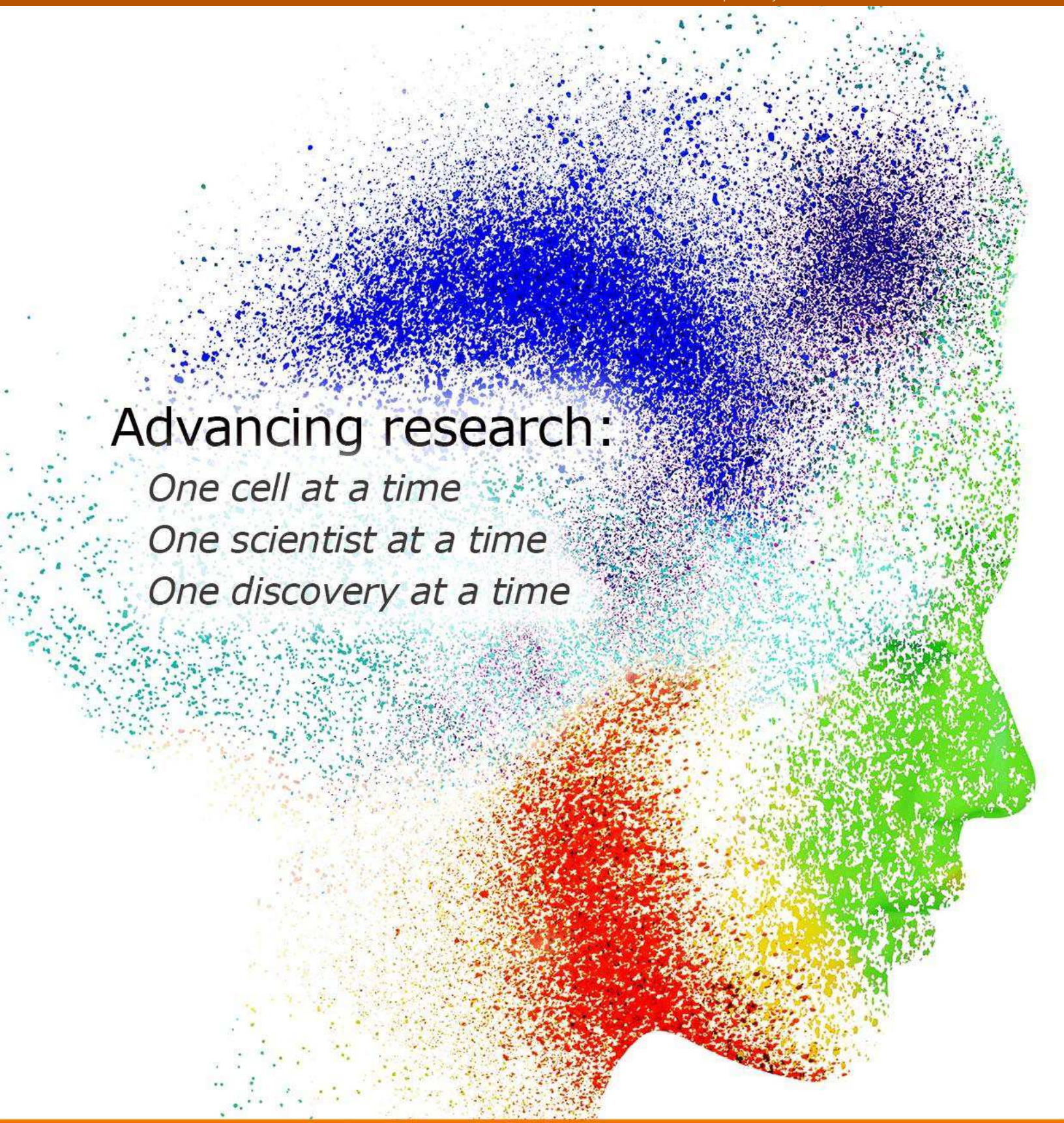

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# Looking for the best immune-checkpoint inhibitor in pre-treated NSCLC patients: An indirect comparison between nivolumab, pembrolizumab and atezolizumab

Francesco Passiglia*, Antonio Galvano*, Sergio Rizzo*, Lorena Incorvaia, Angela Listì, Viviana Bazan and Antonio Russo

Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, Palermo University Hospital, Palermo, Italy

**Immune-checkpoint inhibitors represent the new standard of care in patients with advanced NSCLC who progressed after first-line treatment. This work aim to assess any difference in both efficacy and safety profiles among Nivolumab, Pembrolizumab and Atezolizumab in pre-treated NSCLC patients. Randomized clinical trials comparing immune-checkpoint inhibitor versus docetaxel in pre-treated patients with advanced NSCLC were included and direct comparison meta-analysis of selected trials have been performed. Subsequently the summary estimates of Nivolumab, Pembrolizumab and Atezolizumab emerging from the direct meta-analysis were selected to provide the pooled estimates of hazard ratio (HR) and relative risk (RR) for the indirect comparisons among these agents. A total of 5 studies met the selection criteria and were included in the meta-analysis. Indirect comparisons for efficacy outcomes showed the RR for ORR nivolumab versus atezolizumab 1.66 (95% CI 1.07−2.58), pembrolizumab versus atezolizumab 1.94 (95% CI 1.30−2.90). No significant differences in both PFS and OS have been observed. Indirect comparisons for safety showed the RR for G3-5 AEs nivolumab versus pembrolizumab 0.41 (95% CI 0.29−0.60), nivolumab versus atezolizumab 0.50 (95% CI 0.35−0.72). No significant differences in both pneumonitis and discontinuation rate have been observed. The results of this work revealed that nivolumab and pembrolizumab are associated with a significant increase of ORR as compared to atezolizumab and nivolumab is associated with a significant lower incidence of G3-5 AEs as compared to the other drugs. These evidences could support the oncologists to select the best drug for each patient.**

