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Hot Topic

Choosing wisely first line immunotherapy in non-small cell lung cancer (NSCLC): what to add and what to leave out

C. Proto[a], R. Ferrara[a,*], D. Signorelli[a], G. Lo Russo[a], G. Galli[a], M. Imbimbo[a], A. Prelaj[a], N. Zilembo[a], M. Ganzinelli[a], L.M. Pallavicini[a], I. De Simone[b], M.P. Colombo[c], A. Sica[d,e], V. Torri[b], M.C. Garassino[a]

[a] Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[b] Methodology of Clinical Research Laboratory, Oncology Department, IRCCS Mario Negri Institute for Pharmacologic Research, Milan, Italy
[c] Department of Research, Molecular Immunology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[d] Department of Pharmaceutical Sciences, University of Eastern Piedmont, A. Avogadro, Novara, Italy
[e] Department of Inflammation and Immunology, Humanitas Clinical and Research Center, Rozzano, Milan, Italy

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ABSTRACT

Immunotherapy has dramatically changed the therapeutic scenario in treatment naïve advanced non-small cell lung cancer (NSCLC). While single agent pembrolizumab has become the standard therapy in patients with PD-L1 expression on tumor cells ≥ 50%, the combination of pembrolizumab or atezolizumab and platinum-based chemotherapy has emerged as an effective first line treatment regardless of PD-L1 expression both in squamous and non-squamous NSCLC without oncogenic drivers. Furthermore, double immune checkpoint inhibition has shown promising results in treatment naïve patients with high tumor mutational burden (TMB). Of note, the presence of both negative PD-L1 expression and low TMB may identify a subgroup of patients who has little benefit from immunotherapy combinations and for whom the best treatment option may still be platinum-based chemotherapy. To date, first-line single agent immune checkpoint blockade has demonstrated limited activity in EGFR mutated NSCLC and the combination of immunotherapy and targeted agents has raised safety concerns in both EGFR and ALK positive NSCLC patients. Finally, in EGFR mutated or ALK rearranged NSCLC, atezolizumab in combination with platinum-based chemotherapy and bevacizumab is emerging as a potential treatment option upon progression to first line tyrosine kinase inhibitors.

Introduction

The advent of immunotherapy has radically changed the therapeutic algorithm in non-small cell lung cancer (NSCLC).

Immune checkpoint inhibitors (ICIs), by blocking inhibitory pathways that physiologically control the immune response, restore and sustain the immune system against cancer cells [1].

In particular, the cytotoxic T-lymphocyte–associated-4 (CTLA-4) and the programmed cell death protein 1 (PD-1) are receptors expressed on T cells that interacting with CD80/CD86 [2] and the programmed death-ligand 1 or 2 (PD-L1 or PD-L2) [3], respectively, can promote and favor cancer cells immune evasion.

Several ICIs, blocking the PD-1/PD-L1 and CTLA-4 inhibitory pathways, have been evaluated in NSCLC. Due to their better effectiveness and safety profile compared to chemotherapy, three of them, pembrolizumab, nivolumab (both anti PD-1 antibodies) and atezolizumab (anti PD-L1), are Food and Drug Administration (FDA) and European Medical Agency (EMA) approved monotherapy in NSCLC, pembrolizumab both as first and second line treatment, nivolumab and atezolizumab only in the second line setting.

However, the treatment paradigm of NSCLC is quickly changing and interesting results from phase III trials evaluating first -line ICIs as either monotherapy or combination have been recently published.

An open issue is how to choose the most correct therapeutic strategy and to properly select patients for the different available treatment options. In this review, we aimed to analyze and discuss the topic, highlighting the strengths and the critical aspects of the most recent trials, in order to help clinicians in their choice. In Table 1 and Figs. 1–4 are summarized the main survival data from randomized trials comparing immune checkpoint inhibitors as monotherapy or in combination to standard first line chemotherapy in advanced NSCLC.

* Corresponding author at: Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Via G. Venezian, 1, 20133 Milan, Italy.
E-mail address: roberto.ferrara@istitutotumori.mi.it (R. Ferrara).

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Table 1
Survival results from phase II/III trials exploring PD-(L)-1 inhibitors as monotherapy or in combination with anti-CTLA-4 agents or with standard first line chemotherapy in advanced NSCLC patients.

