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REVIEW ARTICLE

First-Line Immune Checkpoint Inhibition for Advanced Non-Small-Cell Lung Cancer: State of the Art and Future Directions

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Abstract
The advent of PD-(L)1 and CTLA-4 immune check point inhibitors (CPIs) has dramatically changed the treatment landscape of advanced non-small-cell lung cancer (NSCLC). For up to a quarter of patients with advanced NSCLC, CPIs have the potential to induce durable responses with long-term survival outcomes. Since the approval of first-line pembrolizumab for patients whose tumors express a PD-L1 ≥ 50%, several pivotal first-line CPI-based phase 3 studies have been conducted investigating combination treatments combining CPIs with chemotherapy (ChT) or combining different CPIs with or without ChT. As a result, there has been an increase in front-line treatment options for advanced NSCLC, and treatment algorithms are changing very quickly. In fit patients with advanced NSCLC, combination treatments including CPI and ChT are considered the new standard of care with improved clinical outcomes. CPI combination treatments are well tolerated and quality of life also seems to be better when CPIs are implemented in the first-line setting. The aim of this review is to provide a summary of the recently published first-line phase 3 studies investigating CPIs as monotherapy or in combination with other CPIs or ChT in advanced NSCLC, and to suggest possible treatment algorithms.

1 Introduction

The discovery of targeted therapies for specific oncogenic molecular aberrations has led to new therapy options and significant improvements in outcomes for a subset of patients with advanced non-small-cell lung cancer (NSCLC). However, only a minority of patients will have tumors harboring an actionable oncogenic driver, and therefore chemotherapy (ChT) with or without bevacizumab represented the standard of care for several years. The emergence of immunotherapies with check point inhibitors (CPI) and CPI-ChT combinations have radically transformed advanced NSCLC care, leading to revised treatment algorithms. In particular, the use of programmed cell death protein (ligand) 1 (PD-(L)1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) CPI induced a paradigm shift in lung cancer care with the unprecedent potential of those drugs to induce durable responses and long survival outcomes for a subset of patients. Due to higher objective response rates (ORRs) and longer overall survival (OS) when compared to standard ChT (among many registration authorities), the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved the anti-PD-(L)1 antibodies pembrolizumab, nivolumab, and atezolizumab as monotherapy options in the second-line setting after failure of platinum-based ChT [1–4]. Long-term responses have been observed in about 20–25% of patients treated with these CPIs [5, 6].

In the absence of a sensitizing alteration of the epithelial growth factor receptor (EGFR) and the anaplastic lymphoma kinase (ALK), pembrolizumab was approved in 2016 as first-line monotherapy for advanced NSCLC patients with a PD-L1 expression of ≥ 50% due to superiority in ORR, progression free survival (PFS), and OS compared to platinum-based ChT [7, 8]. However, only about 30% of newly diagnosed advanced NSCLC patients harbor a tumor with

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Key Points

For fit patients with advanced NSCLC, immune checkpoint inhibitor-based first-line regimens are considered current standard of care.

Immune checkpoint inhibitors show the potential to induce durable treatment responses in patients with advanced NSCLC and have dramatically improved patients' prognosis in the last few years.

Frontline immune checkpoint inhibitors combined with chemotherapy in patients with advanced NSCLC are well tolerated and improve quality of life.

Independent predictive biomarkers are urgently needed to better select patient who benefit best from checkpoint inhibitor-based treatment regimens.

a high PD-L1 expression and are therefore eligible for this strategy [7].

Recently, multiple phase 3 trials combining PD-(L)1 CPI with ChT (Keynote-407 [9], Keynote-189 [10], IMpower130 [11], IMpower131 [12], IMpower132 [13], IMpower150 [14]) or combining anti-PD-(L)1 plus anti-CTLA4 CPI (CheckMate-227 [15], MYSTIC [16]) emerged in rapid sequence revealing new practice-changing options for advanced treatment-naïve NSCLC patients. The increased number of treatment options is certainly welcomed, but it also generates the challenge of choosing the most appropriate treatment regimen for the individual patient. In this review, we critically review the recently published first-line phase 3 studies investigating CPI-based treatment for advanced NSCLC and suggest possible treatment algorithms as guidance in clinical practice.

2 Anti-PD(L)-1 Monotherapy

2.1 Pembrolizumab (Anti-PD-1)

Following the results of the phase 1 Keynote-001 study (18% treatment-naïve, 82% previously treated NSCLC patients) [17], Keynote-024 was performed to assess the efficacy of pembrolizumab versus platinum-based ChT in advanced NSCLC in patients with a PD-L1 expression of ≥ 50% without activating EGFR mutations or ALK translocations [7]. 305 patients were randomized (1:1) to pembrolizumab or investigator's choice of platinum-based ChT. Notably, crossover from ChT to pembrolizumab was allowed at disease progression. Pembrolizumab demonstrated a significant improvement in 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, $P = 0.005$) over standard ChT. An updated analysis, with a median follow-up of 3 years, showed a median OS of 26.3 versus 14.2 months (HR 0.65, 95% CI 0.50–0.86, $P = 0.001$) in favor of pembrolizumab, despite a 64.2% crossover rate from ChT to pembrolizumab at progression. From patients treated in the investigational arm with frontline pembrolizumab 42.2% received subsequent therapies [18–20]. PFS2 (time of randomization with first-line treatment until progression on second-line treatment) was also substantially improved for pembrolizumab (HR 0.48, 95% CI 0.34–0.66, not reached vs. 8.6 months). The improvement of PFS2 additionally confirms that pembrolizumab should be given in the first-line setting in this population [20]. Patients treated with pembrolizumab also experienced a lower incidence of grade 3–5 toxicity (26.6% vs. 53.3%) and improved quality of life [21].

A recent retrospective multicentre series evaluating 187 patients with PD-L1 expression ≥ 50% treated with first-line pembrolizumab investigated the impact of PD-L1 expression levels on outcomes. All efficacy outcomes were significantly improved in patients with a PD-L1 expression ≥ 90% versus 50–89%: ORR was 60% versus 32.7% ($P < 0.001$), PFS was 14.5 versus 4.1 months (HR 0.50, 95% CI 0.33–0.74, $P < 0.01$) and an OS was not reached (NR) versus 15.9 months (HR 0.39, 95% CI 0.21–0.70, $P = 0.002$) [22].

Keynote-042 was performed to evaluate the efficacy of pembrolizumab across PD-L1 thresholds (≥ 50%, ≥ 20%, and ≥ 1%). Patients were randomized between pembrolizumab and carboplatin plus paclitaxel (squamous cell histology) or carboplatin plus pemetrexed (non-squamous histology) with pemetrexed maintenance therapy for eligible patients (66%). Patients with EGFR-activating mutations and ALK rearrangements were excluded [8]. Pembrolizumab demonstrated a significant improvement in OS across all three PD-L1 thresholds: TPS ≥ 50%: 20 versus 12.2 months, HR 0.69 (95% CI 0.56–0.85, $P = 0.0003$), TPS ≥ 20%: 17.7 versus 13 months, HR 0.77 (95% CI 0.64–0.92, $P = 0.0020$), TPS ≥ 1%: 16.7 versus 12.1 months, HR 0.81 (95% CI 0.71–0.93, $P = 0.0018$) [8]. An exploratory analysis for patients with a PD-L1 expression of 1–49% did not show a difference in OS between the two arms: 13.4 versus 12.1 months, HR 0.92 (95% CI 0.77–1.11).

The very recently published 5-year OS update of the Keynote-001 study (phase 1, pembrolizumab 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks in treatment-naïve (18%) or previously treated (82%) NSCLC patients) proved the potential of pembrolizumab in inducing durable antitumor activity for a subset of patients without new or late-onset toxicity [23]. With longer follow-up, pembrolizumab showed a 5-year OS rate of 23.2% across all PD-L1 strata and of 29.6% for patients with PD-L1 expression ≥ 50%. Despite the limited number of patients and the absence of

a comparator arm, these results contrast remarkably with the historical 5-year OS rate of 5.5% reported in advanced NSCLC treated with ChT only.

