with the magnitude of the benefit, which was strikingly more prominent for "high PD-L1-expressing" patients. However, using PD-L1 staining as a biomarker for the efficacy to CIT faces several limitations, including the current unavailability of a standardized assay to measure it. Indeed, the methodology of immunohistochemistry used to evaluate PD-L1 expression differed between the studies included here. In IMpower130, IMpower131, IMpower132, and IMpower150, PD-L1 expression on tumor-infiltrating immune and tumoral cells were both taken into account. In Checkmate-227, Keynote-407, and Keynote-189, PD-L1 expression was measured on stained tumor cells only. In addition, the use of different antibodies against PD-L1 could also contribute to testing variability between the studies.

CIT consistently reduced the risk of death across most studied subgroups with the exception of those with EGFR/ALK-driven tumors, or squamous histology. The absence of heterogeneity suggests that the lack of statistical significance for OS benefit in EGFR/ALK aberration may be attributed to the small number of enrollees in that particular subgroup. Although an OS benefit was observed in both sexes, females experienced a numerically greater survival advantage. The underlying biological explanation of this difference remains poorly understood and merits further exploration.

Our results are concordant with a recent meta-analysis by Zhou et al. However, several additional aspects were offered by our meta-analysis. It included two additional studies (IMpower130 and IMpower132 trials) and provided updated data of Keynote-189 and IMpower 150 trials. As importantly, it emphasized on the interaction between liver metastasis and clinical outcome, and particularly suggested that VEGF blockade maybe needed to achieve an improved survival among patients with EGFR/ALK molecular aberrations or liver metastasis undergoing therapy with Atezolizumab combined with chemotherapy.

One strength of our study is that the source data were restricted to phase III randomized controlled multicenter clinical trials. All seven studies are comparable in design, quality, and objectives, leading to powered pooled data. However, our study faces a few imperfections: the outcomes according to the investigated subgroups were not always provided by all 7 studies. For instance, the OS data was not available in some of the included studies and immature in others. Full reporting and follow-up of these trials are awaited to update this meta-analysis. Data heterogeneity was observed, and as such, the random effects model was adopted to address this issue. The randomization was not always conducted according to the studied characteristics of interest. It is possible that confounding factors that were not evenly distributed among the studied subgroups have skewed the difference in outcome between them. Because we do not have access to the raw data on each individual enrolled on these trials, our results are suggestive and question generating rather than definitive. As such, future
investigations are needed to address the value of other potential biomarkers for CIT such as tumor mutational burden, intra-tumoral CD8+ T-cell density, gene expression inflammatory signature, etc.

In conclusion, this exploratory analysis reveals that CIT provides a survival advantage over chemotherapy alone in a large proportion of patients with untreated metastatic NSCLC. The improved outcome is remarkable broadly across various patient subgroups, including those in whom single-agent ICI is known to have a modest therapeutic efficacy, such as females, never smokers, individuals with liver metastasis, EGFR/ALK aberration, or those with negative PD-L1 staining. In the instance of EGFR/ALK-driven cancer, the derived benefit is noticeable only when a VEGF inhibitor is part of the CIT combination. Whereas individuals with negative PD-L1 expression experience a survival advantage from chemo-immunotherapy, the magnitude of the added benefit correlate with PD-L1 expression levels. Our findings illustrate the ability of cytotoxic chemotherapy with or without VEGF blockade to potentiate ICI activity, even in tumors described as "poorly immunogenic."

Authors contribution

Study concept and design: H.E.O., A.L.S., Revision of the manuscript: all authors

Disclosure of Potential Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A. 2018. Cancer statistics. CA Cancer J Clin. 68(1):7–30. doi:10.3322/caac.201442.

2. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, et al. 2015. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 373(17):1627–1639. doi:10.1056/NEJMoa1507643.

3. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, et al. 2015. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 373(2):123–135. doi:10.1056/NEJMoa1504627.

4. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han J-Y, Molina J, Kim J-H, Arvis CD, Ahn M-J, et al. 2016. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 387(10027):1540–1550. doi:10.1016/S0140-6736(16)31854-1.

5. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols MC, et al. 2017. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 389(10066):255–265. doi:10.1016/S0140-6736(16)32517-X.

6. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domíne M, Clingan P, Hochmair MJ, Powell SF, et al. 2018. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 378(22):2078–2092. doi:10.1056/NEJMoa1801005.

7. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Rodriguez-Abreu D, Moro-Silibolt D, Thomas CA, Barlesi F, et al. 2018. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 378(24):2288–2301. doi:10.1056/NEJMoa1716948.

8. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazieres J, Hermes B, Çaş Şenler F, Csósz T, Fülöp A, et al. 2018. Pembrolizumab plus chemotherapy in squamous non-small-cell lung cancer. N Engl J Med. 379(21):2040–2051. doi:10.1056/NEJMoa1810865.

9. El-Osta H, Jafari S. 2019. Predictors for clinical benefit of immune checkpoint inhibitors in advanced non-small-cell lung cancer: a meta-analysis. Immunotherapy. 11(3):189–199. doi:10.2217/imt-2018-0086.

10. Lisberg A, Cummings A, Goldman JW, Bornazyan K, Reese N, Wang T, Coluzzi P, Ledezma B, Mendenhall M, Hunt J, et al. 2018. A phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor naive patients with advanced NSCLC. J Thorac Oncol. 13(8):1138–1145. doi:10.1016/j.jtho.2018.03.035.

11. Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, De Angelis F, Domíne M, Clingan P, Hochmair MJ, Powell S, et al. 2019. Outcomes among patients with metastatic nonsquamous NSCLC with liver metastases or brain metastases treated with pembrolizumab plus pemetrexed-platinum: results from the Keynote-189 study. Cancer Res. 79(13). (Suppl; abstract CT043). doi:10.1200/JCO.2018.36.18_suppl.LBA9000.

12. Cappuzzo F, McLeod M, Hussein M, Morabito A, Rittmeyer A, Conter HI, Kopp H, Daniel D, McCune S, Mehail T, et al. 2018. IMpower130: efficacy and safety from a randomised phase III study of carboplatin and nab-paclitaxel with or without atezolizumab in 1L advanced non-squamous NSCLC. Ann Oncol. 29(8). (Suppl; abstract LBA53). doi:10.1093/annonc/mdy807.

13. West H, McLeod M, Hussein M, Morabito A, Rittmeyer A, Conter HI, Kopp H-G, Daniel D, McCune S, Mehail T, et al. 2019. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 20(7):924–937. doi:10.1016/S1470-2045(19)30167-6.

14. Jotte R, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Abreu DR, Hussein M, Soo R, Conter HI, Kozuki T, Silva C, et al. 2018. IMpower131: primary PFS and safety analysis of a randomised phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. J Clin Oncol. 36(18). (suppl; abstract9000). doi:10.1200/JCO.2018.36.18_suppl.LBA9000.

15. Papadimitrakopoulou V, Cobo M, Bordoni R, Dubray-Longeras P, Szalai Z, Ursell G, Novello S, Orlandi F, Ball S, Goldschmidt J, et al. 2018. IMpower132: PFS and safety results with 1L Atezolizumab + Carboplatin/cisplatin + Pemetrexed in stage IV non-squamous NSCLC. J Thorac Oncol. 13(10):S332–S333. (suppl; abstract OA05.07). doi:10.1016/j.jtho.2018.08.262.

16. Socinski M, Jotte R, Cappuzzo F, Mok T, West H, Nishio M, Papadimitrakopoulou V, Orlandi F, Stroyakovskiy D, Thomas C, et al. 2019. IMpower150: analysis of efficacy in patients (pts) with liver metastases (mets). J Clin Oncol. (suppl; abstract9012). doi:10.1200/JCO.2019.37.15_suppl.9012.