STUDY	Treatment arms	mPFS (not selected for PD-L1)	mOS (not selected for PD-L1)	mPFS (PD-L1 -)	mOS (PD-L1 -)	mPFS (PD-L1+)	mOS (PD-L1 +)	mPFS High PD-L1	mOS High PD-L1	Treatment related tox G3/G4 (%)
		HR PFS (not selected for PD-L1)	HR OS (not selected for PD-L1)	HR PFS (PD-L1 -)	HR OS (PD-L1 -)	HR PFS (PD-L1 +)	HR OS (PD-L1 +)	HR PFS High PD-L1	HR OS High PD-L1	
Borghaei et al. (KN 021) (NSq)	Pembrolizumab + platinum-pemetrexed vs platinum-pemetrexed	24 vs 9.3 0.53 (0.33-0.86)	NR vs 21.1 0.56 (0.32-0.95)							41 vs 27
Gandhi et al. (KN 189) (NSq)	Pembrolizumab + platinum-pemetrexed vs platinum-pemetrexed	8.8 vs 4.9 0.52 (0.43-0.64)	NR vs 11.3 0.49 (0.38-0.64)	0.75 (0.53-1.05) §	0.59 (0.38-0.92) §	0.44 (0.34-0.57) ¤	0.47 (0.34-0.66) ¤	0.36 (0.25-0.52) #	0.42 (0.26-0.68) #	67.2 vs 65.8
Hellmann et al. (CCM 227) (Sq+NSq)	Nivolumab + Ipilimumab vs platinum-based CT	7.2 vs 5.5 ¶ | 3.2 vs 5.5 ‡ 0.58 (0.41-0.81) ¶ | 1.07 (0.84-1.35)‡	23 vs 16.7 ¶ | 16.2 vs 12.4 ‡ 0.77 (0.56-1.06) ¶ | 0.78 (0.61-1.00) ‡	7.7 vs 5.3 §¶ | 3.1 vs 4.7 §‡ 0.48 (0.27-0.85) §¶ | 1.17 (0.76-1.81) §‡		 0.62 (0.44-0.88) ¶				31.2 vs 36.1
Rizvi et al. (MYSTIC) (Sq+NSq)	Durvalumab + Tremelimumab Vs platinum based CT				11.9 vs 10.3 § 0.73 (0.51-1.04) §	3.9 vs 5.4‖ 1.05 (0.7-1.5) ‖	11.9 vs 12.9‖ 0.85 (0.61-1.1) ‖		15.2 vs 12.7# 0.77 (0.55-1.07) #	22.1 vs 33.8
Borghaei et al. (CCM 227) (Sq+NSq)	Nivolumab + platinum-based CT vs platinum-based CT			6.2 vs 5.3 §¶ | 4.7 vs 4.7§‡ 0.56 (0.35-0.91) §¶ | 0.87 (0.57-1.33) §‡						52 vs 35
Rizvi et al. (MYSTIC) (Sq+NSq)	Durvalumab Vs platinum based CT				10.1 vs 10.3 § 1.18 (0.85-1.6) §	4.7 vs 5.4 ‖ 0.87 (0.59-1.2) ‖	16.3 vs 12.9 ‖ 0.76 (0.56-1.01) ‖		18.3 vs 12.7# 0.76 (0.55-1.03) #	14.6 vs 33.8
Lopes et al. (KN 042) (Sq+ NSq)	Pembrolizumab vs platinum-based CT					5.4 vs 6.5 ¤ 1.07 (0.94-1.21) ¤	16.7 vs 12.1 ¤ 0.81 (0.71-0.93) ¤	7.1 vs 6.4# 0.81 (0.67-0.99) #	20.0 vs 12.2# 0.69 (0.56-0.85) #	17.8 vs 41
Carbone et al. (CCM 026) (Sq+ NSq)	Nivolumab vs platinum-based CT					4.2 vs 5.9 ǂ 1.15 (0.91-1.45) ǂ	14.4 vs 13.2 ǂ 1.02 (0.80-1.30) ǂ	5.4 vs 5.8 # 1.07 (0.77-1.49) #	15.9 vs 13.9 # 0.90 (0.63-1.29) #	17.6 vs 50.6