2.2 Atezolizumab (Anti-PD-L1)

The IMpower-110 trial randomized 572 treatment-naïve stage IV NSCLC patients, with any tumor histology, no EGFR or ALK alterations and a PD-L1 level of ≥ 1% on tumor cells (TCs) or immune cells (ICs) to receive either atezolizumab (1200 mg every 3 weeks) or up to six cycles of platinum-based, histology-dependent ChT with maintenance pemetrexed therapy in the non-squamous population for eligible patients. Crossover at progression was not permitted by protocol. Three primary populations were analyzed with OS as primary endpoint: Group 1: TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1+; group 2: TC2/3 or IC2/3 = TC ≥ 5% or IC ≥ 5% PD-L1+; group 3: TC1/2/3 or IC1/2/3 = TC ≥ 1% or IC ≥ 1% PD-L1+. For patients treated with atezolizumab, median OS was 20.2 months compared to 13.1 months for patients treated with ChT HR 0.59 (95% CI 0.40–0.89, $P = 0.01$). In an interim analysis presented at the 2019 annual European Society for Medical Oncology (ESMO) meeting, the study only met its primary endpoint in group 1 (TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1+), demonstrating a longer OS (20.2 vs. 13.1 months, HR 0.59, 95% CI 0.40–0.89, $P = 0.0106$) for patients treated with atezolizumab. PFS in group 1 was 8.1 versus 5.0 months (HR 0.63, 95% CI 0.45–0.88; $P = 0.007$) and ORR 38.3% versus 28.6% in favor of atezolizumab [24]. No new or unexpected safety signals appeared. Final results with longer follow-up are awaited.

2.3 Nivolumab (Anti-PD-1)

Nivolumab was evaluated in the phase 3 CheckMate-026 study. Patients with stage IV or recurrent NSCLC and a PD-L1 expression of ≥ 1% were randomized (1:1) to nivolumab or platinum-based ChT [25]. Patients receiving ChT could cross over to nivolumab at progression. While the inclusion criterion was a PD-L1 expression of ≥ 1%, the efficacy analysis was performed in the PD-L1 ≥5% population. The study did not meet its primary end-point of PFS prolongation, showing a PFS (4.2 vs. 5.9 months, HR 1.15 (95% CI 0.91–1.45, $P = 0.25$) and OS (14.4 vs. 13.2 months, HR 1.02 (95% CI 0.80–1.30) for nivolumab and ChT, respectively. Additionally, in a post hoc analysis, nivolumab did not show an OS benefit in patients with a PD-L1 expression of ≥50% (HR 1.07), which cannot be fully explained, but might originate from an imbalance of patients' baseline characteristics in the different treatment arms [25].

The Keynote-024 study provides evidence that pembrolizumab monotherapy is an appropriate treatment choice for fit patients with tumors harboring a PD-L1 expression of ≥ 50%, irrespective of age and tumor histology [7, 18]. Furthermore, the recently presented interim analysis of the IMpower-110 trial, demonstrating a significant OS benefit of atezolizumab over ChT in patients with TC3/IC3, suggests atezolizumab could be an additional valid front-line treatment in this setting [24]. The Keynote-042 trial demonstrated that, in patients with a TPS of 1–49%, first-line pembrolizumab monotherapy was not superior to platinum-based ChT, and therefore a ChT-CPI combination may represent the preferred treatment approach for these patients.

In patients with a high PD-L1 expression and aggressive, rapidly progressive disease with an urgent need to palliate symptoms, a ChT-CPI combination is another valid treatment option after careful evaluation of the patient's comorbidities and preferences. CPI resistance mutations like STK11, LKB1, and KEAP1 are evolving biomarkers that might help physicians selecting the best treatment approach in patients harboring tumors with high PD-L1 expression. The question remains about the magnitude of clinical benefit for patients with a PD-L1 expression ≥ 50% in adding ChT to a CPI or giving a CPI-CPI doublet regimen. Cross-trial comparisons between Keynote-024 and the PD-L1-high subgroup of Keynote-189 show comparable outcomes between ChT-CPI and CPI alone (1-year OS rate of about 70% in each trial). Regarding OS, the ChT-free regimen with ipilimumab plus nivolumab proved to be superior over ChT in PD-L1 positive patients [26]. The efficacy of nivolumab plus ipilimumab was seen independently on any biomarker, indicating the urgent need of appropriate selection factors.

In the absence of direct comparative data, CPI monotherapy seems to be the preferred regimen over ChT-CPI or CPI-doublet treatment for NSCLC patients with a PD-L1 expression ≥ 50% and certainly for patients with a PD-L1 expression ≥ 90% [22], given similar efficacy, better tolerability, and reserving platinum-based ChT as a sequential treatment option at progression.

Table 1 summarizes the efficacy and safety outcomes of first-line CPI monotherapy regimens in advanced NSCLC.

3 Anti-PD-(L)1 plus Chemotherapy (ChT) Combinations

3.1 Pembrolizumab (Anti-PD-1) plus Platinum/Pemetrexed

Pembrolizumab in combination with platinum-pemetrexed ChT was investigated in Keynote-189 [10]. Patients unselected for PD-L1 with non-squamous, stage IV NSCLC without sensitizing EGFR mutation or ALK translocation, were randomized (2:1) to pembrolizumab or placebo plus platinum-pemetrexed. A recently presented updated analysis

confirmed a longer OS (22.0 vs. 10.7 months, HR 0.56, 95% CI 0.45–0.70, $P < 0.00001$) and PFS (9.0 vs. 4.9 months, HR 0.48, 95% CI 0.40–0.58, $P < 0.00001$) for the ChT-CPI arm. ORR was also higher (62.1% vs. 24.3%) in the combination arm. Improved OS was observed across all PD-L1 subgroups (TPS < 1%, ≥ 1%, 1–49%, and ≥ 50%). The OS benefit was observed with similar HRs in patients harboring tumors with high (≥ 50%) PD-L1 expression: HR 0.59 (95% CI 0.39–0.88) and was also significantly longer in patients harboring tumors with a TPS of 1–49% and ≤ 1%, HR 0.62 (95% CI 0.36–0.73) and 0.52 (95% CI 0.36–0.74), respectively. PFS was also longer in all PD-L1 strata with an increasing PFS prolongation benefit, with higher PD-L1 expression: ≥ 50%, HR 0.36 (95% CI 0.26–0.51), 1–49%, HR 0.51 (95% CI 0.36–0.73) and ≤ 1%, HR 0.64 (95% CI 0.47–0.89) [27]. ORR was 47.6% versus 18.9% (TPS < 1%) and 61.4% versus 22.9% (TPS ≥ 50%) for ChT-CPI and ChT, respectively [10]. PFS2 (time of randomization with first-line treatment until progression on second-line treatment) was also significantly longer (17.0 vs. 9.0 months) in the ChT-CPI group across all PD-L1 subgroups (HR 0.49, 95% CI 0.40–0.59, $P < 0.00001$) [27], leading to the conclusion that pembrolizumab given in the first-line setting, within the Keynote-189 regimen, maximizes clinical outcomes for NSCLC patients. Adverse events leading to death were seen in 6.7% and 5.9% in the CPI-ChT-combination and the ChT-only groups, respectively. In general, ChT-CPI was reasonably well tolerated; however, immune-related adverse events of any grade were twice as common with ChT-CPI compared to ChT only (22.7% vs. 11.9). In the investigational arm a higher rate of any grade nephritis (1.7% vs. 0%) any grade acute kidney injury (5.2% vs. 0.5%) and any grade pneumonitis (4.4% vs. 2.5%) was reported. As expected, severe (≥ grade 3) immune-related adverse events were more common in the CPI combination: Hypothyroidism (0.5% vs. 0%), colitis (0.7% vs. 0%), hepatitis (1% vs. 0%), and pancreatitis (0.5% vs. 0%). Of note, three patients died of CPI-associated pneumonitis in the investigational arm. Patients who received ChT-CPI also had a higher (13.8% vs. 7.9%) treatment-related discontinuation rate. Seventy-five percent of patients were treated with carboplatin but notably there was similar OS, PFS, and ORR for carboplatin and cisplatin as a backbone in the ChT-CPI arm. A post hoc analysis evaluating patients with liver metastases ($n = 115$; 18%) (this was not a stratification factor) and stable brain metastases ($n = 108$; 17.5%) confirmed better outcomes for the investigational arm. The median OS was 12.6 versus 6.6 months (HR 0.62, 95% CI 0.39–0.98) in the subgroup with liver metastases and 19.2 versus 7.5 months (HR 0.41, 95% CI 0.24–0.67) in the subgroup with brain metastases [28]. These results highlight that the ChT-CPI therapy may also be beneficial in these historically poor prognostic groups.

