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Review

# First-line immune checkpoint blockade for advanced non-small-cell lung cancer: Travelling at the speed of light

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ABSTRACT

The development of PD-1, PD-L1 and CTLA-4 immune checkpoint inhibitors (CPI) has revolutionised the treatment of advanced non-small cell lung cancer (NSCLC). The potential of immunotherapy (IO) to induce durable responses for a subset of patients represents a therapeutic milestone. After the approval of front-line single agent pembrolizumab, IO-based combinations are rapidly entering clinical practice resulting in a fast change of treatment algorithms for advanced NSCLC. We hereby summarize the recent first-line phase 3 trials evaluating PD-(L)1 blockade plus chemotherapy (ChT) and PD-1 plus CTLA-4 CPI for advanced NSCLC and provide potential treatment recommendations.

## 1. Introduction

First major improvements in NSCLC care have been achieved by the identification of targetable oncogenic alterations together with specific targeted therapies. However, the vast majority of Caucasian lung cancer patients do not present with a targetable driver mutation and standard cytotoxic chemotherapy (ChT) and anti-angiogenic strategies represented the cornerstones of systemic lung cancer treatment for decades. Nowadays, the treatment of advanced Non-Small-Cell Lung Cancer (NSCLC) is radically transforming. The emergence of programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) immune checkpoint inhibitors (CPI) established a new era of lung cancer care and the potential of CPI to induce durable responses and long term survival for a subset of patients represents a therapeutic milestone. Due to rapidly evolving data on CPI alone or in combination in the first-line setting for advanced NSCLC, treatment algorithms are changing quickly.

PD-(L)1 inhibitors nivolumab, pembrolizumab and atezolizumab are FDA- (U. S. Food and Drug Administration) and EMA (European Medicines Agency) -approved as second-line therapies for patients with advanced NSCLC who have failed platinum-based chemotherapy. These drugs demonstrated higher objective response rates (ORR), longer overall survival (OS) and better toxicity profile when compared to standard docetaxel [1–4]. Furthermore, about 20% of those patients seem to achieve long term survival [5,6].

In 2016, pembrolizumab has been approved as first-line monotherapy treatment in patients with advanced *epithelial growth factor receptor (EGFR)* and *anaplastic lymphoma kinase (ALK)* negative NSCLC harbouring a PD-L1 expression of ≥50% due to higher ORR, longer progression free survival (PFS) and OS compared to standard platinum based ChT [7,8]. However, only about a third of newly diagnosed advanced NSCLC patients have a tumor with a PD-L1 expression of ≥50% and therefore are suitable for first-line pembrolizumab [7].

In very recent times, several phase 3 studies have emerged in rapid succession presenting compelling results of new first-line treatment

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options with PD-(L1) blockade plus chemotherapy combinations (KEYNOTE-189 [9], KEYNOTE-407 [10], IMpower130 [11], IMpower131 [12], IMpower132 [13], IMpower150 [14]) and anti-PD-(L)1 plus anti-CTLA4 combination therapy (CheckMate-227 [15], MYSTIC [16]). The recently presented data in the first-line setting certainly increase the number of potential therapeutic options but also generate the challenge of choosing the most appropriate treatment regimen for the individual patient.

In this manuscript we discuss and critically appraise the recently reported first-line studies with CPI for advanced NSCLC and provide a potential treatment algorithm to aid treatment planning in clinical practice.

## 2. Anti-PD-1 monotherapy

### 2.1. Pembrolizumab

The phase 3 KEYNOTE-024 study assessed the efficacy of frontline pembrolizumab compared to platinum-based ChT for advanced NSCLC patients with a PD-L1 expression (tumor proportion score – TPS) of ≥50% without an activating EGFR or ALK aberration [7]. Of 1934 screened patients, a suitable sample for PD-L1 testing was available in 1653 patients of which 500 showed a PD-L1 expression of ≥50%. Ultimately, 305 out of 1934 screened patients were randomized to either receive pembrolizumab 200mg three-weekly (n = 154) for a minimum of 2 years or investigator's choice platinum-based ChT (n = 151). Pembrolizumab demonstrated a significant improvement of ORR (45% vs. 28%), PFS (10.3 vs. 6.0 months, hazard ratio (HR), 0.50; 95% confidence interval (CI), 0.37-0.68; P < 0.001) and OS (HR, 0.60; 95% CI, 0.41-0.89; P = 0.005). Updated median OS was reported as 30.2 months (HR, 0.63; 95% CI, 0.47-0.86; P = 0.002) despite 43.7% crossover from ChT to pembrolizumab on progression [17]. Safety, tolerability and quality-of-life (QoL) analyses were also in favour of pembrolizumab [18]. Grade 3–5 treatment-related adverse events were half as frequent in the IO group (26.6% vs. 53.3%).

In the phase 3 study KEYNOTE-042, 1274 patients with advanced NSCLC and a TPS ≥ 1% were randomly allocated to receive 200 mg pembrolizumab every three weeks up to 2 years or carboplatin plus paclitaxel (squamous cell histology) and carboplatin plus pemetrexed (non-squamous cell histology) for up to 6 cycles, with optional pemetrexed maintenance therapy [8]. Patients with tumors harbouring an activating EGFR mutation or ALK rearrangement were not eligible. Efficacy of pembrolizumab was evaluated at three PD-L1 thresholds: ≥50%, ≥20% and ≥1%. Pembrolizumab resulted in a significant improvement of OS in all three groups: 20.2 vs. 12.2 months (HR, 0.69; 95% CI, 0.56-0.85; P = 0.0003) in patients with a TPS ≥ 50%, 17.7 vs. 13.0 months (HR, 0.77; 95% CI, 0.64-0.92; P = 0.002) in patients with a TPS ≥ 20% and 16.7 vs. 12.1 months (HR, 0.81; 95% CI, 0.71-0.93; P = 0.0018) in patients with a TPS ≥ 1% (whole study population). An exploratory analysis for patients with a PD-L1 expression of 1–49% did not show any difference in OS between the two arms (13.4 vs. 12.1 months, HR, 0.92; 95% CI, 0.77–1.11). Therefore it seems that the OS benefit in the pembrolizumab arm is driven mostly by patients with a PD-L1 expression of ≥50%. Notably, crossover from ChT to pembrolizumab upon progression was not allowed, and only about 20% of patients in the ChT arm received subsequent CPI therapy at progression. This possibly negatively impacts the OS for patients in the ChT arm and is therefore increasing the perceived benefit of pembrolizumab over ChT [1,2,4].