Reck et al. (KN 024) (Sq+ NSq)	Pembrolizumab vs platinum-based CT							10.3 vs 6.0 # 0.50 (0.37-0.68) #	30 vs 14.2 # 0.63 (0.46-0.88) #	26.6 vs 53.3
Socinski et al. (IMpower-150) ITT- WT (NSq)	Atezolizuamab+bevacizumab+carboplatin+paclitaxel vs Carboplatin+paclitaxel+bevacizumab	8.3 vs 6.8 0.62 (0.52-0.74)	19.2 vs 14.7 0.78 (0.64-0.96)	7.1 vs 6.9 ϕ 0.77 (0.61-0.99) ϕ	17.1 vs 14.1 ϕ 0.82 (0.62-1.08) ϕ	8.3 vs 6.6 † 0.56 (0.41-0.77) †	20.3 vs 16.4† 0.80 (0.55-1.15)†	12.6 vs 6.8* 0.39 (0.25-0.60)*	25.2 vs 15.0* 0.70 (0.43-1.13) *	60 vs 51
Impower 150 EGFR and ALK+ (NSq)	Atezolizumab+bevacizumab+carboplatin+paclitaxel vs Carboplatin+paclitaxel+bevacizumab	9.7 vs 6.1 0.59 (0.37-0.94)	NE vs 17.5 0.54 (0.29-1.03)							
Cappuzzo et al. (IMpower 130) (NSq) ITT-WT	Atezolizumab + carboplatin+ nabpaclitaxel vs Carboplatin+nab-paclitaxel	7.0 vs 5.5 0.64 (0.54-0.77)	18.6 vs 13.9 0.79 (0.64-0.98)	6.2 vs 4.7 ϕ 0.72 (0.56-0.91) ϕ	15.2 vs 12.0 ϕ 0.81 (0.61-1.08) ϕ	8.3 vs 6.0† 0.61 (0.43-0.85)†	23.7 vs 15.9† 0.70 (0.45-1.08)†	6.4 vs 4.6 * 0.51 (0.34-0.77)*	17.3 vs 16.9* 0.84 (0.51-1.39)*	73 v 60
IMpower 130 EGFR and ALK+ (NSq)	Atezolizumab + carboplatin+ nabpaclitaxel vs Carboplatin+nab-paclitaxel	7.0 vs 6.0 0.75 (0.36-1.54)	14.4 vs 10 0.98 (0.41-2.31)							
Papadimitrakopoulou et al. (IMpower 132) (NSq)	Atezolizumab+ platinum-pemetrexed vs Platinum-pemetrexed	7.6 vs 5.2 0.60 (0.49-0.72)	18.1 vs 13.6 0.81 (0.64-1.03)	8.5 vs 4.9 ϕ 0.45 (0.31-0.64) ϕ		6.2 vs 5.7† 0.80 (0.56-1.16) †		10.8 vs 6.5* 0.46 (0.22-0.96) *		54 vs 39
Jotte el at. (IMpower 131)	Atezolizumab+carboplatin+nab-paclitaxel vs	6.3 vs 5.6	14 vs 13.9	5.7 vs 5.6 ϕ	13.8 vs 12.5 ϕ	6.0 vs 5.6 †	12.4 vs 16.6†	10.1 vs 5.5*	23.6 vs 14.1*	69 vs
(Sq)	carboplatin+nab-paclitaxel	0.71 (0.60-0.85)	0.96 (0.78-1.18)	0.81 (0.64-1.03) ϕ	0.86 (0.65-1.15) ϕ	0.70 (0.53-0.92) †	1.34 (0.95-1.90)†	0.44 (0.27-0.71)*	0.56 (0.32-0.99)*	58
Paz-Ares (KN 407) **(Sq)**	Pembrolizumab+carboplatin-paclitxel/nab-paclitaxel vs Carboplatin-paclitaxel/ nab-paclitaxel	6.4 vs 4.8 0.56 (0.45-0.70)	15.9 vs 11.3 0.64 (0.49-0.85)	6.3 vs 5.3§ 0.68 (0.47-0.98) §	15.9 vs 10.2 § 0.61 (0.38-0.98) §	7.2 vs 5.2 • 0.56 (0.39-0.80)•	14.0 vs 11.6• 0.57 (0.36-0.90)•	8.0 vs 4.2 # 0.68 (0.47-0.98)#	NR vs NR # 0.64 (0.37-1.10) #	69.8 vs 68.2