3.2 Pembrolizumab (Anti-PD-1) plus (Nab-) Paclitaxel/Carboplatin

Combination ChT-CPI was evaluated in squamous NSCLC patients in the phase 3 Keynote-407 trial. Patients with stage IV disease ($n = 559$), regardless of PD-L1 expression, were randomized (1:1) to pembrolizumab/placebo plus carboplatin and paclitaxel or nab-paclitaxel. OS and PFS were longer with the ChT-CPI regimen [9]. Updated survival analyses showed an OS of 17.1 versus 11.6 months (HR 0.71, 95% CI 0.58–0.88, $P < 0.001$) and PFS of 8.0 versus 5.1 months (HR 0.57, 95% CI 0.47–0.69, $P < 0.0001$) [29]. ORR was 62.6% versus 38.4%. PFS2 was significantly longer in the ChT-CPI arm (13.8 vs. 9.1 months, HR 0.59, 95% CI 0.49– 0.72). The OS, PFS, and PFS2 benefit was evident in all investigated PD-L1 strata (TPS < 1%, 1–49%, and ≥ 50%) with a more prominent PFS benefit in subgroups with a higher PD-L1 expression. The incidence of grade ≥ 3 treatment-related adverse events was similar (69.8% vs. 68.2%) between the two arms [29]. There was no difference in OS, PFS, and ORR according to the chosen taxane (paclitaxel vs. nab-paclitaxel) [30].

3.3 Atezolizumab (Anti-PD-L1) plus Carboplatin/ Paclitaxel and Bevacizumab

Atezolizumab was initially investigated in combination with carboplatin/paclitaxel in the phase 3 IMpower-150 study. 1,202 metastatic non-squamous patients were randomized (1:1:1) to receive atezolizumab plus carboplatin plus paclitaxel (ACP), bevacizumab plus carboplatin plus paclitaxel (BCP), or atezolizumab plus BCP (ABCP), followed by maintenance atezolizumab, bevacizumab, or both [14]. Patients were enrolled regardless of PD-L1 status and those with a sensitizing EGFR mutation or ALK translocation were eligible only after failure or toxicity of at least one prior tyrosine kinase inhibitor (TKI) therapy. Ninety-one (7.5%) EGFR-mutant patients and 40 (3.3%) patients with ALK translocations were included. The two primary end-points were investigator-assessed PFS in the intention-to-treat (ITT), wild type (WT) population and OS in the ITT population. In the WT population, median PFS was longer (8.3 vs. 6.8 months, HR 0.62 (95% CI 0.52–0.74, $P < 0.001$) in the ABCP group than the BCP group; PFS was also longer in those with sensitizing EGFR mutations or ALK translocations, 9.7 versus 6.1 months, HR 0.59 (95% CI 0.37–0.94) and in the entire ITT population. PFS benefit was demonstrated across PD-L1 stratification and in key subgroups including baseline liver metastases (stratification factor) and patients with KRAS mutations [14]. Median OS in the WT population was improved with the addition of atezolizumab, (19.2 vs. 14.7 months in the BCP group, HR 0.78, 95% CI 0.64–0.96, $P = 0.02$). Consistent benefit in OS

Table 1 First-line monotherapy checkpoint inhibitor treatment regimens for advanced NSCLC

Study name	Primary endpoint (s)	Treatment arms	PFS (mths)	Hazard ratio (95% CI)	*P* value	OS (mths)	Hazard ratio (95% CI)	*P* value	Patients receiving IO at progression (%)	Grade 3-5 toxicity (%)	Treatment-related discount rate (%)
KEYNOTE-024	PFS	Pembrolizumab (PD-L1 ≥50%)	10.3	0.50 (0.37–0.68)	$P < 0.001$	30.2	0.63 (0.47–0.86)	$P = 0.02$	43.7	26.6	7.1
		ChT[&] (PD-L1 ≥50%)	6.0			14.2				53.3	10.7
IMpower-110	OS	Atezolizumab (PD-L1 ≥1%)	8.1 (TC3/IC3)[%]	0.63 (0.45–0.88)	$P = 0.007$	20.2 (TC3/IC3)[%]	0.59 (0.40–0.89)	$P = 0.01$	On study: no crossover permitted Off study: 28.9	12.9	6.3
			7.2 (TC2/3 or IC2/3) [%]	0.67 (0.52–0.88)	$P = 0.003$	18.2 TC2/3 or IC2/3) [%]	0.72 (0.52–0.99)	$P = 0.04$			
			5.7 TC1/2/3 or IC1/2/3) [%]	0.77 (0.63–0.94)	$P = 0.003$	17.5 (TC1/2/3 or IC1/2/3) [%]	0.83 (0.65–1.07)	$P = 0.14$			
		ChT[&] (PD-L1 ≥1%)	5.0 (TC3/IC3)[%]			13.1 (TC3/IC3)[%]				44.1	16.3
			5.5 TC2/3 or IC2/3) [%]			14.9 TC2/3 or IC2/3) [%]					
			5.5 (TC1/2/3 or IC1/2/3) [%]			14.1 (TC1/2/3 or IC1/2/3) [%]					
KEYNOTE-042	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	On study: no crossover permitted Off study: 20	17.8	9
			6.2 (PD-L1≥20%)	0.94 (0.80–1.11)	N/R	17.7 (PD–L1≥20%)	0.77 (0.64–0.92)	*P*=0.002			
			5.4 (PD-L1≥1%)	1.07 (0.94–1.21)	N/R	16.7 (PD–L1≥1%)	0.81 (0.71–0.93)	*P*=0.018			
						13.4 (PD–L1 1–49%)	0.92 (0.77–1.11)	N/R			
		ChT[&] (PD-L1 ≥1%)	6.4 (PD-L1≥50%)			12.2 (PD–L1≥50%)				41	9.4
			6.6 (PD-L1≥20%)			13.0 (PD–L1≥20%)					
			6.5 (PD-L1≥1%)			12.1 (PD–L1≥1%)					
						12.1 (PD–L1 1–49%)					
CheckMate-026	PFS	Nivolumab (PD-L1 ≥1%)	4.2	1.15 (0.91–1.45)	P=0.25	14.4	1.02 (0.80–1.30)	N/R	60.0	18.0	10
		ChT[&] (PD-L1 ≥1%)	5.9			13.2				51.0	13