### 2.2. Nivolumab

The phase 3 study CheckMate-026 assessed nivolumab in previously untreated patients with advanced NSCLC and a PD-L1 expression of ≥1% in the absence of a sensitizing EGFR mutation or activating ALK rearrangement [19]. Five hundred and forty-one patients were randomly assigned to receive nivolumab every 2 weeks until progressive disease/intolerable toxicity or platinum-based ChT. The phase 3 study CheckMate-026 assessed nivolumab in previously untreated advanced NSCLC patients with a PD-L1 expression of ≥1%, in the absence of a sensitizing EGFR mutation or activating ALK gene rearrangement [19]. Five hundred and forty-one patients were randomly assigned to receive nivolumab every 2 weeks until progressive disease/intolerable toxicity or platinum-based ChT. Even though inclusion criterion was a PD-L1 expression of ≥1% the efficacy analysis was performed in the PD-L1 ≥ 5% population. The study failed to meet the primary endpoint as there was no difference in PFS between the two arms (HR, 1.15; 95% CI, 0.91–1.45; P = 0.25). There was also no improvement in OS (HR, 1.02; 95% CI, 0.80–1.30) in the intention to treat population and in a post-hoc analysis for the subgroup of patients with a PD-L1 expression ≥50% (HR, 1.07; 95% CI, 0.77–1.49).

## 3. Anti-PD-(L)1 plus chemotherapy combinations

Recently, several phase 3 trials combining PD-(L)1 blockade plus ChT or PD-(L)1 plus CTLA-4 blockade have been published and brought several new first-line treatment options for advanced NSCLC.

### 3.1. Pembrolizumab plus Platinum/Pemetrexed

The phase 3 study KEYNOTE-189 assessed the efficacy of pembrolizumab or placebo in combination with pemetrexed plus cisplatin or carboplatin in patients with advanced non-squamous NSCLC without sensitizing EGFR or ALK alteration, irrespective of PD-L1 expression. Pembrolizumab was given concurrently for the first 4 cycles of ChT followed by pemetrexed and pembrolizumab maintenance [9]. Patients in the chemo-IO arm achieved a longer OS (11.3 months versus not reached (NR), HR, 0.49; 95% CI, 0.38-0.64, P < 0.001) corresponding to a 20% improvement of the 1-year OS rate (from 49.4%–69.2%). The improvement in OS was observed across all evaluated PD-L1 subgroups (TPS < 1%, ≥1%, 1–49% and ≥50%) with the greatest difference seen in patients with a TPS ≥ 50% (HR, 0.42; 95% CI, 0.26-0.68; P = 0.0001) but also statistically significant in patients with a TPS of 1–49% (HR, 0.55; 95% CI, 0.34-0.90; P = 0.0081) and in patients with a TPS of < 1% (HR, 0.59; 95% CI, 0.38-0.92; P = 0.0095). In PD-L1 negative patients, there was no difference in PFS between the two arms (HR, 0.75; 95% CI, 0.53–1.05) leaving an uncertainty in terms of durable responses in those patients. ORR was 47.6% vs. 18.9% (TPS < 1%) and 61.4% vs. 22.9% (TPS ≥ 50%) for Chemo-IO and standard ChT, respectively. The IO-combination treatment was well tolerated but patients in the chemo-IO group had a higher incidence of nephritis (1.7% vs. 0%) and a higher incidence of acute kidney injuries (5.2% vs. 0.5%) which only resolved in 47% of the patients and led to discontinuation of all study drugs. Treating oncologists should be aware of this potential toxicity and would need to consider careful monitoring of kidney function in patients treated with this regimen. Overall the combination treatment showed a higher treatment-related discontinuation rate of 13.8% versus 7.9% in the chemotherapy only arm.

In an exploratory analysis of KEYNOTE-189, the clinical outcomes were assessed by the investigator's choice of the platinum backbone (cisplatin or carboplatin) in combination with pembrolizumab and pemetrexed. Three quarters of all patients were treated with carboplatin. The OS benefit with cisplatin and carboplatin was similar with a HR of 0.41 (95% CI, 0.24-0.69) and 0.52 (95% CI, 0.39-0.71), respectively. Hazard ratio for PFS (0.44, 95% CI, 0.30-0.65 vs. 0.55, 95% CI 0.44-0.70) and ORR (49% vs 47%) were comparable for cisplatin and carboplatin subgroups. There was also no difference in the rate of grade 3–5 adverse events (AEs). According to this analysis, both cisplatin and carboplatin are reasonable choices in combination with pembrolizumab and pemetrexed in the first-line setting for metastatic non-squamous NSCLC [20].

### 3.2. Pembrolizumab plus (nab-)Paclitaxel/Carboplatin

The phase 3 trial KEYNOTE-407 randomized 559 advanced squamous NSCLC patients to either ChT plus placebo or ChT plus pembrolizumab, regardless of PD-L1 expression [10]. ChT consisted of 4 cycles of carboplatin every three weeks plus either paclitaxel three-weekly or nab-paclitaxel weekly, at physician's discretion. The IO-ChT combination showed a marked benefit in all efficacy measures. OS increased from 11.3 to 15.9 months (HR, 0.46; 95% CI, 0.49-0.85; P = 0.0008), PFS improved from 4.8 to 6.4 months (HR, 0.56; 95% CI, 0.45-0.70; P < 0.0001) and ORR increased from 38.4% to 57.9%. The benefit of OS and PFS was consistent across all PD-L1 subgroups (TPS < 1%, 1–49% and ≥50%). Incidence of treatment-related AEs was similar between arms and no new safety signals were found. A recently presented exploratory analysis did not show a difference in efficacy in terms of OS, PFS and ORR according to the chosen taxane (paclitaxel vs. nab-paclitaxel) [21].