The advent of immunotherapy has represented one of the most important innovations in the treatment of lung cancer over the last decades. Differently from other treatment strategies, modulating the immune system offers the potential for long-term survival outcomes with a very tolerable safety profile. Both anti-programmed death-1 (PD1)/programmed death ligand-1 (PDL1) monoclonal antibodies (MoAbs) demonstrated promising anti-tumor activity in early Phase I trials, leading to about 20% of objective response rates (ORR) in pre-treated and unselected NSCLC patients.[1–3] These encouraging data have subsequently led to the design of four Phase III randomized trials comparing single agent immune-checkpoint inhibitor (ICI) versus standard chemotherapy in second-line setting, whose final results have recently revolutioned the treatment paradigm of lung cancer. Particularly the CheckMate 017 and 057 studies demonstrated a significant overall survival (OS) benefit in favor of the anti-PD1 MoAb nivolumab over docetaxel in pre-treated NSCLC patients with squamous and non-squamous histology, respectively.[4,5] Similarly in the KEYNOTE-010 study the anti-PD1 MoAb pembrolizumab significantly improved OS compared to docetaxel as second-line treatment in patients with PDL1-positive NSCLC.[6] Finally the anti-PDL1 Atezolizumab has shown a significant superiority over docetaxel in the Phase III OAK trial including NSCLC patients who failed prior platinum-based chemotherapy,[7] confirming the efficacy data previously emerged from the randomized Phase II POPLAR study.[8] As regards the toxicity, all the ICIs have shown a very tolerable safety profile, with a significant lower incidence of any grade and severe toxicities as compared with the standard chemotherapy. However the inhibition of the PD1-axis has been associated with new emerging autoimmune-toxicities, including also the development of severe pneumonitis which have led to treatment-related deaths in clinical trials.[4–7] Overall, the results of all these studies convincingly and consistently demonstrated that PD1/PDL1 inhibitors are

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*F.P., A.G. and S.R. contributed equally to this work
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**Correspondence to:** Prof. Antonio Russo, MD, PhD, Medical Oncology Director, Department of Oncology - A.O.U.P. "P. Giaccone" University Hospital, 2013 ESMO Designated Centres of Integrated Oncology and Palliative Care, Via del Vespro 129, 90127 Palermo, Italy, Tel.: ± 39-091-6552759, Fax: ±39-091-6554529, E-mail: antonio.russo@usa.net

**What's new?**

**In advanced non-small cell lung cancer (NSCLC), failure of first-line therapy is followed by the use of immune checkpoint inhibitors (ICIs), which have superior survival benefits compared to standard chemotherapy. Three ICIs are available for pre-treated NSCLC patients: atezolizumab, nivolumab, and pembrolizumab. The present meta-analysis examined differences in efficacy and safety profiles between these agents. Indirect comparisons of data on clinical outcomes from five studies included in the meta-analysis reveal significant differences in efficacy and toxicity between atezolizumab and nivolumab and between atezolizumab and pembrolizumab. The findings warrant further investigation given their potential impact on drug selection for NSCLC patients.**

more effective and better tolerated than the second-line single agent chemotherapy, thus representing the new standard of care for NSCLC patients who experienced progression after platinum combinations.[9] To date we have two anti-PD1 MoAbs, nivolumab and pembrolizumab, and one anti-PDL1 MoAb, atezolizumab, approved as second and/or further lines treatment options in patients with advanced NSCLC. Even if still limited by a lack of standardization of testing methods, the immune-histochemical (IHC) detection of tumor PDL1 expression remains the only predictive biomarker approved for clinical use. Indeed the majority of these studies revealed that the benefit of anti-PD1/PDL1 inhibitors increased accordingly with the tumor PDL1-expression.[10] However only pembrolizumab approval was limited to the PDL1-positive NSCLC, whereas both nivolumab and atezolizumab may be currently used regardless of tumor PDL1 status.[9] Since clinicians have now three different immune-checkpoint inhibitors with a very similar indication, how might they chose the best agent for the second-line treatment of NSCLC patients? In absence of direct comparisons among these ICIs, it remains crucial identify any differences in both efficacy and toxicity profiles which may help clinicians to select the best drug for each patient. Therefore, we performed a systematic review and meta-analysis of all Phase II/III randomized clinical trials comparing PD1/PDL1 inhibitors versus docetaxel in pre-treated NSCLC patients.

## Material and Methods

### Search strategy

We searched for randomized clinical trials (RCTs) including patients with histologically proven diagnosis of advanced NSCLC which compared the immune-checkpoint inhibitors nivolumab, pembrolizumab and atezolizumab with the standard second-line chemotherapy regimen Docetaxel. We searched for RCTs using Medline (PubMed), Embase-databases and Cochrane-Library up to February 2017, with no language restrictions. We used the following search terms: "immunotherapy," "PD1," "PDL1," "nivolumab," "pembrolizumab," "atezolizumab," "lung cancer," "non-small cell lung cancer," "NSCLC". Relevant abstracts from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and World Conference on Lung Cancer (WCLC) were included. We also explored the ClinicalTrials.gov website (www.clinicaltrials.gov) to search for unpublished data and ongoing studies.