PFS progression-free survival, *OS* overall survival, *N/R* not reported [&]Platinum-based chemotherapy [#]Grade 3-4 AE [%]TC (tumor cells)3/IC (Immune cells)3 = TC ≥ 50%/IC ≥ 10% PD-L1+; TC2/3 or IC2/3 = TC ≥ 5% or IC ≥ 5% PD-L1+; TC1/2/3 or IC1/2/3 = TC ≥ 1% or IC ≥ 1% PD-L1+

was seen across all PD-L1 subgroups treated with ABCP versus BCP. In the subgroup analysis, longer median OS was reported in the patients with baseline liver metastases treated with ABCP ($n = 52$) versus BCP ($n = 57$): 13.3 versus 9.4 months (HR 0.52, 95% CI 0.33–0.82) [31]. In patients with a sensitizing EGFR mutation who had previously received a TKI ($n = 50$), there was a trend towards improved OS [not estimable vs 17.5 months, HR 0.39 95% CI 0.14–1.07)] with ABCP vs BCP. In patients with a sensitizing EGFR mutation who had previously received a TKI ($n = 50$), there was a trend towards improved OS [not estimable vs. 17.5 months, HR 0.39 (95% CI 0.14–1.07)] with ABCP versus BCP. As multiple previous studies including meta-analyses showed no benefit of single-agent CPI treatment in patients with EGFR-mutant NSCLC, the addition of bevacizumab to a CPI might add clinical efficacy in this population, but further prospective confirmatory data are required in this setting [31]. The safety profile was acceptable and baseline QoL/function was maintained throughout [32, 33].

3.4 Atezolizumab (Anti-PD-L1) plus (Nab)-Paclitaxel/Carboplatin

The IMpower-130 regimen has been clarified and the information about how many patients receiving pemetrexed switch maintenance therapy has been added: "Atezolizumab with or without carboplatin plus nab-paclitaxel was investigated in the phase 3 IMpower-130 study. Non-squamous patients ($n = 723$) were randomized (2:1) between ChT-CPI ($n = 451$) or ChT alone ($n = 228$). In both arms, platinum-based ChT was given for four to six cycles. Atezolizumab was used as maintenance in the ChT-CPI group and switch maintenance pemetrexed was available in the control arm. In total 21% of patients treated in the control arm had switch maintenance pemetrexed therapy after the induction ChT [11]. Patients were enrolled regardless of PD-L1 status and those with sensitizing EGFR mutations or ALK translocations were allowed only if progression occurred or unacceptable toxicity after prior TKI therapy. Stratification was performed according to PD-L1 expression, baseline liver metastases, and EGFR/ALK status. Co-primary endpoints were investigator-assessed PFS and OS in the ITT WT population. The addition of atezolizumab improved PFS (7.0 vs. 5.5 months, HR 0.64, 95% CI 0.54–0.77, $P < 0.0001$) and OS (18.6 vs. 13.9 months, HR 0.79, 95% CI 0.64–0.98, $P = 0.033$) in the ITT population. Improved PFS was identified across PD-L1 subgroups in the atezolizumab group; however, OS benefit was not significant across the pre-defined subgroups, possibly due to a high (59.2%) crossover rate. No difference was identified in PFS (HR 0.75, 95% CI 0.36–1.54) or OS (HR 0.98, 95% CI 0.41–2.31) for patients with baseline liver metastases or EGFR/ALK mutation treated with atezolizumab [11].

The IMpower131 study randomized unselected patients with advanced squamous NSCLC to receive atezolizumab plus carboplatin/paclitaxel (CP), atezolizumab plus carboplatin/nab-paclitaxel (CnP), or CnP only. Stratification was performed according to PD-L1 expression and presence of baseline liver metastasis [12]. PFS and OS were co-primary endpoints assessed in the ITT population. CnP +/− atezolizumab was the initial test setting. Updated final survival results showed that, in the PD-L1 unselected ITT population, the addition of atezolizumab to CnP did not improve OS (14.2 vs. 13.5 months, HR 0.88, 95% CI 0.73–1.0, $P = 0.16$). In the subgroup of patients with a TC3/IC3, OS was significantly higher (23.4 vs. 10.2 months, HR 0.48, 95% CI 0.29–0.81) in the atezolizumab/CnP group [34]. No new safety signals were identified with the combination.

3.5 Atezolizumab (Anti-PD-L1) plus Pemetrexed/Platinum

The IMpower-132 study evaluated atezolizumab in combination with platinum/pemetrexed in stage IV non-squamous NSCLC patients without EGFR or ALK molecular aberration and irrespective of PD-L1 status. Patients were randomized between atezolizumab plus ChT (carboplatin or cisplatin/pemetrexed) followed by atezolizumab and pemetrexed maintenance or platinum/pemetrexed alone. Co-primary endpoints were investigator assessed PFS and OS [13]. PFS was longer (7.6 vs. 5.2 months; HR 0.60, 95% CI 0.49–0.72, $P < 0.0001$) in the chemo-CPI arm. A PFS benefit with atezolizumab was demonstrated with both carboplatin and cisplatin but was not seen in patients with baseline liver metastases (4.4 vs. 4.0 months; HR 0.77, 95% CI 0.47–1.25). In an exploratory analysis the correlation of PD-L1 expression level (high = TC3 or IC3, low = TC1/2 or IC1/2 and negative = TC0 and IC0) and PFS has been investigated. While in the PD-L1 high and the PD-L1 negative group a marked PFS benefit was seen in favor of the CPI-ChT combination (PD-L1 high: HR 0.46, 95% CI 0.22–0.69; PD-L1 negative: HR 0.45, 95% CI 0.31–0.64) there was no difference in patients with tumors with a low PD-L1 expression (PD-L1 low: HR 0.80, 95% CI 0.56–0.1.16), which biologically is not obviously explained. At the interim analysis, significance was not met for an OS benefit with atezolizumab plus ChT (HR 0.81, 95% CI 0.64–1.03, $P = 0.079$) [13].

Keynote-189 showed a significant improvement in PFS and OS across all PD-L1 subgroups for pembrolizumab plus platinum/pemetrexed. Despite a slightly higher incidence of grade 3–5 adverse events in the investigational arm, the QoL analysis in Keynote-189 showed an improved tolerability and better symptom control compared to ChT [35]. The 1.7% rate of nephritis and 5.2% for acute kidney injury with pembrolizumab plus ChT requires careful monitoring of the patient's renal function. Platinum/pemetrexed plus atezolizumab (Impower-132 regimen) showed an improvement in PFS

(HR of 0.6) over ChT alone. At the interim analysis, there was also a longer OS which did not cross the boundaries of significance [13]. The benefit was indeed seen irrespectively of PD-L1 expression, age, smoking status, and ethnicity, but without statistically significant OS benefit of atezolizumab plus platinum-pemetrexed there are better treatment options to take into account. Atezolizumab plus bevacizumab/carboplatin/paclitaxel (IMpower-150 regimen) resulted in a significant improvement of PFS and OS over ChT alone with a high ORR (63.5%) across PD-L1 strata in patients with and without liver metastases at baseline [36]. In Impower-130, the addition of atezolizumab to carboplatin/nab-paclitaxel improved both PFS (HR 0.64) and OS (HR 0.79) compared to ChT, although OS improvement did not cross the boundaries of significance. This is potentially due to a high (59.2%) crossover rate from ChT to CPI at progression [11].

The addition of a CPI to first-line platinum-based ChT improved efficacy in patients with squamous cell lung cancers across several studies. In Keynote-407, the combination of pembrolizumab plus carboplatin and (nab-)paclitaxel led to an unprecedented PFS (HR 0.56) and OS (HR 0.64) improvement over ChT, irrespective of PD-L1 expression [37]. Carboplatin/nab-paclitaxel plus atezolizumab evaluated in IMpower-131 demonstrated a longer PFS (HR 0.71) over ChT in the first interim analysis, however, the benefit did not translate into longer OS [34]. In patients harboring tumors with a PD-L1 expression of 1–49%, the ChT-CPI arm seems to derive a detrimental effect (HR 1.34), which is difficult to explain. The conflicting OS results from Keynote-407 and IMpower-131 indicate that different CPIs might not be interchangeable. Furthermore, in Keynote-407, approximately 60% of patients received paclitaxel and 40% nab-paclitaxel, whereas in the IMpower-131 study all patients were treated with nab-paclitaxel, which may explain the potential impact on efficacy. Additionally, the individual development of anti-drug antibodies (ADAs) against different CPIs might explain variable outcomes and toxicity profiles by choosing different CPIs [38]. After drug exposure ADAs are able to reduce drug availability leading to a possible decrease in antitumor activity and deterioration of clinical outcomes [39].