(*continued on next page*)

Table 1 (*continued*)

	Trial with Single agent IO	Trial with IO+CT	Trial with IO+IO
¶ Tumor Mutational Burden ≥ 10 mutations per megabase, ‡ Tumor Mutational Burden < 10 mutations per megabase § in PD-L1 Tumor Proportional Score (TPS) <1% ‖ in PD-L1 TPS ≥ 25% ¤ in PD-L1 TPS ≥ 1% ǂ in PD-L1 TPS ≥ 5% # in PD-L1 TPS ≥ 50% Φ in PD-L1 TC0/ and IC/0 * in PD-L1 TC3 or IC3 WT population † in PD-L1 TC1/2 or IC1/2 • in PD-L1 TPS 1-49% IO=immune checkpoint inhibitors, CT=chemotherapy, Sq=Squamous, NSq=Non-squamous, tox= treatment related adverse events grade 3-4 (not necessary of immunological etiology)			

Single agent immunotherapy

Pembrolizumab, a monoclonal antibody (mAb) directed against the PD-1 receptor, is the only approved single agent immunotherapy as first line treatment in metastatic NSCLC.

In the non-randomized phase I **Keynote 001** trial, single-agent pembrolizumab showed a significant benefit in treatment naïve NSCLC patients, achieving a 58.3% of response rate (RR), a median progression free survival (PFS) of 12.5 months and a 24-months overall survival (OS) rate of 60.6% in patients with a PD-L1 tumor proportion score (TPS) ≥ 50% [4]. Due to the significance of these results, the PD-L1 TPS ≥ 50% was estabilished as the cut-off to select patients for the use of pembrolizumab as a single agent in first-line treatment. Moreover, promising data for second line pembrolizumab in PD-L1 positive (TPS ≥ 1%) patients were reported [5], therefore pembrolizumab monotherapy was compared to first line platinum-based chemotherapy in treatment naïve advanced NSCLC patients, without EGFR mutation or ALK rearrangement and harboring a PD-L1 TPS ≥ 50% (**Keynote 024,** open label phase III trial**)** [6].

Patients were randomized to receive intravenous (iv) pembrolizumab 200 mg (flat dose) every 3 weeks or standard chemotherapy chosen according to the histology. PFS assessed by blinded, independent, central radiologic review (BICR) was the primary endpoint, OS, ORR, and safety were secondary endpoints. Crossover was allowed.

At the primary analysis, pembrolizumab showed its superiority over chemotherapy with improvement in overall response rate (ORR = 44.8 vs 27.8%, $p < 0.001$), median PFS (10.3 vs 6 months; HR 0.50; 95% CI: 0.37–0.68; $p < 0.001$) (Table 1) and median OS (median not reached, HR 0.6, 95% CI: 0.41–0.89) (Table 1, Fig. 1). To note that 43.7% of patients in the chemotherapy arm switched to pembrolizumab at the time of disease progression so a significant OS advantage was probably hidden by crossover. Fewer grade 3 or 4 treatment related adverse events were reported with pembrolizumab than chemotherapy (26.6% vs 53.3%) and immune mediated adverse events were documented in 9.7% of patients in the pembrolizumab arm.

Due to these data, FDA, in October 2016, and EMA, in December 2016, granted approval for pembrolizumab as first-line treatment in metastatic NSCLC with no EGFR or ALK alterations and high PD-L1 expression (TPS ≥ 50%).

After a longer follow-up of 25 months, the updated HR for OS was 0.63 (95% CI: 0.47–0.86) and the median OS in the pembrolizumab arm 30 months (95% CI 18.3-NR) compared to 14.2 months (95% CI 9.8–19) in the chemotherapy arm (Table 1, Fig. 1), despite a crossover rate of 62.3% [7]. In addition, PFS2, (the progression free survival after a second line treatment) was significantly better in the pembrolizumab arm with a difference in median PFS of about 10 months (18.3 vs 8.4 months, HR 0.54) [8].

Another anti-PD-1 inhibitor, nivolumab, was evaluated as first line treatment in advanced NSCLC, due to the survival benefit over standard second line chemotherapy showed in two distinct phase III trials [9,10].

In the multicohort phase 1 Checkmate 012, durable responses and favorable safety profile in NSCLC patients treated with first line nivolumab monotherapy were reported, with a RR of 50% and a median PFS of 10.6 months in patients with PD-L1 expression level of 5% or higher [11].