### Selection criteria

According to the aforementioned search clinical trials were taken into account if they met the following inclusion criteria: (*i*) patients with histologically proven diagnosis of NSCLC; (*ii*) patients who failed prior platinum chemotherapy regimens (*iii*) studies comparing single agent anti-PD1/PDL1 MoAb versus docetaxel (*iv*) studies reporting efficacy outcomes, including ORR, PFS, OS; (*v*) studies reporting safety outcomes, including Grade 3–5 adverse events (G3–G5 AEs), pneumonitis and discontinuation rate.

We excluded ongoing studies and observational trials in order to minimize the risk of bias. In case of articles with multiple follow up over time, we selected those reporting the most updated data.

### Data extraction

Data extraction and assessment was made independently by two different authors (A.G. and F.P.) and disagreement were solved by discussion with another author (A.R.). Quality judgement of selected trials was made following the Cochrane Handbook for Systematic Reviews of Interventions reported criteria,[11] including: sequence generation, selective outcome reporting, blinding of participants, personnel and outcome assessors; incomplete outcome data and allocation concealment. We defined as "+" a feature at low risk of bias, as "–" a feature at high risk of bias and as "?" if data were insufficient for a more precise judgement. Two independent reviewers (A.G, F.P.) evaluated the selective outcome reporting bias and disagreements were solved by consensus.

### Statistical analysis

The analyzed outcomes for both direct and indirect comparisons were OS, PFS, ORR, G3–G5 AEs, pneumonitis and discontinuation rate. In addition ORR, PFS and OS were stratified according to the tumor PD-L1 expression status. Since different cut-offs were used to define PD-L1 positivity in clinical trials, we selected PD-L1 $> 1\%$ as reference cut-off to identify PD-L1+ patients in our analysis because it was recently approved for clinical use in pre-treated NSCLC patients. As mentioned before, the KEYNOTE-010 trial enrolled only PD–L1+ patients, thus it was not included in the pooled analysis of PD–L1– patients. We used hazard ratios (HRs) as measure to assess the association for PFS and OS (even when stratified into PD-L1 positive or negative

cohorts, with a 95% confidence interval (CI)). For the other outcomes (ORR, AE, pneumonitis and discontinuation rate) we extracted number of events over total patients included in each arm using Relative Risks (RRs) as measures of association. In the first phase, we performed three direct comparison meta-analysis including all selected trials which evaluated immune-checkpoint inhibitors versus docetaxel (nivolumab *vs*. docetaxel, pembrolizumab *vs*. docetaxel, atezolizumab *vs*. docetaxel). To do this, we calculated the logarithm of HRs (logHRs) and its standard error for each RCT included in this analysis. As result, we used the standard meta-analytic technique to obtain the pooled estimate for all of these comparisons.[12] Since nivolumab, pembrolizumab and atezolizumab used the same control arm (docetaxel), subsequently we used the same meta-analytical technique to perform an indirect comparison between such three immunotherapeutic agents. thus we selected the summary estimates of nivolumab, pembrolizumab and atezolizumab emerging from the prior meta-analysis to provide the pooled estimates of HR and OR for the indirect comparisons of nivolumab versus pembrolizumab, nivolumab versus atezolizumab and pembrolizumab versus atezolizumab. These computations were made using the method described by Glenny and Bucher,[13,14] because of its ability to maintain the randomization advantage of each trial providing an estimate of the comparisons between treatments. Considering what above mentioned, if we assumed Nivo/es as the estimate of the direct comparison between nivolumab versus docetaxel and pembro/es as the estimate of the direct comparison between pembrolizumab and docetaxel, we performed the indirect comparison of nivolumab versus pembrolizumab as follow: Nivo/Pembro_indirect (logHR)= Nivo/es(logHR) – Pembro/es(logHR). For the variance, the indirect comparison was computed as follow: Var (log Nivo/Pembro_indirect) = (Var log Nivo/es) + (Var log Pembro/es).[13–15] Heterogeneity between studies was explored using $\chi^2$ and I-square tests. We used the random effect-based model by Der Simonian and Laird to perform meta-analysis if I-square value was higher than 75% (it was considered as at high risk of heterogeneity). If not, we used the fixed effect-based Mantel-Haenszel model.[16,17] As regards the risk of bias across studies, we performed a publication bias analysis using Egger's test providing the respective Funnel Plot. The meta-analysis was designed according to the PRISMA—guidelines for reporting of systematic reviews.[18] We used Cochrane RevMan ver. 5.3 statistical software to perform the meta-analysis and Comprehensive Meta – Analysis ver. 2.0 to assess the risk of publication bias (Egger's Test). All the *p*-values were considered as statistically significant if $p < 0.05$.

## Results

The search for literature identified a total of 648 records, of which 69 were excluded because duplicates; 489 records were excluded because reviews, letters or commentaries; 72 records because were non-randomized clinical trials or did not compare single agent immunotherapy versus chemotherapy in pre-treated NSCLC patients. A total of ten trials were assessed for eligibility and five were excluded because they were abstracts of subsequent published papers. Finally, a total of five studies met all the inclusion/exclusion criteria and were included in the meta-analysis (Fig. 1). The clinical outcomes of the included trials are reported in the Tables 1 and 2.