### 3.3. Atezolizumab plus Carboplatin/Paclitaxel and Bevacizumab

The phase 3 study IMpower-150 was the first study evaluating the addition of atezolizumab to carboplatin/paclitaxel. More than one thousand and two hundred PD-L1-unselected patients with chemotherapy-naïve advanced non-squamous NSCLC, were randomly allocated to receive either atezolizumab plus carboplatin/paclitaxel (ACP) followed by atezolizumab maintenance or atezolizumab plus bevacizumab plus carboplatin/paclitaxel (ABCP) followed by atezolizumab and bevacizumab maintenance or bevacizumab plus carboplatin/paclitaxel (BCP) followed by bevacizumab maintenance [14]. Patients with a sensitizing EGFR or ALK aberration were eligible if they had progression or unacceptable toxicity after at least one line of tyrosine kinase inhibitor (TKI) therapy. In total 91 (7.5%) EGFR mutant patients and 40 (3.3%) with ALK-rearranged tumors were included. The trial's principal question was to assess whether the addition of atezolizumab to BCP provided a clinical benefit. In the Intention-To-Treat wild-type (ITT WT) population, PFS (8.3 vs. 6.8 months, HR, 0.62; 95% CI 0.52-0.74; P < 0.001) and OS (19.2 vs 14.7 months, HR 0.78; 95% CI 0.64-0.96; P = 0.016) were significantly longer with the addition of atezolizumab to BCP. OS subgroup analysis for ABCP vs. BCP showed a consistent trend of benefit across all PD-L1 subgroups. An exploratory analysis showed no difference in PFS for patients who received 4 vs. 6 cycles of ChT [22]. The IMpower-150 study showed a tolerable safety profile and baseline QoL as well as physical functioning were maintained under treatment [23,24].

Improved median OS with ABCP vs. BCP was also seen in patients with baseline liver metastases (13.3 months [ABCP, n = 52] vs. 9·4 months [BCP, n = 57], HR 0.52; 95% CI 0.33–0.82) [25]. Of 58 patients with a sensitizing EGFR mutation, 26 received ABCP and 32 BCP. Of note, 8 patients did not have prior TKI treatment as requested by the study protocol. The subgroup analysis of patients with a sensitizing EGFR mutation after TKI failure (n = 50) showed an improvement in overall survival in favour of ABCP compared to BCP. Median OS with ABCP was not estimable (NE) vs. 17.5 months (HR, 0.39; 95% CI 0.14–1.07) [25].

### 3.4. Atezolizumab plus (nab)-Paclitaxel/Carboplatin

In the phase 3 study IMpower-130, 723 patients with advanced, treatment-naïve non-squamous NSCLC were randomized to either receive ChT (carboplatin plus nab-paclitaxel) or ChT plus atezolizumab. Switch maintenance pemetrexed was allowed in the control arm [11]. Patients were unselected for PD-L1 expression and were stratified according to sex, absence/presence of liver metastases and PD-L1 expression (*PD-L1-high*: PD-L1 ≥ 50% on tumor cells (TC) or ≥10% on tumor infiltrating immune cells (IC), *PD-L1-low*: PD-L1 1–49% on TC or 1–9% on IC, *PD-L1-negative*: PD-L1 < 1% on TC and IC). Patients with sensitizing EGFR or ALK aberration were eligible on progression or due to unacceptable toxicity after appropriate TKI therapy. Co-primary endpoints were PFS and OS in the ITT EGFR/ALK WT population. Combination therapy with atezolizumab plus carboplatin/nab-paclitaxel (CnP) showed longer PFS (5.5 vs. 7.0 months; HR 0.64; 95% CI, 0.54-0.77; P < 0.0001) and OS (13.9 vs. 18.8 months, HR 0.79; 95% CI 0.64-0.98; P = 0.033). Notably the 1-year PFS rate increased from 14.1% to 29.1%. A statistically significant PFS improvement in the atezolizumab arm was seen in all PD-L1 predefined subgroups but there was only a trend for OS benefit in all three PD-L1 strata, possibly due to 59.2% crossover from ChT to IO. There was no improvement in PFS or OS for patients with liver metastases at baseline, treated with atezolizumab. An investigator-assessed subgroup analysis of 44 EGFR mutant or ALK positive patients did not show an improvement of PFS (HR, 0.75; 95% CI 0.36–1.54) or OS (HR, 0.98; 95% CI 0.41–2.31) in the experimental arm.

The IMpower-131 trial randomized 1021 untreated patients with advanced squamous NSCLC into three study arms: atezolizumab plus carboplatin/paclitaxel (CP) or atezolizumab plus carboplatin/nab-paclitaxel (CnP) or CnP. Patients were unselected for PD-L1 expression, and stratified for gender, PD-L1 expression and presence/absence of liver metastases [12]. The two co-primary endpoints of the study were PFS and OS in the ITT population. The study was designed to formally test initially atezolizumab/CP vs. atezolizumab/CnP. If OS was significant, then atezolizumab/CP would be tested against CnP. The addition of atezolizumab to CnP demonstrated a longer PFS (6.3 vs. 5.6 months, HR 0.71; 95% CI 0.60-0.85; P = 0.0001) relating to a doubling of the 1-year PFS rate from 12.0% to 24.7%. PFS improvement was observed across all PD-L1 subgroups. At the first interim analyses, no difference in OS was found when adding atezolizumab to CnP. A subgroup analysis showed OS improvement in patients with high (TC 3/IC 3) PD-L1 expression (23.6 vs.14.1 months, HR, 0.56; 95% CI 0.32-0.99) but no difference in OS in the PD-L1 low (TC2/IC2) or PD-L1 negative (TC0/IC0) patients. Atezolizumab plus CnP showed a manageable toxicity profile with no new safety signals.