17. Reck M, Mok TSK, Nishio M, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Rodríguez-Abreu D, Moro-Silibolt D, et al. 2019. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Lancet Respir Med. 7(5):387–401. doi:10.1016/S2213-2600(19)30084-0.

18. Borghaei H, Hellmann M, Paz-Ares L, Ramalingam S, Reck M, O’Byrne K, Bhagavatheeswaran P, Nathan F, Brahmer J. 2018. Pembrolizumab (Nivo) + platinum-doublet chemotherapy (ChemO) vs ChemO as first-line (1L) treatment for advanced non-small-cell lung cancer (NSCLC) with <1% tumor PD-L1 expression: results from CheckMate 227. J Clin Oncol. 36(15). (suppl; abstract 9001). doi:10.1200/JCO.2018.36.15_suppl.9001.
19. Conforti F, Pala L, Bagnardi V, De Pas T, Martinetti M, Viale G, Gelber RD, Goldhirsch A. 2018. Cancer immunotherapy efficacy and patients’ sex: a systematic review and meta-analysis. Lancet Oncol. 19(6):737–746. doi:10.1016/S1470-2045(18)30261-4.
20. Ma Y, Adjemian S, Mattarollo SR, Yamazaki T, Aymercic L, Yang H, Portela Catani JP, Hannami D, Duret H, Steegh K, et al. 2013. Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-presenting cells. Immunity. 38(4):729–741. doi:10.1016/j.immuni.2013.03.003.
21. Wang Z, Till B, Gao Q. 2017. Chemotherapeutic agent-mediated elimination of myeloid-derived suppressor cells. Oncoimmunology. 6(7):e1331807. doi:10.1080/2162402X.2017.1331807.
22. Chaudhary B, Elkord E. 2016. Regulatory T cells in the tumor microenvironment and cancer progression: role and therapeutic targeting. Vaccines. 4(3):E28. doi: 10.3390/vaccines4030028
23. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, et al. 2015. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 348(6230):124–128. doi:10.1126/science.aaa1348.
24. Voron T, Colussi O, Marchetia E, Pernot S, Nizard M, Pointet A-L, Latreche S, Bergaya S, Benhamouda N, Tanchot C, et al. 2015. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. J Exp Med. 212(2):139–148. doi:10.1084/jem.20140559.
25. Wallin JJ, Bendell JC, Funke R, Szol M, Korski K, Jones S, Hernandez G, Mier J, He X, Hodi FS, et al. 2016. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. Nat Commun. 7:12624. doi:10.1038/ncomms12624.
26. Masuda C, Yanagisawa M, Yorozu K, Kurasawa M, Furugaki K, Ishikura N, Iwai T, Sugimoto M, Yamamoto K. 2017. Bevacizumab counteracts VEGF-dependent resistance to erlotinib in an EGFR-mutated NSCLC xenograft model. Int J Oncol. 51(2):425–434. doi:10.3892/ijo.2017.4036.
27. Tumeh PC, Hellmann MD, Hamid O, Tsai KK, Loo KL, Gubens MA, Rosenblum M, Harview CL, Taube JM, Handley N, et al. 2017. Liver metastasis and treatment outcome with anti-PD-1 monoclonal antibody in patients with melanoma and NSCLC. Cancer Immunol Res. 5(5):417–424. doi:10.1158/2326-6066.CIR-16-0325.
28. Patel SP, Kurzrock R. 2015. PD-L1 expression as a predictive biomarker in cancer immunotherapy. Mol Cancer Ther. 14(4):847–856. doi:10.1158/1535-7163.MCT-14-0983.
29. Zhou Y, Chen C, Zhang X, Fu S, Xue C, Ma Y, Fang W, Yang Y, Hou X, Huang Y, et al. 2018. Immune-checkpoint inhibitor plus chemotherapy versus conventional chemotherapy for first-line treatment in advanced non-small cell lung carcinoma: a systematic review and meta-analysis. J Immunoother Cancer. 6(1):155. doi:10.1186/s40425-018-0477-9.