The open-label phase III trial **Checkmate 026** evaluated the effectiveness and safety of nivolumab versus standard doublet chemotherapy in stage IV NSCLC patients with ≥1% PD-L1 expression. Patient with EGFR or ALK driver alterations were excluded. The primary endpoint was PFS, as assessed by BICR, among patients with a PD-L1 expression level of 5% or more. Nivolumab was administered iv at the dose of 3 mg/kg every 2 weeks. At the time of disease progression crossover was allowed for patients in the chemotherapy arm. Among the predefined subgroup of 423 patients with PD-L1 ≥5%, nivolumab didn't show an improvement in PFS as compared to chemotherapy (4.2 vs 5.9 months; HR: 1.15; 95% CI: 0.91–1.45; p = 0.25) and median OS

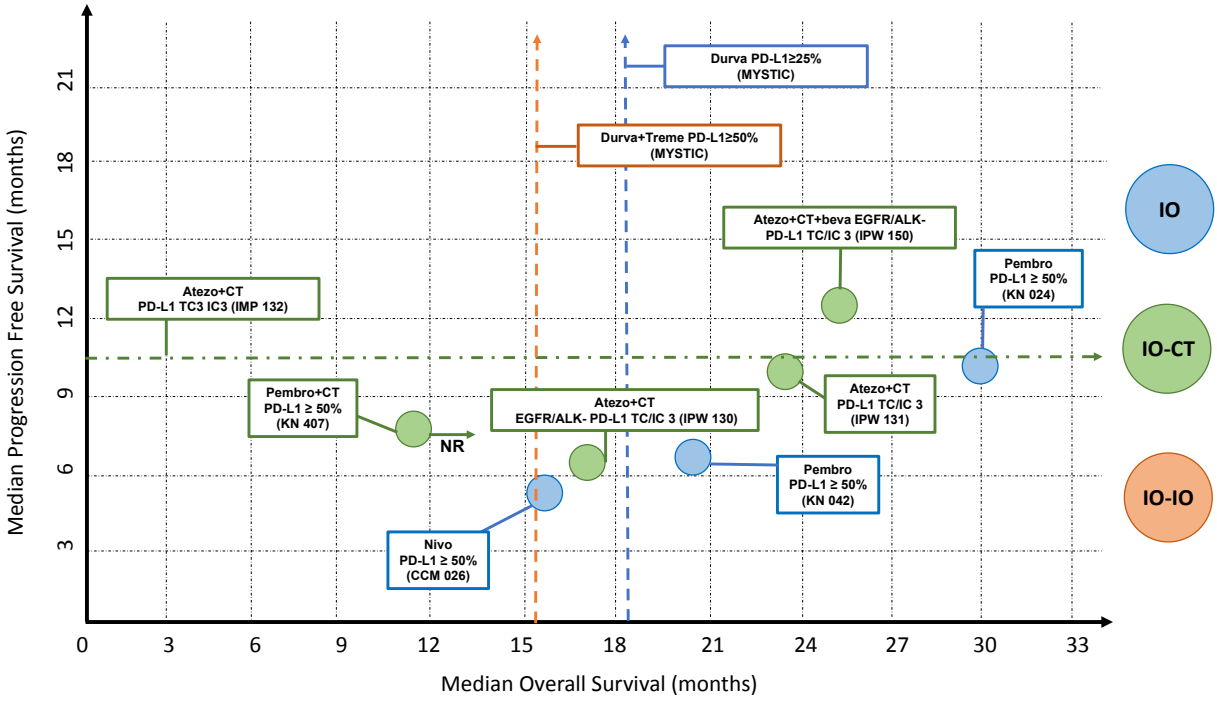

Fig. 1. Survival results from phase III trials exploring PD-(L)-1 inhibitors in "high" PD-L1 NSCLC patients. Dashed arrows without round are for trials with not available data on progression free or overall survival.