Table 2 summarizes the efficacy and safety outcomes of first-line CPI plus ChT combination treatments in advanced NSCLC.

4 Anti-PD-(L)1 plus Anti-CTLA-4 Combination

4.1 Ipilimumab (Anti-CTLA-4) plus Nivolumab (Anti-PD-1)

The phase 3 study CheckMate-227 addressed multiple questions regarding the role of first-line nivolumab and nivolumab-based regimens in advanced NSCLC without sensitizing alterations, irrespective of tumor histology. Patients with a PD-L1 expression of ≥ 1% ($n = 1189$) were enrolled in Part 1a of the study and randomized in a 1:1:1 ratio to receive nivolumab plus low-dose ipilimumab ($n = 396$) or histology-based ChT ($n = 397$) or nivolumab monotherapy ($n = 396$). Patients with < 1% PD-L1 expression ($n = 550$) were enrolled in Part 1b of the study and randomized 1:1:1 to either receive nivolumab plus ipilimumab ($n = 187$), ChT ($n = 186$), or ChT plus nivolumab ($n = 177$) [15]. The independent co-primary endpoints were PFS in patients harboring tumors with a high (≥ 10 mutations per mega base, mut/Mb) tumor-mutational burden (TMB), irrespective of PD-L1 expression level and OS in patients with tumors expressing PD-L1 ≥ 1% in the nivolumab plus ipilimumab arm compared to ChT. Whilst the study was ongoing, the trial protocol was amended to add the co-primary endpoint of PFS in TMB-high patients on the basis of emerging data on TMB. The cut-off of ≥ 10 mut/Mb was chosen in accordance with the results of CheckMate-568 [40]. Hellmann et al. reported initial results for PFS in the TMB-high population treated with nivolumab/ipilimumab versus ChT [15]. Out of the 1739 randomly assigned patients, 94.8% had tumor samples available for TMB assessment. 1004 patients (57.7%) had valid data for TMB-based efficacy analyses and 444 (44.2%) had at least 10 mut/Mb. Of those patients, 139 were treated with ipilimumab plus nivolumab and 160 patients with histology-based ChT. PFS was longer (7.2 vs. 5.4 months, HR 0.58, 95% CI 0.41–0.81; $P = 0.0002$) in the CPI-doublet compared to the ChT arm. The PFS benefit was consistent irrespective of PD-L1 expression and tumor histology. Updated results did not show a difference in OS when patients were stratified by TMB. OS in the TMB-high population was 23.03 versus 16.72 months (HR 0.77; 95% CI 0.56–1.06) for the CPI doublet and ChT, respectively. OS in the TMB-low population was 18.2 versus 12.42 months (HR 0.78; 95% CI 0.61–1.00) for CPI doublet and ChT, respectively [41].

Results of the second co-primary endpoint of OS in patients with PD-L1 ≥ 1% treated with nivolumab plus ipilimumab versus ChT were recently reported (part 1b). Patients treated with nivolumab plus ipilimumab demonstrated longer OS (17.1 vs. 14.9 months, HR 0.79, 97.72% CI 0.65–0.96, $P = 0.007$) over ChT [26]. An exploratory analysis investigated the role of PD-L1 expression levels (≥ 50% vs. 1–49%) as a potential predictive biomarker. In patients with PD-L1 expression of 1–49%, the nivolumab-ipilimumab arm did not achieve a longer OS compared to the other treatment arms, suggesting that the benefit seen in the ITT was mostly driven by patients with PD-L1 expression ≥ 50%. Of note, the median duration of response was 23.2 months with nivolumab plus ipilimumab versus 6.2 months with ChT. Of patients with a treatment response under

Table 2 First-line checkpoint inhibitor monotherapy plus chemotherapy combination regimens for advanced NSCLC

Study name	Primary endpoint(s)	Treatment arms	PFS (mths)	Hazard ratio (95% CI)	*P* value	OS (mths)	Hazard ratio (95% CI)	*P* value	Patients receiving IO at progression (%)	Grade 3-5 toxicity (%)	Treatment-related discount rate (%)
KEYNOTE-189	PFS OS	Pembrolizumab plus ChT[&] (non squamous, any PD-L1)	9.0	0.48 (0.40–0.58)	$P < 0.001$	22.0	0.56 (0.45–0.70)	$P < 0.001$	32.5	67.2	13.8
		ChT[&] (non squamous, any PD-L1)	4.9			10.7				65.8	7.9
KEYNOTE-407	PFS OS	Pembrolizumab plus ChT[&] (squamous, any PD-L1)	8.0	0.57 (0.47–0.69)	$P < 0.001$	17.1	0.71 (0.58–0.88)	$P < 0.001$	42.5	69.8	13.3
		ChT[&] (squamous, any PD-L1)	5.1			11.6				68.2	6.4
IMpower-130	PFS OS	Atezolizumab plus ChT[&] (non squamous, any PD-L1)	7.0	0.64 (0.54–0.77)	$P < 0.0001$	18.6	0.79 (0.64–0.89)	$P = 0.033$	40.8	73.2[#]	26.4
		ChT[&] (non squamous, any PD-L1)	5.5			13.9				60.3[#]	22
IMpower-131	PFS OS	Atezolizumab plus ChT[&] (squamous, any PD-L1)	6.3	0.71 (0.60–0.85)	$P = 0.0001$	14.2	0.88 (0.73–1.00)	$P = 0.16$	42.1	73.0[#]	29
		ChT[&] (squamous, any PD-L1)	5.6			13.5				66.0[#]	17
IMpower-132	PFS OS	Atezolizumab plus ChT[&] (non squamous, any PD-L1)	7.6	0.60 (0.49–0.72)	$P < 0.0001$	18.1	0.81 (0.64–1.03)	$P = 0.0797$	37.1	62[#]	24
		ChT[&] (non squamous, any PD-L1)	5.2			13.6				54[#]	18
IMpower-150	PFS OS	Atezolizumab plus Bevacizumab plus ChT[&] (non squamous)	8.3	0.62 (0.52–0.74)	$P < 0.001$	19.2	0.78 (0.64–0.69)	$P = 0.02$	31.7	55.7[#]	32.6
		Bevacizumab plus ChT[&] (non squamous)	6.8			14.7				47.7[#]	24.9

PFS progression-free survival, *OS* overall survival [&]Platinum-based chemotherapy [#]Grade 3-4 AE [%]TC (tumor cells)3/IC (Immune cells)3 = TC ≥ 50%/IC ≥ 10% PD-L1+; TC2/3 or IC2/3 = TC ≥ 5% or IC ≥ 5% PD-L1+; TC1/2/3 or IC1/2/3 = TC ≥ 1% or IC ≥ 1% PD-L1+

nivolumab-ipilimumab, half showed an ongoing treatment response at 2 years.

The authors also reported the results of an exploratory analysis in the PD-L1 negative population where OS was longer [17.2 vs. 12.2 months, HR 0.62 (95% CI 0.48–0.78)] in the nivolumab-ipilimumab arm versus ChT. This was not observed for nivolumab-ipilimumab versus nivolumab plus ChT (OS 17.2 versus 15.2 months, HR 0.78, 95% CI 0.60–1.02).