### 3.5. Atezolizumab plus Pemetrexed/Platinum

The IMpower-132 trial investigated the efficacy of atezolizumab in combination with ChT in treatment-naïve advanced non-squamous NSCLC in the absence of an activating EGFR or ALK alteration, irrespective of PD-L1 expression. 578 patients were randomly assigned to receive either atezolizumab plus ChT (cis- or carboplatin/pemetrexed) followed by atezolizumab plus pemetrexed maintenance or ChT alone followed by pemetrexed maintenance [13]. Co-primary endpoints were investigator-assessed PFS and OS. The combination of atezolizumab-ChT resulted in longer PFS (7.6 vs. 5.2 months, HR, 0.60; 95% CI 0.49-0.72; P < 0.0001). The 1-year PFS rate doubled from 17% to 35% and the ORR improved from 32% to 47%. PFS improvement for the atezolizumab arm was seen independently of age (≥65 years vs. < 65 years, ethnicity (Asian vs. non-Asian) and smoking history. There was no improvement in PFS for patients with liver metastases at baseline (4.4 vs. 4.0 months, HR, 0.77; 95% CI, 0.47–1.25). With a median follow up of 14.8 months, the efficacy boundary had not been crossed for OS (HR 0.81, 95% CI:0.64-1.03, p = 0.0797).

## 4. Anti-PD-(L)1 plus anti-CTLA-4 combination

### 4.1. Ipilimumab plus nivolumab

The phase 3 trial CheckMate-227 was designed to investigate two cohorts defined by PD-L1 expression (≥1% vs. < 1%) in previously untreated squamous or non-squamous advanced NSCLC patients without a sensitizing EGFR or ALK alteration. A total of 1739 patients were included. Patients with a TPS ≥ 1% (n = 1189) were randomized to receive nivolumab (3 mg/kg every two weeks) plus ipilimumab

(1 mg/kg every 6 weeks), nivolumab monotherapy or histology-based ChT. Patients with a TPS < 1% (n = 550) were randomized to receive nivolumab plus ipilimumab, nivolumab plus histology-based ChT or histology-based ChT alone [15]. With the study ongoing, the protocol was amended to include a new co-primary endpoint, namely PFS in patients with a high tumor mutational burden (TMB), across both enrolled cohorts, irrespective of PD-L1 expression. A cut-off of ≥10 mutations per megabase (mut/Mb) was chosen to define high TMB according to the results of the CheckMate-568 [26]. Consequently, 299 patients (17.2%) were available with high TMB tumors. Of note, TMB testing could only be performed in 58% of potentially eligible patients. 139 (8%) patients were treated with ipilimumab plus nivolumab and 160 patients (9.2%) with histology-based ChT. In patients with a high TMB, PFS was longer (7.2 vs. 5.4 months, HR; 0.58, 95% CI 0.41-0.81; P = 0.0002) in the ipilimumab plus nivolumab arm. The PFS benefit was consistent in the subgroups of patients with a TPS of ≥1% (HR, 0.62; 95% CI 0.44-0.88) as well as in patients with a TPS of < 1% (HR, 0.48; 95% CI, 0.27-0.85), and was seen irrespective of tumor histology. After 12 months, 68% of patients treated with the IO doublet were still alive compared to only 25% in the ChT arm. The incidence of grade 3–5 AEs was 31.2% versus 36.1% for the IO combination and ChT arm, respectively. Ipilimumab plus nivolumab showed a manageable toxicity profile and patient reported outcomes demonstrated an early and sustained improvement in health-related quality of life for the IO combination [27].

### 4.2. Durvalumab plus tremelimumab

The MYSTIC trial enrolled 1118 patients with metastatic NSCLC who were randomly allocated to durvalumab alone, durvalumab plus tremelimumab, or ChT [16]. The primary endpoints were OS for durvalumab (D) versus ChT, and OS and PFS for durvalumab plus tremelimumab (D + T) versus ChT in patients with PD-L1 expression ≥25% in tumor cells. A total of 488 patients (44%) had PD-L1 expression of ≥25%. Durvalumab alone or with tremelimumab did not improve OS or PFS compared to ChT. The authors presented an exploratory analysis for OS according to blood TMB (bTMB) using a cut off of ≥16 mut/Mb. In the population with bTMB ≥16 mut/Mb, OS was 11 vs. 16.5 vs. 10.5 months for D, D + T and ChT, respectively.

## 5. Discussion

It is important to note that, at the time of writing this manuscript, there are no trials addressing a direct head-to-head comparison between recently presented first-line regimens containing anti-PD-(L)1 drugs in association with chemotherapy and or bevacizumab. Cross-trial comparisons are only hypothesis generating and cannot be used as solid ground to guide a treatment strategy. (Table 1 summarizes efficacy and safety results of the recent first-line IO studies).

In patients whose tumors harbour a PD-L1 expression ≥50%, the KEYNOTE-024 study provides strong evidence that pembrolizumab monotherapy may be the preferential treatment, irrespective of tumor histology or patient's age. Results from KEYNOTE-042 study showed that first-line pembrolizumab monotherapy in the population with a TPS of 1%–49% may not be better than platinum-based ChT and therefore revealing a potential argument for using a ChT-IO combination in this patients. Considering ChT-pembrolizumab in patients with a PD-L1 expression of ≥50% might be a treatment option in patients with clinically aggressive disease or for patients in need for quick treatment response due to relevant symptoms after careful consideration of tolerability and patients preferences. Notably the 1-year OS rates for KEYNOTE-189 (non-squamous) and KEYNOTE-407 (squamous), were 73.0% and 63.2% respectively, which is comparable to the 70.3% 1-year OS rate reported in KEYNOTE-024 without the additional ChT-related toxicity. A head to head comparison between pembrolizumab +/- ChT is lacking. A recently presented meta-analysis, using the KEYNOTE-024 and the KEYNOTE-189 subgroup data, compared pembrolizumab monotherapy to pembrolizumab in combination with ChT in patients with a PD-L1 expression of ≥50%. The addition of ChT to pembrolizumab did not result in an statistically significant improvement of OS (HR, 0.70; 95% CI, 0.38–1.30; P = 0.26) or PFS (HR, 0.72; 95% CI, 0.45–1.16; P = 0.18) [28]. A front-line treatment with the four drug regimen atezolizumab/bevacizumab/carboplatin/paclitaxel (IMpower-150) with potentially higher risk of AEs compared to a CPI monotherapy may not be the preferred strategy in patients with PD-L1 expression of ≥50%, without liver metastases.