### Direct comparisons

*Nivolumab versus docetaxel.* Two RCTs (Check-Mate017 and Check-Mate057) compared nivolumab versus docetaxel in a total of 854 patients with advanced NSCLC who progressed after first-line platinum-chemotherapy. Pooled results showed statistically significant differences in favor of nivolumab in terms of both OS (HR 0.68, 95% CI 0.57–0.80; Supporting Information Fig. S1) and ORR (RR 1.68, 95% CI 1.21–2.34; Supporting Information Fig. S2). Conversely PFS was not significantly different between the two treatments arms (HR 0.77, 95% CI 0.52–1.13; Supporting Information Fig. S3). As regard toxicities, nivolumab was associated with a lower incidence of both G3/G5 AEs (RR 0.17, 95% CI 0.13–0.24) and treatment discontinuation (RR 0.48, 95% CI 0.25–0.94) compared to Docetaxel. Conversely a significant higher risk of pneumonitis was observed in the nivolumab arm as compared with chemotherapy arm (RR 9.22, 95% CI 1.73–49.10; Supporting Information Fig. S4). Splitting ORR, PFS and OS according to the tumor PD-L1 expression, we also noted a significant benefit in favor of nivolumab for all the above mentioned endpoints in the PD–L1+ population, whereas no benefit has been observed in the PD-L1- patients.

*Pembrolizumab versus docetaxel.* The Phase III KEYNOTE-010 trial randomized a total of 1,034 patients who progressed after a platinum-based doublet chemotherapy to three treatment arms including pembrolizumab at two different dosage (2 and 10 mg/kg) and docetaxel. Of note, this study enrolled a selected PD-L1+ population. Pooled results showed that pembrolizumab was significantly superior to docetaxel in terms of OS (HR 0.66, 95% CI 0.57–0.77; Supporting Information Fig S1), PFS (HR 0.83, 95% CI 0.74–0.94; Supporting Information Fig. S3) and ORR (RR 1.96, 95% CI 1.48–2.59; Supporting Information Fig. S2). As for nivolumab, pembrolizumab cohort reported a significant benefit regarding the risk of G3/G5 AEs (RR 0.41, 95% CI 0.33–0.50) while the incidence of pneumonitis was significantly higher with pembrolizumab as compared to docetaxel arm (RR 2.34, 95% CI 1.21–4.52; Supporting Information Fig. S4).

*Atezolizumab versus docetaxel.* Atezolizumab is an anti PD-L1 monoclonal antibody that was compared to docetaxel in a total of 1137 pre-treated NSCLC patients included in the Phase II POPLAR and Phase III OAK studies. As pooled results, we obtained no significant improvements in terms of ORR (RR 1.01, 95% CI 0.76–1.35; Supporting Information Fig. S2) and PFS (HR 0.95, 95% CI 0.83–1.08; Supporting Information Fig. S3), while only OS resulted significantly longer with atezolizumab in the overall population (HR 0.73, 95% CI 0.63–0.85; Supporting Information Fig. S1). Atezolizumab maintained a significant OS benefit regardless