The incidence of grade 3–4 adverse events in the nivolumab-ipilimumab, ChT, and nivolumab monotherapy arm were 33%, 36%, and 19%, respectively. The incidence of any grade adverse events leading to treatment discontinuation was higher with nivolumab/ipilimumab (18%) than with ChT (9%) and nivolumab alone (12%), which makes the IO/IO combination a less favorable treatment option [26].

Results of part 2 of the CheckMate-227 trial were recently presented at the ESMO-IO congress. Part 2 investigated frontline nivolumab (360 mg every 3 weeks) plus histology-based ChT versus ChT in advanced NSCLC regardless of PD-L1 expression. The primary endpoint was OS in the non-squamous population. The study did not meet the primary endpoint, as OS was 18.8 and 15.6 months (HR 0.86, 95% CI 0.69–1.00, $P = 0.18$) for nivolumab plus ChT and ChT, respectively. In all randomized patients and in the squamous-cell population (secondary endpoints) the median OS was 18.3 versus 14.7 months (HR 0.81, 95% CI 0.67–0.97) and 18.3 versus 12.0 months (HR 0.69, 95% CI 0.50–0.97) for the combination arm and ChT arm, respectively. Objective response rates in the non-squamous, squamous, and the overall population were 48.1 versus 29.3%, 59.8 versus 32.4%, and 51.5 versus 30.2%, respectively favoring the ChT-IO combination [42].

Irrespective of tumor histology, CheckMate-227 investigated nivolumab plus ipilimumab in the first-line setting for advanced NSCLC. The design of CheckMate-227 has several limitations, which need to be kept in mind when interpreting the data. Firstly, in PD-L1-positive patients, nivolumab/ipilimumab was compared to ChT and nivolumab but not to a IO-ChT triplet, which is one of the current standards of care for patients with advanced NSCLC. Secondly, the trial was designed to formally assess OS in PD-L1 positive patients only. The assessment of PD-L1 negative patients randomized to nivolumab/ipilimumab versus ChT versus nivolumab/ChT was not a primary endpoint but a prespecified exploratory analysis. The study demonstrated longer OS (HR 0.79) over ChT in the PD-L1 ≥ 1% population. Part 2 showed no OS benefit of nivolumab plus Cht versus ChT in the non-squamous population.

4.2 Durvalumab (Anti-PD-L1) plus Tremelimumab (Anti-CTLA-4)

The MYSTIC trial enrolled 1118 patients with metastatic NSCLC who were randomized to receive durvalumab (D) 4-weekly until disease progression, durvalumab 4-weekly until disease progression plus tremelimumab 4-weekly for four cycles (D+T) or platinum-based ChT for up to six cycles [16]. Primary endpoints were OS for D versus ChT, and OS and PFS for D+T versus ChT in patients with a PD-L1 expression ≥ 25% in tumor cells. A total of 488 patients (44%) had a PD-L1 expression of ≥ 25%. Durvalumab alone or with tremelimumab failed to improve PFS and OS compared to ChT. Durvalumab alone achieved a longer OS (16.3 vs. 12.9 months) than ChT, but this did not cross the boundaries for statistical significance (HR 0.79, 97.5% CI 0.56–1.02). Patients treated with D+T showed an OS of 11.9 months leading to an HR versus ChT of 0.85, 98% CI 0.61–1.17. D+T led to a PFS of 3.9 months versus 5.4 months with ChT (HR 1.05, 99.% CI 0.72–1.53). An exploratory analysis adjusting for the effect of post-study immunotherapy on OS concluded that a high proportion in the ChT arm received subsequent IO as a possible confounding factor. The adjusted OS was higher (16.2 vs. 11.5 months, 95% CI 0.49–0.90, $P = 0.002$) in patients with PD-L1 ≥ 25% treated with D compared to ChT. An exploratory analysis evaluated survival according to TMB in blood (bTMB) and tissue (tTMB). Patients with a high bTMB (≥ 20 mut/Mb) and tTMB (≥ 10 mut/Mb) achieved a longer OS in favor of D+T over ChT (bTMB ≥ 20 mut/Mb: OS 21.9 vs. 10.0 months, HR 0.49, 95% CI 0.32–0.74; tTMB ≥ 10 mut/Mb: OS 16.6 vs. 11.9 months, HR 0.72, 95% CI 0.48–1.09) [43]. The incidence of grade 3–4 treatment-related adverse events was 33.8% versus 14.6% versus 22.1% for D+T, D, and ChT, respectively [16]. As PD-L1 expression emerged as a predictive biomarker while the trial was ongoing, the investigators decided to only include patients with a PD-L1 expression of ≥ 25% representing only 44% of the initially randomized population, leading to a significant loss of statistical power. Additionally, in various trials investigating the MYSTIC-trial combination, no significant signal could have been generated, in particular not for the addition of tremelimumab to durvalumab. Therefore, multiple potentially also drug-related reasons may have caused the failure of the trial.

5 Anti-PD-(L)1 plus Anti-CTLA-4 Combination plus ChT

5.1 Ipilimumab (Anti-CTLA-4) plus Nivolumab (Anti-PD-1) plus Two Cycles of Histology-Adapted ChT

In the phase 3 CheckMate 9LA trial 719 patients with treatment-naïve advanced NSCLC without oncogenic molecular abberation were randomized to either receive nivolumab (360 mg intravenously 3-weekly up to 2 years) plus ipilimumab (1 mg/kg up to 2 years) together with two cycles of histology-adapted ChT or four cycles of histology-adapted ChT. Pemetrexed maintenance was allowed in patients with tumors harboring a non-squamous histology. OS was 14.1 months versus 10.7 months in favor of the CPI-containing regimen (HR 0.69; 95% CI 0.55–0.87, $P = 0.0006$) corresponding to a 1-year OS rate of 63% versus 47%. OS benefit was consistent in all investigated PD-L1 strata (< 1%, ≥ 1%, 1–49%, > 50%) and independent of histology. PFS was also improved in the investigational arm, corresponding to a HR of 0.68 (95% CI 0.57–0.82), referring to a 1-year PFS rate of 33% versus 18% in favor of the CPI-containing regimen. Grade 3–4 adverse events were more common in the CPI-based arm: 47% versus 38%. The most common adverse events of any grade were: nausea, anemia, asthenia, and diarrhea. Nivolumab/ipilimumab plus two cycles of ChT seems to be an active new treatment option in the first-line setting for advanced NSCLC. However, one has to keep in mind that the comparator arm in CheckMate 9LA was ChT only, a control arm that does not reflect the current standard of care anymore, which is Cht plus a CPI. Furthermore, CPI doublets are an attractive approach when ChT and the corresponding toxicity with it can be spared.

Table 3 summarizes the efficacy and safety outcomes of first-line CPI doublet regimens in advanced NSCLC.

6 Discussion

Several first-line phase 3 clinical trials evaluating CPI have been presented over the last couple of years, increasing treatment options and reshaping the therapeutic strategy for patients with advanced NSCLC. Notably, within the variety of the recently reported CPI-based first-line regimens for advanced NSCLC, there is lack of a direct head-to-head comparison, and cross-trial evaluations must be performed with caution. Figure 1 summarizes potential therapy options for treatment-naïve advanced non-squamous NSCLC. Figure 2 summarizes potential therapy options for treatment-naïve advanced squamous NSCLC.