Fig. 1 shows a possible first-line treatment algorithm for advanced non-squamous NSCLC. The KEYNOTE-189 trial provided solid data for pembrolizumab plus pemetrexed/(cis)carboplatin demonstrating a significant PFS and OS benefit over ChT with a HR of 0.49 and a benefit consistency across all PD-L1 subgroups. Despite the longest PFS of all reviewed trials (8.8 months) KEYNOTE-189 showed a lack of PFS benefit in the subgroup of PD-L1 negative patients. A QoL analysis in KEYNOTE-189 showed an improved tolerability and better control of symptoms compared to ChT alone, despite a slightly higher incidence of grade 3–5 AEs in the investigational arm [29]. The occurrence of 1.7% nephritis and 5.2% of acute kidney injuries is urging caution in patient monitoring and potentially requesting treatment modification especially looking at a pemetrexed maintenance therapy. The same ChT regimen, pemetrexed/(cis)carboplatin, combined with atezolizumab showed a significant PFS benefit over ChT in the IMpower-132 trial with an HR of 0.60 with a consistent beneficial trend, irrespective of PD-L1 expression, age, smoking status and ethnicity (Asian vs. non-Asian). OS data were not mature and not statistically significant at the interim analysis (13.6 vs. 18.1 months) suggesting atezolizumab plus platinum based ChT as an additional possible treatment regimen. The IMpower-150 regimen (atezolizumab plus bevacizumab plus carboplatin/paclitaxel) showed PFS and OS superiority over bevacizumab plus carboplatin/paclitaxel with an ORR of 63.5%. The regimen showed a consistent trend of benefit across all PD-L1 levels as well as in patients with and without liver metastases. The IMpower-130 regimen (atezolizumab plus nab-paclitaxel/carboplatin) showed clear superiority in PFS despite a 20% rate of Pemetrexed switch maintenance therapy in the control arm. The PFS benefit was consistent across all PD-L1 predefined subgroups. The OS benefit did not reach statistical significance in all three PD-L1 strata, possibly due to high (59.2%) crossover from ChT to IO on progression.

In a subset of patients with a high TMB (≥10 mut/Mb) the combination of ipilimumab plus nivolumab showed a significant PFS benefit with a HR of 0.58 compared to ChT, leading to higher 1-year PFS-rate (13% versus 43%). Mature OS data are still awaited. The change of the study design in CheckMate-227, with redefining the primary endpoints during the study reduces the trial's statistical power for OS analyses due to small sample size of TMB-high patients. More solid and prospective analyses with TMB stratification are needed to clarify. It seems more likely that TMB will be seen as a quantitative continuous biomarker rather than a binary one. Furthermore, several issues remain around validation of TMB testing methodologies (Next-Generation-Sequencing vs. Whole-Exome-Sequencing) for use in routine clinical practice, a topic that is currently investigated in a number of ongoing harmonization studies. Ipilimumab plus nivolumab had a higher (30%) incidence of SAEs compared to approximately 10% SAEs rate reported in the ChT-IO combination studies, suggesting that the ipimumab/nivolumab combination will not be suitable for all patients.

The results of several ongoing combination studies (*CheckMate-9LA*: [nivolumab/ipilimumab plus ChT], *POSEIDON*: [durvalumab/tremelimumab plus ChT]) [30,31] investigating two and four drug regimens of PD-(L)1 plus CTLA-4 inhibition +/- ChT are eagerly awaited and will reveal further knowledge of efficacy and tolerability in this setting.

For fit patients with advanced squamous NSCLC and a PD-L1 expression of < 50% pembrolizumab plus carboplatin/(nab)-paclitaxel is the IO-based frontline treatment with the most convincing evidence as

**Table 1**
Summary of efficacy and safety results of first-line IO based studies for NSCLC.

| Trial | Primary Endpoint(s) | Treatment arms | PFS (months) | HR (95% CI) | P value | OS (months) | HR (CI) | P value | Patients receiving IO at progression (%) | G3-5 Toxicity (%) | Treatment related discontinuation rate (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| KEYNOTE-024[1] | PFS | Pembrolizumab (PD-L1 ≥50%) | 10.3 | | | 30.2 | | | | 26.6 | 7.1 |
| | | ChT[&] (PD-L1 ≥50%) | 6.0 | 0.50 (0.37-0.68) | P < 0.001 | 14.2 | 0.63 (0.47-0.86 | P = 0.02 | 43.7 | 53.3 | 10.7 |
| CheckMate-026[2] | PFS | Nivolumab (PD-L1 ≥1%) | 4.2 | | | 14.4 | | | | 18.0 | 10 |
| | | ChT[&] (PD-L1 ≥1%) | 5.9 | 1.15 (0.91-1.45) | P = 0.25 | 13.2 | 1.02 (0.80-1.30) | N/R[*] | 60.0 | 51.0 | 13 |
| KEYNOTE-042[3] | OS | Pembrolizumab (PD-L1 ≥1%) | 7.1 (PD-L1 ≥ 50%) | 0.81 (0.67-0.99) | P = 0.017 | 20.0 (PD-L1 ≥ 50%) | 0.69 (0.56-0.85) | P = 0.0003 | | 17.8 | 9 |
| | | | | 0.94 (0.80-1.11) | N/R[*] | 17.7 (PD-L1 ≥ 20%) | 0.77 (0.64-0.92) | P = 0.002 | | | |
| | | | 6.2 (PD-L1 ≥ 20%) | 1.07 (0.94-1.21) | N/R[*] | 16.7 (PD-L1 ≥ 1%) | 0.81 (0.71-0.93) | P = 0.018 | | | |
| | | | 5.4 (PD-L1 ≥ 1%) | | | 13.4 (PD-L1 1-49%) | 0.92 (0.77-1.11) | N/R[*] | On study: no crossover permitted | | |
| | | ChT[&](PD-L1 ≥1%) | | | | 12.2 (PD-L1 ≥ 50%) | | | | 41 | 9.4 |
| | | | 6.4 (PD-L1 ≥ 50%) | | | 13.0 (PD-L1 ≥ 20%) | | | Off study: 20 | | |
| | | | 6.6 (PD-L1 ≥ 20%) | | | 12.1 (PD-L1 ≥ 1%) | | | | | |
| | | | 6.5 (PD-L1 ≥ 1%) | | | 12.1 (PD-L1 1-49%) | | | | | |
| KEYNOTE-189[4] | PFS | Pembrolizumab plus ChT[&] (non | 8.8 | | | 11.3 | | | | 67.2 | 13.8 |
| | OS | squamous, any PD-L1) | | 0.52 (0.43-0.64) | P < 0.001 | | 0.49 (0.38-0.46) | P < 0.001 | 32.5 | | |
| | | ChT[&] (non squamous, any PD-L1) | 4.9 | | | not reached | | | | 65.8 | 7.9 |
| KEYNOTE-407[5] | PFS | Pembrolizumab plus ChT[&] | 6.4 | | | 15.9 | | | | 69.8 | 13.3 |
| | OS | (squamous, any PD-L1) | | 0.56 (0.45-0.70) | P < 0.001 | | 0.64 (0.49-0.85) | P < 0.001 | 42.5 | | |
| | | ChT[&] (squamous, any PD-L1) | 4.8 | | | 11.3 | | | | 68.2 | 6.4 |
| IMpower-130[6] | PFS | Atezolizumab plus ChT[&] (non | 7.0 | | | 18.6 | | | | 73.2[#] | 26.4 |
| | OS | squamous, any PD-L1) | | 0.64 (0.54-0.77) | P < 0.0001 | | 0.79 (0.64-0.89) | P = 0.033 | 40.8 | | |
| | | ChT[&] (non squamous, any PD-L1) | 5.5 | | | 13.9 | | | | 60.3[#] | 22 |
| IMpower-131[7] | PFS | Atezolizumab plus ChT[&] | 6.3 | | | 14.3 | | | | 73.0[#] | 29 |
| | OS | (squamous, any PD-L1) | | 0.71 (0.60-0.85) | P = 0.0001 | | 0.96 (0.78-1.18) | P = 0.69 | 42.1 | | |
| | | ChT[&] (squamous, any PD-L1) | 5.6 | | | 13.9 | | | | 66.0[#] | 17 |
| IMpower-132[8] | PFS | Atezolizumab plus ChT[&] (non | 7.6 | | | 18.1 | | | | 62[#] | 24 |
| | OS | squamous, any PD-L1) | | 0.60 (0.49-0.72) | P < 0.0001 | | 0.81 (0.64-1.03) | P = 0.0797 | 37.1 | | |
| | | ChT[&] (non squamous, any PD-L1) | 5.2 | | | 13.6 | | | | 54[#] | 18 |