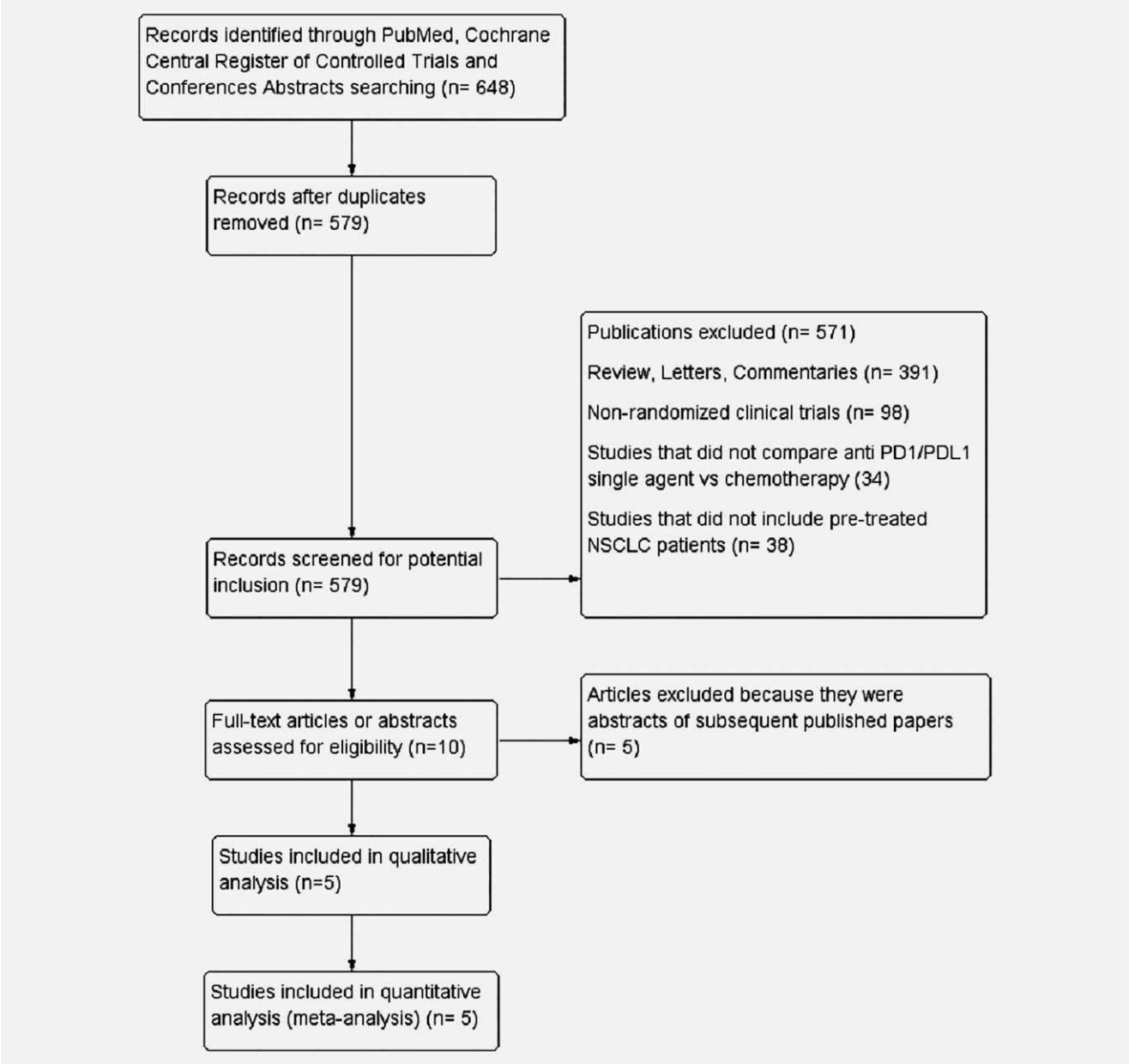


**Figure 1.** Flow-chart of trials selection process.

of tumor PD-L1 expression status. Similarly to the other two monoclonal antibodies atezolizumab showed also a more tolerable toxicity profile, with a significant lower incidence of G3/G5 AEs (RR 0.34, 95% CI 0.28–0.41) and discontinuation rate (RR 0.43, 95% CI 0.30–0.62), and an increased risk for pneumonitis (RR 8.77, 95% CI 1.12–68.92; Supporting Information Fig. S4).

### Indirect comparisons

We used the meta-analytic technique to perform an indirect comparison between nivolumab, pembrolizumab and atezolizumab pooled results on ORR, PFS, OS (for both PD–L1+ and PD–L1– cohorts if previously reported), G3/G5 AEs, pneumonitis and discontinuation rate.

*Nivolumab versus pembrolizumab.* The results of our analysis did not show any significant differences in the efficacy endpoints (ORR, PFS, OS) between these two anti-PD1 inhibitors, even if considering only the PD–L1+ population. Nivolumab was associated with a significant reduction of G3/G5 AEs (RR 0.41, 95% CI 0.29–0.60) together with a not significant increment of the risk of pneumonitis (RR 3.94, 95% CI 0.65–23.79) or discontinuation rate (Fig. 2).

*Nivolumab versus atezolizumab.* The results of our analysis revealed a significant higher ORR in favor of nivolumab (RR 1.66, 95% CI 1.07–2.58) both in the overall and in the PD–L1+ population. No significant advantages in favor of nivolumab

**Table 1.** Clinical outcomes of the trials included in the pooled-analysis

| Study (reference) | Drug | ORR n.[1] | PFS HR (95% CI) | OS HR (95% CI) | AEs G3–5 n.[1] | Pneumonitis n.[1] | Discontinuation rate n.[1] |
|---|---|---|---|---|---|---|---|
| CheckMate017[4] | Nivolumab | 26/131 | 0.62 (0.47–0.81) | 0.59 (0.44–0.79) | 9/131 | 6/131 | 6/135 |
| | Docetaxel | 12/129 | | | 71/129 | 0/129 | 10/137 |
| CheckMate057[5] | Nivolumab | 56/292 | 0.92 (0.77–1.1) | 0.73 (0.59–0.89) | 30/287 | 8/287 | 6/292 |
| | Docetaxel | 36/290 | | | 144/268 | 1/268 | 15/290 |
| KEYNOTE010[6] | Pembrolizumab (2 mg/kg) | 62/344 | 0.88 (0.74–1.05) | 0.71 (0.58–0.88) | 43/339 | 16/339 | 4/345 |
| | | | | | 109/309 | 6/309 | 10/343 |
| | Docetaxel | 32/343 | | | | | |
| KEYNOTE010[6] | Pembrolizumab | 64/346 | 0.79 (0.66–0.94) | 0.61 (0.49–0.75) | 55/343 | N.A | 6/346 |
| | | | | | 109/309 | | 10/343 |
| | (10 mg/kg) Docetaxel | 32/343 | | | | | |
| POPLAR[8] | Atezolizumab | 21/144 | 0.94 (0.72–1.23) | 0.73 (0.53–0.99) | 16/144 | 4/144 | 11/144 |
| | Docetaxel | 21/143 | | | 52/143 | 0/144 | 30/143 |
| OAK[7] | Atezolizumab | 58/425 | 0.95 (0.82–1.10) | 0.73 (0.62–0.87) | 90/609 | 4/609 | 8/425 |
| | Docetaxel | 57/425 | | | 247/578 | 0/578 | 19/425 |

[1]The number of patients reported corresponds to the number of patients evaluable.
Abbreviations: ORR, overall response rate; PFS, progression free survival; OS, overall survival; PD-L1, programmed death-ligand 1; n., number; HR, hazard ratio; CI, confidence interval; N.A, not available.