Although most of the CPI-based trials excluded patients harboring sensitizing alterations, the IMpower-130 (nab-paclitaxel/carboplatin plus atezolizumab) and IMpower-150 trial (atezolizumab/carboplatin/paclitaxel/bevacizumab) included EGFR- and ALK-positive NSCLC patients who failed at least one line of standard TKI therapy. The IMpower-130 trial did not show any PFS and OS improvement in the atezolizumab arm. The IMpower-150 trial demonstrated improved efficacy when atezolizumab was added to bevacizumab plus ChT. The quadruplet regimen resulted in an OS benefit (HR of 0.54) for EGFR- or ALK-positive patients questioning the potential of an anti-angiogenic agent in combination with ChT and IO for molecular-driven tumors. Due to the exploratory nature and small sample size of this analysis these data must be interpreted with caution. Several prospective trials in this setting are ongoing (NCT04099836, NCT04042558, NCT04245085, NCT03991403) and results are eagerly awaited. According to phase 2 data and meta-analytic investigations patients with EGFR-mutant or ALK-rearranged NSCLC, single-agent CPI therapy did not show a survival benefit, even in patients with a high PD-L1 expression [44, 45].

Bevacizumab might also play a role in patients with liver metastases. In the Impower-150 trial patients with liver metastases derived a survival benefit (HR 0.52; 95% CI 0.33–0.82), whilst this was not seen for patients with liver metastases treated with chemo-IO regimens not containing bevacizumab (IMpower-130, Impower-131, IMpower-131). The liver's microenvironment is known to contain immunosuppressive myeloid cells expressing VEGFR2. Targeting VEGFR2 on those cells, bevacizumab might overcome the local immune-suppression and increase the efficacy of a CPI in the liver [46, 47].

A recently presented post hoc subgroup analysis of Keynote-189 investigated the efficacy of pembrolizumab plus ChT in patients with liver or brain metastases at baseline and showed an OS improvement in these subgroups of patients too [28]. These results also strengthen the role of pembrolizumab plus ChT in these poor prognostic populations, with similar efficacy to the overall study population and without new safety signals.

All CPI-based first-line trials only allowed entry to patients with stable and/or treated brain metastases. The treatment approach for these patients remains challenging, as clinical outcome is poor. Bevacizumab showed encouraging efficacy with acceptable toxicity when combined with carboplatin/paclitaxel in patients with untreated brain metastasis in the BRAIN study [48]. Therefore, the addition of a CPI to that regimen might be a safe and effective option.

As all ChT-CPI combination studies were conducted with the standard full-dose ChT regimens, the question remains if

Table 3 First-line CPI-doublet regimens in advanced NSCLC

Study name	Primary endpoint (s)	Treatment arms	PFS (mths)	Hazard ratio (95% CI)	*P* value	OS (mths)	Hazard ratio (95% CI)	*P* value	Patients receiving IO at progression (%)	Grade 3–5 toxicity (%)	Treatment-related discount rate (%)
CheckMate-227	PFS in TMB-high patients (part 1a)	Ipilimumab plus Nivolumab (any PD-L1, high TMB)	7.2	0.58 (0.41–0.81)	$P = 0.0002$	23.0	0.78 (0.61–1.06)	N/R	30.0	31.2[#]	17.4
		ChT[&] (any PD-L1, high TMB)	5.4			16.7				36.1[#]	8.9
	OS in PD-L1 ≥1% patients (part 1b)	Ipilimumab plus Nivolumab (PD-L1 ≥1%)				17.7	0.79 (0.56–0.96)	$P = 0.007$		33[#]	18
		ChT[&] (PD-L1 ≥1%)				14.9				36[#]	9
MYSTIC	PFS OS	Durvalumab plus Tremelimumab (PD-L1≥25%)	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
		ChT[&] (PD-L1≥25%)	5.4			12.9				46.0[#]	15.1
	OS	Durvalumab (PD-L1≥25%)	4.7	0.87 (0.59–1.28)	$P = 0.324$	16.3	0.76 (0.56–1.01)	$P = 0.036$	39.5	40.4[#]	11.4
		ChT[&] (PD-L1≥25%)	5.4			12.9				46.0[#]	15.1
CheckMate 9LA	PFS OS	Nivolumab/Ipilimumab 2 cycles ChT[&]	6.7	0.68 (0.57–0.82)	N/R	14.1	0.69 (0.55–0.87)	$P = 0.0006$	N/R	47[#]	19
		4 cycles ChT[&]	5.0			10.7				38.0[#]	7

PFS progression-free survival, *OS* overall survival, *N/R* not reported [&]Platinum-based chemotherapy [#]Grade 3-4 AE [%]TC (tumor cells)3/IC (Immune cells)3 = TC ≥ 50%/IC ≥ 10% PD-L1+; TC2/3 or IC2/3 = TC ≥ 5% or IC ≥ 5% PD-L1+; TC1/2/3 or IC1/2/3 = TC ≥ 1% or IC ≥ 1% PD-L1+

a dose-reduced chemotherapy would still preserve the efficacy of a ChT-CPI combination with improved tolerability and accessibility of the treatment for a broader patient population. Additionally, there is a clear need for solid data answering the question if combined ChT-CPI is also safe and effective in patients with poor performance status (PS 2).

Predictive biomarkers beyond PD-L1 expression are needed to better select patients for CPI-based therapies and to maximize clinical outcomes. Tissue-based tumor mutational burden (TMB) seemed to be a promising biomarker in predicting benefit for patients treated with CPI. Several analyses proved TMB to be an independent predictor with no association with PD-L1 expression levels [25, 49]. Stratified based on TMB, several trials showed an association of improved PFS and ORR in lung cancer patients harboring tumors with a high TMB [15, 49–51]. So far, different TMB scoring systems have been investigated in several trials using Next-Generation-Sequencing (NGS), but there is still a lack of a harmonized methodology to measure and validate TMB. In CheckMate-026, an exploratory analysis showed that patients with high TMB (≥ 243 somatic mutations) tumors who received nivolumab had a longer PFS (9.7 vs. 5.8 months, HR 0.62; 95% CI 0.38–1.00) and higher ORR (47% vs. 28%). However, no difference in OS was found irrespective of TMB levels [25].

In an exploratory analysis of the MYSTIC trial, patients with a high blood-based TMB (bTMB) treated with durvalumab plus tremelimumab achieved a longer PFS and OS compared to CPI monotherapy or ChT [43]. The phase 2 trial CheckMate-568 (nivolumab/ipilimumab in advanced treatment-naïve NSCLC) established a cut-off of ≥ 10 mut/Mb (TMB-high) versus < 10 mut/Mb (TMB-low). This cut-off was also investigated in CheckMate-227. This trial initially showed a higher (13% vs. 43%) 1-year PFS rate in favor of nivolumab plus ipilimumab compared to ChT in TMB-high patients [15, 41]. However, in the recently published OS analysis, tissue TMB was not predictive for an OS benefit for nivolumab/ipilimumab versus ChT [26].

Exploratory analyses of Keynote-010 and Keynote-042 trials evaluated the impact of TMB on clinical outcomes. In both studies, TMB was associated with OS, PFS, and ORR for the pembrolizumab arms. However, TMB was not associated with outcomes for ChT in either study. Improvements in OS, PFS, and ORR were only observed for patients with high TMB (≥ 175 mutations per exome) receiving pembrolizumab [52]. Further exploratory analyses investigated the association of TMB and clinical outcomes in Keynote-21 (cohort C and G), Keynote-189, and Keynote-407 trials. TMB was not significantly associated with clinical efficacy of CPI-ChT or ChT alone, irrespective of tumor histology,