(*continued on next page*)

**Table 1** (*continued*)

| Trial | Primary Endpoint(s) | Treatment arms | PFS (months) | HR (95% CI) | P value | OS (months) | HR (CI) | P value | Patients receiving IO at progression (%) | G3-5 Toxicity (%) | Treatment related discontinuation rate (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| IMpower-150[9] | PFS | Atezolizumab plus Bevacizumab | 8.3 | | | 19.2 | | | | 55.7# | 32.6 |
| | OS | plus ChT& (non squamous) | | 0.62 (0.52-0.74) | P < 0.001 | | 0.78 (0.64-0.69) | P = 0.02 | 31.7 | | |
| | | Bevacizumab plus ChT& (non squamous) | 6.8 | | | 14.7 | | | | 47.7# | 24.9 |
| CheckMate-227[10] | PFS | Ipilimumab plus Nivolumab | 7.2 | | | 23.0 | | | | 31.2# | 17.4 |
| | OS | (any PD-L1, high TMB) | | 0.58 (0.41-0.81) | P = 0.0002 | | 0.78 (0.61-1.06) | N/R* | 30.0 | | |
| | | ChT& (any PD-L1, high TMB) | 5.4 | | | 16.7 | | | | 36.1# | 8.9 |
| MYSTIC[11] | PFS | Durvalumab plus Tremelimumab | 3.9 | 1.05 (0.72-1.53) | P = 0.705 | 11.9 | 0.85 (0.61-1.17) | P = 0.20 | 39.5 | 47.7# | 20.2 |
| | OS | (PD-L1 ≥ 25%) | | | | | | | | | |
| | | ChT& (PD-L1 ≥ 25%) | 5.4 | | | 12.9 | | | | 46.0# | 15.1 |
| | OS | Durvalumab (PD-L1 ≥ 25%) | 4.7 | | | 16.3 | | | | 40.4# | 11.4 |
| | | ChT& (PD-L1 ≥ 25%) | 5.4 | 0.87 (0.59-1.28) | P = 0.324 | 12.9 | 0.76 (0.56-1.01) | P = 0.036 | 39.5 | 46.0# | 15.1 |

& Platinum based chemotherapy, *N/R= not reported, #Grade 3-4 AE.


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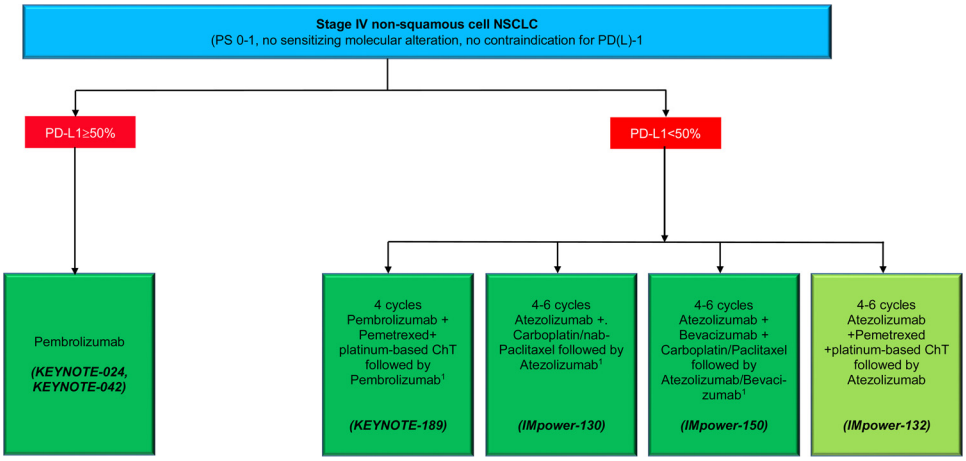


**Fig. 1.** Possible treatment suggestion for immunotherapy based first-line treatment options for Stage IV non-squamous cell NSCLC. [1]Preferred regimens.