**Table 2.** Outcomes measures stratified according to the tumor PD-L1 expression status or delete the reference as appropriate, maintaining the numerical order of the references

| Study (reference) | Drug | ORR (PD–L1+) n.[1] | ORR (PD–L1–) n.[1] | PFS (PD–L1+) HR (95% CI) | PFS (PD–L1–) HR (95% CI) | OS (PD–L1+) HR (95% CI) | OS (PD–L1–) HR (95% CI) |
|---|---|---|---|---|---|---|---|
| CheckMate017[4] | Nivolumab | 11/63 | 9/54 | 0.67 (0.44–1.01) | 0.66 (0.43–1.00) | 0.69 (0.45–1.05) | 0.58 (0.37–0.92) |
| | Docetaxel | 6/56 | 5/52 | | | | |
| CheckMate057[5] | Nivolumab | 38/123 | 10/108 | 0.70 (0.53–0.94) | 1.19 (0.88–1.61) | 0.59 (0.43–0.82) | 0.90 (0.66–1.24) |
| | Docetaxel | 15/123 | 15/101 | | | | |
| KEYNOTE010[6] | Pembrolizumab (2 mg/kg) | 62/344 | N.A | 0.88 (0.74–1.05) | N.A | 0.71 (0.58–0.88) | N.A |
| | Docetaxel | 32/343 | | | | | |
| KEYNOTE010[6] | Pembrolizumab (10 mg/kg) | 64/346 | N.A | 0.79 (0.66–0.94) | N.A | 0.61 (0.49–0.75) | N.A |
| | Docetaxel | 32/343 | | | | | |
| POPLAR[8] | Atezolizumab | 26/144 | 11/144 | 0.85 (0.63–1.16) | 1.12 (0.72–1.77) | 0.59 (0.40–0.85) | 1.04 (0.62–1.75) |
| | Docetaxel | 24/143 | 14/143 | | | | |
| OAK[7] | Atezolizumab | 43/241 | 14/180 | 0.91 (0.74–1.12) | 1.00 (0.80–1.25) | 0.74 (0.58–0.93) | 0.75 (0.59–0.96) |
| | Docetaxel | 36/222 | 21/199 | | | | |

[1]The number of patients reported corresponds to the number of patients evaluable.
Abbreviations: ORR, overall response rate; PFS, progression free survival; OS, overall survival; PD-L1, programmed death-ligand 1; n., number; HR, hazard ratio; CI, confidence interval; N.A, not available.

were observed for both PFS and OS, except for a not significant trend toward a PFS improvement in the PD-L1+ group. Nivolumab was associated with a significant lower risk for G3/G5 AEs (RR 0.50, 95% CI 0.35–0.72) and no substantial higher risk of pneumonitis or discontinuation rate (Fig. 2).

*Pembrolizumab versus atezolizumab.* The results of our analysis revealed a significant higher ORR in favor of pembrolizumab (RR 1.94, 95% CI 1.30–2.90) in the PD–L1+ population. As regard AEs, pneumonitis and discontinuation rate, no significant differences have been observed between