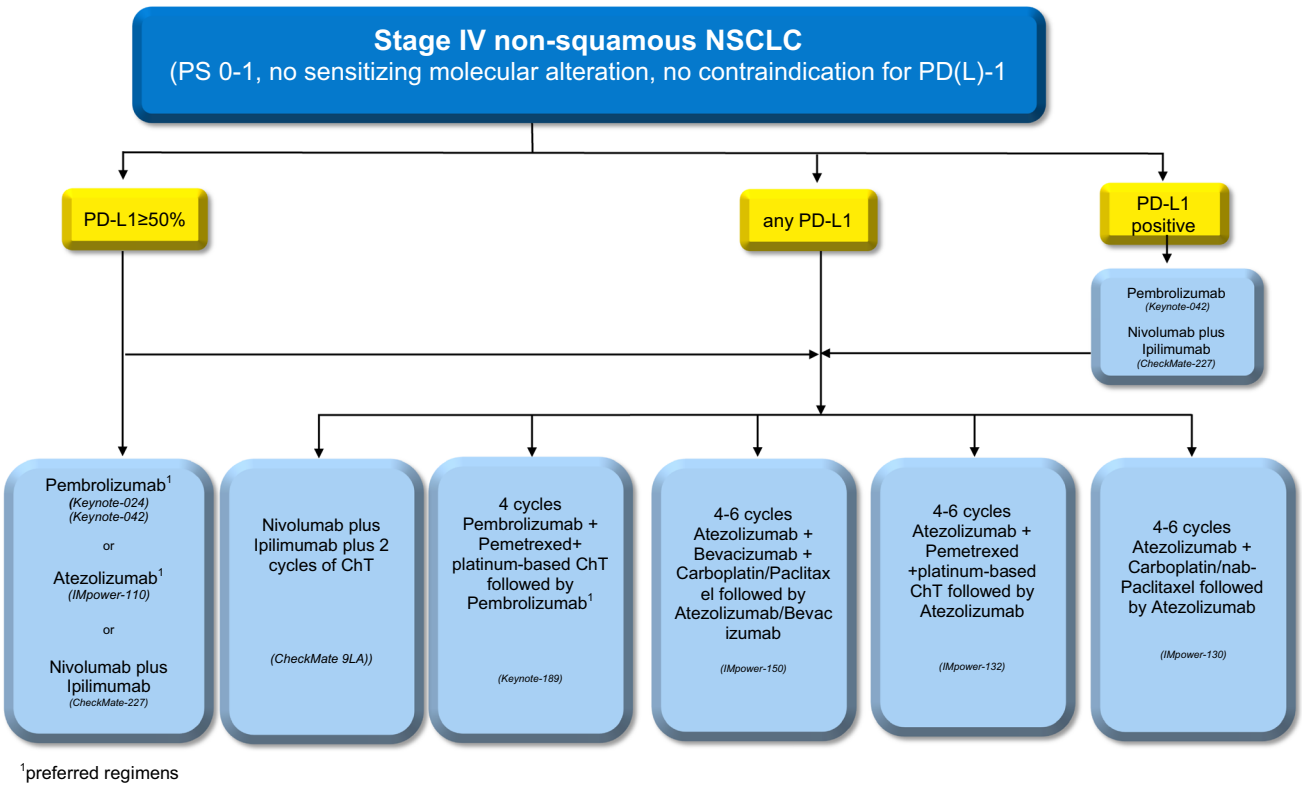

Fig. 1 CPI-based treatment first-line options for advanced non-squamous NSCLC

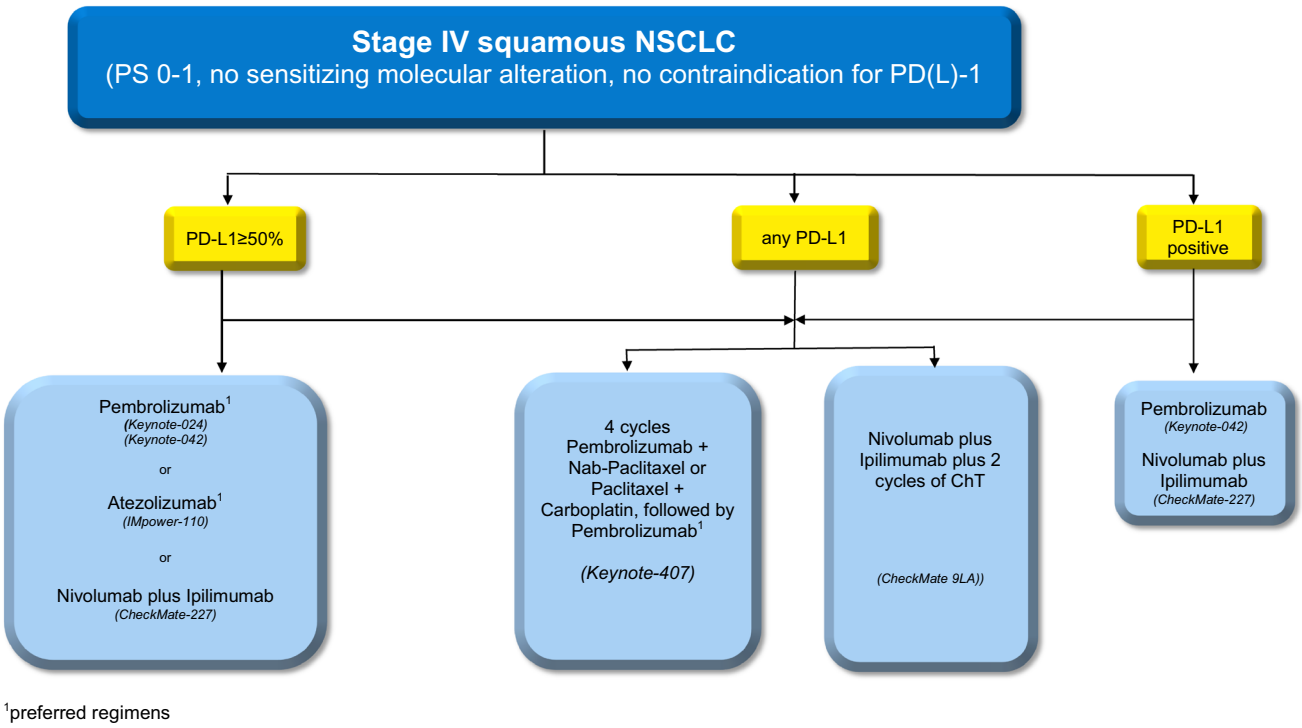

Fig. 2 CPI-based treatment first-line options for advanced squamous cell NSCLC

across all evaluated trials [52]. While TMB seemed to provide additional information in the pembrolizumab monotherapy studies regarding clinical benefit, TMB did not hold any predictive value in the pembrolizumab plus ChT or ipilimumab plus nivolumab combination studies. A better understanding of the potential role of TMB as a predictive biomarker is needed before it is used for decision making in clinical practice.

It is very important to bear in mind that all patients enrolled in the large phase 3 trials discussed above are highly selected and may not represent the patient population seen in daily clinical practice. For example, the screen failure rate for Keynote-407 and Keynote-024 was 28% and 75%, respectively. Additionally, the reviewed studies showed substantial heterogeneity in efficacy outcomes of their comparator arms, which directly impacts the degree of clinical benefit expressed as hazard ratios. The OS in the ChT arm of the Keynote-189 trial, for example, was lower than expected. On the other hand, the ChT comparator arm in IMpower-131 showed the highest efficacy ever demonstrated with that regimen. Furthermore, there are trials ongoing investigating CPI in special pouplations like those with pre-existing autoimmunity, PS2, HIV, etc. [53]. In addition, the high costs of CPI and especially the CPI combination treatments make those drugs not accessible in less developed countries.

In conclusion, CPI-based combination regimens represent the new standard of care for fit (PS 0–1) patients with advanced NSCLC in the absence of contraindications to CPI. It will be very important to report real-word data to assess the true efficacy and safety of these regimens in daily clinical practice.

Declarations

Conflict of interest Author RC has received honoraria and consultancy fees from AstraZeneca, Roche, MSD, and Bristol Myers Squibb. Author MR has received honoraria for lectures and consultancy fees from Abbvie, Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, Celgene, Merck, MSD, Novartis, Pfizer, and Roche. Authors CJA, HA, AO, and AD have no conflicts of interest.

Ethical standards This article meets all the ethical standards.

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