investigated in the KEYNOTE-407 trial. The regimen demonstrated a PFS advantage with a HR of 0.56, a substantial OS benefit with a 36% risk reduction for death and an absolute benefit of 4.6 months compared to ChT alone. Importantly, the OS benefit was consistent in all subgroups, regardless of PD-L1 expression. On the basis of the results of the IMpower-131 study, atezolizumab plus carboplatin/(nab)-paclitaxel may be considered as an alternative treatment option. The addition of atezolizumab to ChT showed a significant PFS benefit with an HR of 0.71, however, the beneficial effect did not translate into a significant OS prolongation. In the subgroup with a PD-L1 expression of 1–49%, the treatment showed a detrimental effect with an unfavourable HR of 1.34, which is not fully understood. The results from KEYNOTE-407 and IMpower-131 study sound a note of caution that different CPIs might not be easily interchangeable. Furthermore, the individual development of anti-drug-antibodies (ADA) against CPI might explain variable outcomes and toxicity profiles by choosing different CPI. ADA might be able to alternate CPI's pharmacokinetic in neutralizing the drug or enhance drug clearance. The issue with measuring ADA is the big difference in assay sensitivity which might influence the variable degrees of measured ADA prevalence for different CPI [32]. Similarly to non-squamous NSCLC patients, there might be a role for a front-line combination of ipilimumab plus nivolumab in the subset of squamous NSCLC patients with a high TMB (≥10 mut/Mb) as investigated in the CheckMate-227 study. These data are biologically plausible, however at the moment they remain preliminary and not robust enough (small patient number, secondary analysis) to draw definite conclusions or to give advisory suggestions. Fig. 2 shows a potential treatment algorithm for advanced squamous cell NSCLC patients.

Both IMpower-130 (nab-paclitaxel/carboplatin plus atezolizumab) and IMpower-150 (atezolizumab/carboplatin/paclitaxel plus bevacizumab) enrolled patients with EGFR and ALK positive tumors who had failed at least one line of appropriate TKI therapy. In the subgroup analyses there was a trend for improved OS for EGFR mutant and ALK positive patients treated with the bevacizumab-containing regimen in IMpower-150 (HR for EGFR/ALK positive group: 0.54; 95% CI, 0.29–1.03, HR for patients with a sensitizing EGFR mutation: 0.39, 95% CI, 0.14–1.07). This potential benefit in OS was not seen without bevacizumab in IMpower-130 (HR, 0.98; 95% CI, 0.41–2.31). Studies that investigated single agent IO in patients with activating EGFR mutation clearly demonstrated a lack of OS benefit in this population even in patients with high PD-L1 expression [33,34]. The potential signal of activity in EGFR or ALK positive patients seen in IMpower-150 would need prospective validation and due to the exploratory nature and the small sample sizes of the analysed subgroups these data must be interpreted with caution.

The synergism of bevacizumab with atezolizumab seems also to be relevant for patients with liver metastases. In IMpower-150, the addition of bevacizumab to atezolizumab plus carboplatin/paclitaxel revealed an OS benefit in patients with liver metastases (HR 0.52; 95% CI 0.33–0.82) [25]. This benefit was not reported in the IMpower-130, -131 and -132, which investigated regimens without bevacizumab. The liver immune environment is known to contain immune-suppressive myeloid cells expressing VEGFR2, a fact that would explain the ability of bevacizumab to overcome this immune suppression in decreasing these cells and leading to an improved efficacy of a immune CPI in the liver [35,36]. These subgroup analyses also have to be interpreted with caution due to their retrospective character and the small sample sizes.

A retrospective exploratory subgroup analysis of the KEYNOTE-189 trial, presented at the 2019 Annual American Association of Cancer Research (AACR) meeting, evaluated survival outcomes in patients with presence or absence of liver or brain metastases at baseline. 115 of 616 patients (18%) presented with baseline liver metastases. The pembrolizumab plus pemetrexed/platinum combination showed an OS improvement from 6.6 to 12.6 months (HR 0.62, 95% CI, 0.39-0.98) in patients with liver metastases and from 13.2 to 23.7 months (HR 0.58, 95% CI, 0.45-0.74) in patients without liver metastases. [37]. 108 of

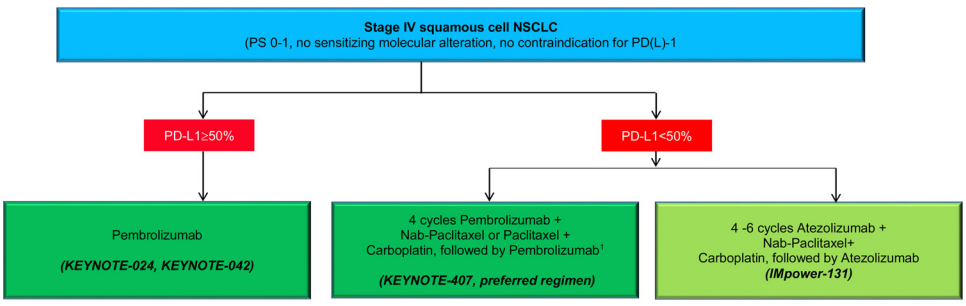


**Fig. 2.** Possible treatment suggestion for immunotherapy based first-line treatment options for Stage IV squamous cell NSCLC.

616 patients (17.5%) presented with stable baseline brain metastases. The pembrolizumab plus pemetrexed/platinum combination showed an OS improvement from 7.5 to 19.2 months (HR 0.41, 95% CI, 0.24-0.67) in patients with brain metastases, and an improvement from 12.1 to 22.4 (HR 0.59, 95% CI, 0.46-0.75) for patients without brain metastases. Similarly to the overall population, the risk of death was reduced by approximately a half in the IO/ChT combination irrespective of the presence or absence of liver or brain metastases and no new safety signals were identified.

On the basis of available data, it is challenging to suggest the best treatment approach for patients with pre-existing brain metastases. All IO-based first-line registration studies only included patients with treated and stable brain metastases. As bevacizumab demonstrated encouraging efficacy and acceptable safety with first-line paclitaxel and carboplatin in patients with NSCLC and asymptomatic, untreated brain metastases in the BRAIN study [38] a bevacizumab containing IO based regimen might possibly be a safe and effective option in this setting.