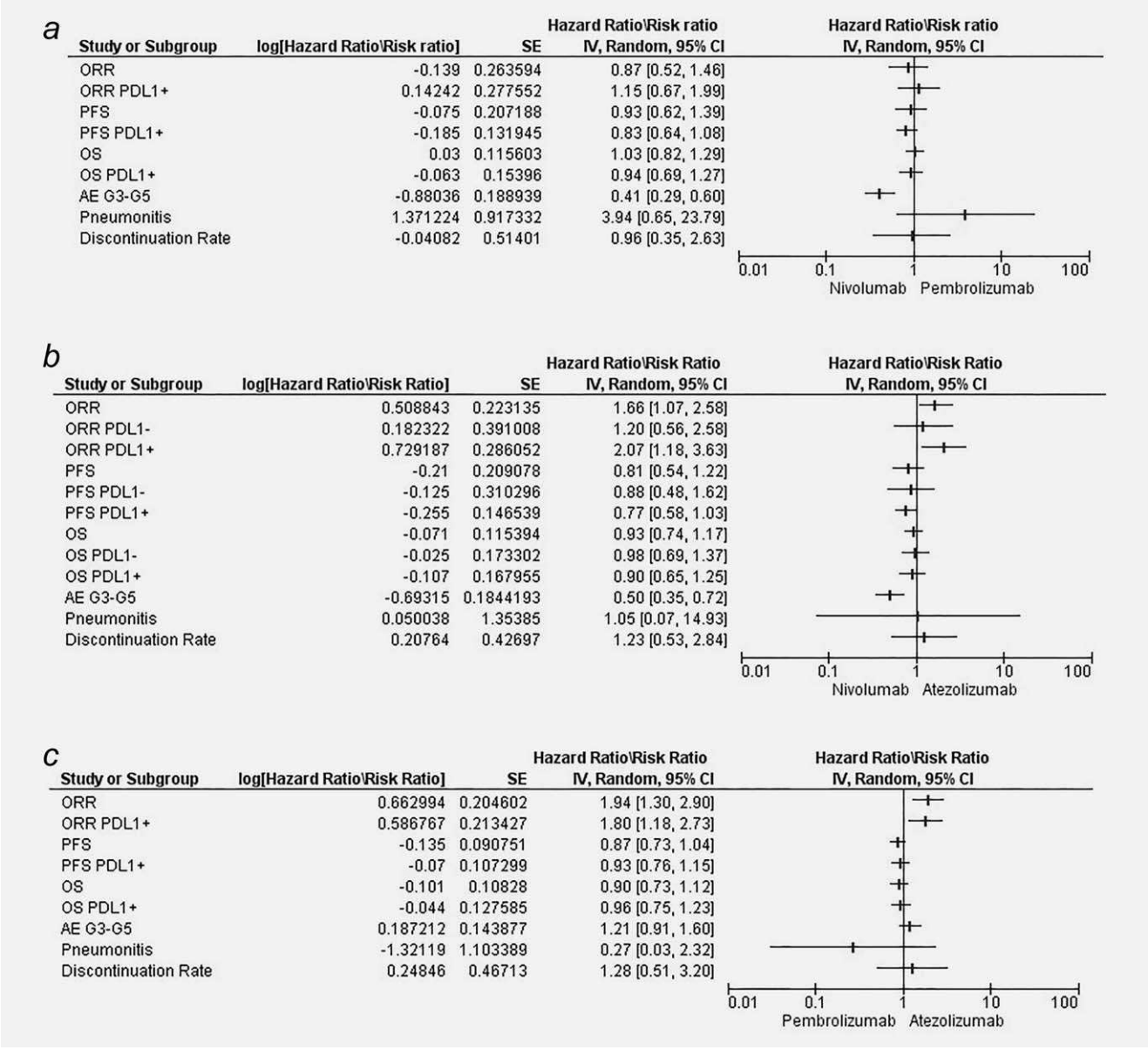


**Figure 2.** Forest plots for all indirect comparisons among immunecheck-point inhibitors in pre-treated NSCLC patients: nivolumab vs. pembrolizumab (*a*); nivolumab vs. atezolizumab (*b*); pembrolizumab vs. atezolizumab (*c*).

these two compounds, except for a not significant trend toward a higher incidence of G3/G5 AEs (RR 1.21, 95% CI 0.91–1.60) in the atezolizumab arm (Fig. 2).

### Risk of bias assessment (QUADAS-2 tool)

Test for publication bias assessment was not reported due to the small number of studies included in each comparison (Egger's test is reliable with at least three studies included in the analysis). The overall quality of the included studies was evaluated using the CONSORT checklist statement. In our analysis, we found a good average quality of all included trials. All trials reported a high risk of performance bias (blinding of participants and personnel) due to the open-label structure. All trials except KEYNOTE-010 reported an unclear risk of detection bias because authors did not specify the role of each researcher in the trial conduction. Finally, only Check-Mate017 and Check-Mate057 trials of nivolumab reported an unclear risk of selection bias because authors did not specify how do they randomize every patient into the study arms (lack of random sequence and allocation). No significant risk detected for attrition and selective reporting biases (Fig. 3).

## Discussion

To date we have three different agents including two PD1 inhibitors nivolumab and Pembrolizumab and one PDL1 inhibitor atezolizumab approved as standard treatment options for pre-treated NSCLC patients. On the basis of the results of the

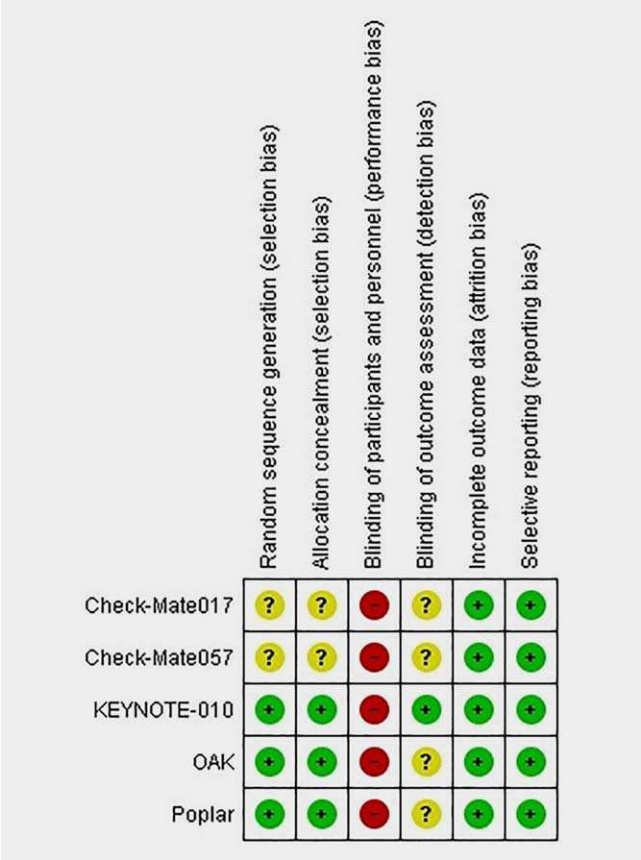


**Figure 3.** Risk of bias of selected trials summary [Color figure can be viewed at wileyonlinelibrary.com]

CheckMate 017[4] and 057[5] studies nivolumab received approval in both squamous and non-squamous histologies, regardless of tumor PD-L1 expression, while the KEYNOTE-010 trial[6] led to the subsequent approval of pembrolizumab only in patients with a threshold level of tumor PD-L1 expression >1%. Recently the clinical world of oncologists was again excited by the final results of the Phase III OAK trial,[7] showing that the PD-L1 inhibitor atezolizumab was superior to docetaxel in previously treated and unselected patients. In absence of an acute need for another ICI with a very similar indication, how might these agents distinguish themselves as compelling treatment options? Since we will likely never see direct comparison studies, this work represent an attempt to indirectly compare these three agents, in order to identify any potential differences in both activity and toxicity profiles, which could help clinicians in their daily practice. This meta-analysis included five randomized studies which compared PD1/PDL1 inhibitors versus docetaxel in pre-treated NSCLC patients. The trial design, the setting and the OS as primary outcome, were the same in all these studies. However, differently from the studies of nivolumab and atezolizumab, which enrolled patients not selected for PDL1-status and subsequently stratified outcomes according to the tumor PDL1 expression, the KEYNOTE-010 trial of pembrolizumab included only patients with a threshold level of tumor PD-L1 expression >1%, thus producing a potential selection bias. For this reason they were not included in the pooled analysis of PD–L1– patients, while were taken into account in the analysis of PD–L1+ population. The results of this work demonstrated a significant increase in ORR with both the anti PD1 MoAb nivolumab and pembrolizumab as compared to the anti-PDL1 atezolizumab in the overall population and in PDL1-positive patients, while no activity differences between nivolumab and pembrolizumab have been observed. None of the three ICIs was statistically superior in terms of both PFS and OS. However a not significant trend toward a PFS benefit was observed for the anti-PD1 nivolumab over atezolizumab, particularly in the subgroup of patients with PDL1-positive tumors. Only KEYNOTE-010 study[6] of pembrolizumab had an independent radiological review while the radiological evaluation interval differed among the majority of the studies, thus potentially influencing the final results. However, the risk of detection bias related to the determination of ORR endpoint is low, since the assessment of this outcome was consistent and homogeneous across all included studies. A potential biological explanation of the major activity observed with PD1 inhibitors could be find in their ability to simultaneously block the binding between PD1 receptor and both its natural ligands, PDL1 and PDL2; while the anti-PDL1 MoAb atezolizumab is able to block only the PDL1, not influencing the interaction between PD1 and PDL2.[19] Very interesting are the safety differences emerging from our indirect comparisons which revealed a significant lower incidence of all Grade 3–5 AEs during nivolumab therapy as compared with both pembrolizumab and atezolizumab treatments. However if we focus on immune-related toxicities, pembrolizumab has emerged as the best tolerated agent, since it was associated with the lower incidence of autoimmune pneumonitis as compared with the other two checkpoint inhibitors, even if it is not statistically significant. There are some limitations to the analysis of toxicity data. Indeed, as we mentioned before we reported only treatment-related AEs, but it is obvious that the attribution of an AE as treatment-related could be somewhat subjective and heterogeneous between clinical trials and drugs. Another observation is that pembrolizumab-related AEs were reported for both the two different dosages of 2 mg/kg and 10 mg/kg investigated in the KEYNOTE-010, and this could have led to a relative overestimation of the drug-related toxicity, since the lower dose of 2 mg/kg is currently approved for clinical use. Finally, the lower incidence of pneumonitis observed with pembrolizumab should be cautiously interpreted in light of the toxicity data reported in the different included studies. Indeed the absence of pneumonitis events described in the chemotherapy arms of both nivolumab and atezolizumab trials could have produced an overestimation of pulmonary toxic potential of both these agents, ultimately influencing the final results of our analysis. Furthermore no significant differences in treatment discontinuation rate have been observed among the three approved immune-checkpoint inhibitors. The majority of oncologists have long considered the different ICIs targeting PD1 or PDL1 as equally effective and clinically interchangeable options. However, despite some limitations, the results of our meta-analysis first revealed some additional differences among these agents, which

could guide clinicians in their treatment decisions. Particularly PD1 inhibitors nivolumab and pembrolizumab could be preferred options for patients with higher tumor burden or symptomatic disease, to whom the decrease of tumor volume represents a primary objective. Nivolumab seems to be generally better tolerated than the other two agents. However for patients with baseline respiratory diseases, which usually have higher risk to develop autoimmune-pneumonitis, pembrolizumab could be considered as the preferred option, even if the several above described limitations regarding safety analysis require further investigation. The role for immunotherapy in lung cancer is rapidly evolving thanks to the advent of new exciting data from randomized trials investigating both anti-PD1 and anti-PDL1 inhibitors in first-line setting.[20,21] The KEYNOTE-024 study[20] first compared pembrolizumab versus platinum-doublets chemotherapy in untreated EGFR/ALK wild-type NSCLC patients whose tumors expressed high-level (>50%) PD-L1 expression. The study met its primary endpoint of PFS (HR: 0.50, 95%CI: 0.37–0.68; $p < 0.005$) favoring pembrolizumab over first-line chemotherapy and leading to a paradigm shift in first-line. Indeed for about 30% of NSCLC patients with tumor PD-L1 >50% the optimal strategy now is starting with Pembrolizumab as upfront treatment. However for the majority of patients with lower-level, negative, or unknown PDL1 status who won't receive immunotherapy in first-line, the PD1 inhibitors nivolumab and pembrolizumab and the PDL1 inhibitor atezolizumab represent the new standard second-line options. Particularly the use of pembrolizumab is restricted to PDL1-positive patients, while both nivolumab and atezolizumab have been approved regardless of tumor PDL1 status.[9] Despite the regulatory recommendations the majority of studies including pretreated NSCLC patients showed that even if the benefit of ICIs increased accordingly to the tumor PDL1-expression, PDL1 negative patients also benefited from ICIs,[4–7] suggesting that, because of its low sensibility (72%) and specificity (58%), PDL1 status alone is not an appropriate biomarker to exclude pretreated patients from immunotherapy. Thus, beyond PDL1 expression, how to choose among three different drugs approved in the same setting? The results of our work revealed some interesting differences in both activity and safety profiles among these ICIs. Considering the limitations and the potential bias related to indirect comparisons, these evidences should not considered as a decisional tool to establish the superiority of one drug to another. However, they could only serve as a scientific support to help the oncologists in their clinical decisions in order to select the best drug for each patient.

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