The IO-based combinations seem well tolerated in PS 0–1 patients. However, there is no data to guide use in patients with PS 2-3. It is still not clear if full-dose ChT is really needed to enhance the activity of CPI or if a dose-reduced ChT strategy could preserve the beneficial combination effect with better tolerability for a broader spectrum of patients.

Innovative predictive biomarkers, beyond PD-L1 expression, are urgently needed to improve patient selection and treatment outcomes. TMB is an emerging predictor of response. A retrospective unplanned exploratory analysis assessed the impact of TMB on treatment with nivolumab in the CheckMate-026 study. A high TMB ($\geq$243 somatic mutations assessed by whole-genome-sequencing) indicated a trend towards longer PFS (HR, 0.62; 95% CI, 0.38–1.00) and higher ORR in favour of nivolumab. In the same analysis, the three TMB strata (high, intermediate and low) occurred to be independently distributed, irrespective of PD-L1 expression [19]. In the CheckMate-227 study, a high TMB lead to longer PFS in patients treated with ipilimumab plus nivolumab compared to ChT. A recently published analysis investigated the correlation between TMB (assessed by whole-genome-sequencing) and response to ipilimumab plus nivolumab in 75 NSCLC patients treated in the phase I CheckMate-012 study [39]. TMB was found to be a strong predictor of efficacy for ipilimumab plus nivolumab with significantly higher TMB in patients with a complete or partial response (CR/PR) compared to patients with stable disease of progressive disease (SD/PD) (P = 0.0004). Furthermore, high TMB was associated with a durable clinical benefit (PR or SD > 6 months). No correlation between TMB and PD-L1 expression was detected, once again highlighting TMB as an independent predictor for immune therapy [40]. However, in the CheckMate-026 the PFS-benefit did not translate into an OS benefit and OS data of CheckMate-227 are still awaited. Notably, in both studies the TMB assessment was done retrospectively and further prospective analyses are needed. Another potential predictive biomarker is T-effector-signature-expression, which was prospectively evaluated in IMpower-150. It is defined as messenger RNA expression of three different genes (PD-L1, CXCL9, INF-y) as a surrogate for PD-L1 expression and was measured by real-time PCR on tumor tissue at baseline. In the OAK trial, T-effector gene signature expression occurred to be a more sensitive biomarker for a PFS benefit than PD-L1 expression [41]. In the IMpower-150 study, patients with a high T-effector gene signature-expression (Teff-high) had a longer PFS (11.3 vs. 6.8 months, HR, 0.51; 95% CI, 0.38- 0.86; P < 0.001) when treated with ABCP compared to BCP and also a trend toward longer OS (25.0 vs. 16.7 months, HR, 0.83; 95% CI, 0.59–1.17) [14]. Interferon-$\gamma$ messenger RNA gene expression, tumor infiltrating lymphocytes (TILS) and tumor environmental infiltrating lymphocytes are also promising predictors under investigation [42–44].

One of the major limitations of tissue based biomarkers in lung cancer is that about 30% of all patients have inadequate tumor tissue for biomarker testing [45]. Blood based TMB (bTMB) is a non-invasive biomarker with the potential to independently predict clinical benefit. Blood based TMB has been prospectively evaluated in the phase 2 B-F1RST trial and has shown its benefit as a predictive marker for front-line single agent atezolizumab in advanced NSCLC [46]. Patients with a high (score $\geq$16) bTMB achieved a significantly higher ORR than patients with a low (score < 16) bTMB (28.6% vs. 4.4%; P < 0.0002). Furthermore, bTMB high patients showed a non-significant trend for longer PFS (4.6 vs. 3.7 months, HR, 0.66; 90% CI 0.42–1.02) and OS (NR vs. 13.1 months, HR, 0.77; 90% CI, 0.41–1.43) compared to bTMB low patients. Results from the B-FAST trial, where patients with high bTMB are randomized to front-line atezolizumab or platinum-based ChT will shed more light on the predictive potential of bTMB [47].

Bringing all active agents to the front-line leaves the challenge of finding active subsequent treatments. To date, there is very little understanding of the mechanisms of immune-resistance at relapse. Salvage regimens like docetaxel +/- antiangiogenics, gemcitabine or vinorelbine show limited efficacy. Re-introducing a platinum-based ChT after a longer period of IO maintenance could to be a reasonable treatment approach. Combining IO with immune-stimulating cytokines to overcome immune resistance is part of ongoing research [48,49].

It is to keep in mind that patients in the all phase 3 CPI-trials discussed above are highly selected with screening failure rates from 28% in KEYNOTE-407 up to 74% in KEYNOTE-24 and therefore real life data is awaited and of utmost importance. Furthermore, the trials were substantially heterogeneous and different in regard of the published efficacy outcomes of the control arms which also contributes to the published hazard ratios of clinical efficacy measures. For example, OS for platinum/pemetrexed in KEYNOTE-189 was lower than expected while the highest efficacy ever was reported for carboplatin/nab-Paclitaxel in IMpower-131.

The reviewed studies add important evidence and clearly strengthen the role of IO in the first-line setting of advanced NSCLC. Particularly in patients with low (TPS 1–49%) or negative PD-L1 expression a chemotherapy plus IO combination regimen represents the best treatment in terms of efficacy but, if not available due to local approval or resources, chemotherapy alone remains an acceptable strategy.

In conclusion, the recent findings affirm the importance of IO in the first-line for advanced NSCLC and suggest IO to be considered the new standard of care for patients with newly diagnosed advanced NSCLC with good performance status (0–1) and the absence of contraindications for IO.

## Author contribution

**Christoph Ackermann**

No conflict of interests

**Fabrice Barlesi**

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**Raffaele Califano**

Honoraria and consultancy fees: AstraZeneca, Roche, MSD and Bristol Myers Squibb

**Martin Reck**

Honoraria for lectures and consultancy from Abbvie, Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, Celgene, Merck, MSD, Novartis, Pfizer, Roche.

**Luis Paz-Ares**

Honoraria for lectures and consultancy from Lilly, MSD, BMS, Roche, Pharmamar, Merck, Astra-Zeneca, Novartis, Boehringer, Celgene, Servier, Sysmex, Amgen, Incyte, Pfizer, Ipsen, Adacap

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