was similar between the two arms: 14.4 vs 13.2 months (HR 1.02; 95% CI, 0.80 to 1.30) (Table 1, Fig. 2). Toxicity profile was better with nivolumab than chemotherapy with 17.6% vs 50.6% of patients having grade 3–4 adverse events (AEs), respectively, and no new safety data emerged from this trial [12]. In a post-hoc analysis, nivolumab failed again to show a benefit over chemotherapy in patients with higher PD-L1 expression levels (PD-L1 TPS ≥50%) [12]. It is unknown why the two anti-PD-1 antibodies showed such different results in first line setting. Probably patient selection may be the primary cause, however potential pharmacologic differences between the two antibodies may also exist. Doubts on the PD-L1 tests (Dako 22C3 and Dako 28-8 for pembrolizumab and nivolumab, respectively), PD-L1 cut-off point (50% with pembrolizumab vs 5% with nivolumab) and PD-L1 role as a biomarker emerged from this comparison [13]. Due to the use of different tests and cut offs to select patients in the two studies (50% vs 5%, respectively), the sensitivity of the used clones may be different so patients defined as strong PD-L1 positive in the Keynote 024 may not be the same of those in the Checkmate 026 trial. In Checkmate 026, the subgroup of patients with PD-L1 expression ≥50% was higher in the control arm compared to the nivolumab arm (74.1% vs 53.2%) [12]. In addition, a higher percentage of never smokers was included in Checkmate 026 (11%) [12] compared to Keynote 024 (3%) [6], suggesting a higher proportion of patients with low mutational load in the nivolumab trial. Finally, the turnaround time from patient selection to treatment, based on PD-L1 expression, is not reported in Keynote 024 but is expected to be frequently longer than one month. There is a high probability that patients with relatively indolent disease were favored for inclusion in the Keynote study [13]. On the other hand, a delay of 2 months between diagnosis and randomization has been reported for Checkmate 026, and patients with worse clinical condition may have been enrolled in this study. Another major difference between the two trials was the permission to include patients after radiotherapy: in the Keynote 024, prior radiation therapy of > 30 Gy was not allowed within 6 months before starting treatment, on the contrary a high percentage (about 37%) of patients were enrolled in the Checkmate trial after receiving radiotherapy. This aspect may have potentially conditioned effectiveness of nivolumab changing the microenvironment and the responsivity to ICI.

Although Checkmate 026 trial failed to show a benefit for nivolumab as first line treatment in NSCLC patients with PD-L1 ≥5%, an exploratory analysis reported better results with nivolumab than chemotherapy among patients selected by high TMB, assessed by whole exome sequencing (WES), in terms of RR (47% vs 28%) and median PFS (9.7 vs 5.8 months, HR 0.62; 95% CI, 0.38 to 1.00); OS did not show differences in the two groups probably due to the high crossover rate in the chemotherapy arm (68%). Of note, patients treated with nivolumab characterized by both high TMB and high PD-L1 (≥50%) showed better RR than those with only one or neither of these marker (75% vs 32% vs 16%, respectively). Patients with low/medium TMB showed better PFS with chemotherapy than nivolumab (6.9 vs 4.1 months; HR 1.82, 95% CI 1.30–2.55). Intriguingly, in PD-L1 ≥1% patients, TMB was independent from PD-L1 expression and if we consider patients with low/medium TMB but higher PD-L1 (≥50%), fewer than 10% were progression-free at 18 months when treated with nivolumab [12]. However, this was not a pre-specified analysis. Currently, only patients with PD-L1 TPS ≥ 50% can receive single agent immunotherapy (pembrolizumab) as first line treatment in clinical practice and they account for a maximum of 30% of all advanced NSCLC patients.

To extend the use of immunotherapy to a larger population, recently the open label phase III **Keynote 042** investigated the role of pembrolizumab versus chemotherapy as first line treatment in NSCLC patients with PD-L1 TPS ≥ 1% and no sensitizing EGFR mutations or ALK rearrangements [14]. Patients were randomized to receive iv pembrolizumab 200 mg every 3 weeks for up to 35 cycles or carboplatin combined to either paclitaxel or pemetrexed according to tumor histology for up to 6 cycles. The primary endpoint was OS sequentially tested in the pre-specified subgroups with PD-L1 TPS ≥50%, ≥20%, ≥1%. PFS and RR in the same subgroups and safety in the whole population (TPS ≥1) were secondary endpoints. First line pembrolizumab significantly improved survival over platinum-based chemotherapy, with a median OS of 20.0 vs 12.2 months (HR 0.69, 95% CI 0.56–0.85), 17.7 vs 13.0 months (HR 0.77, 95% CI 0.64–0.92), 16.7 vs 12.1 months (HR 0.81, 95% CI 0.71–0.93) in patients with PD-L1 TPS ≥50%, ≥20%, ≥1%, respectively (Table 1, Figs. 1 and 2). An exploratory

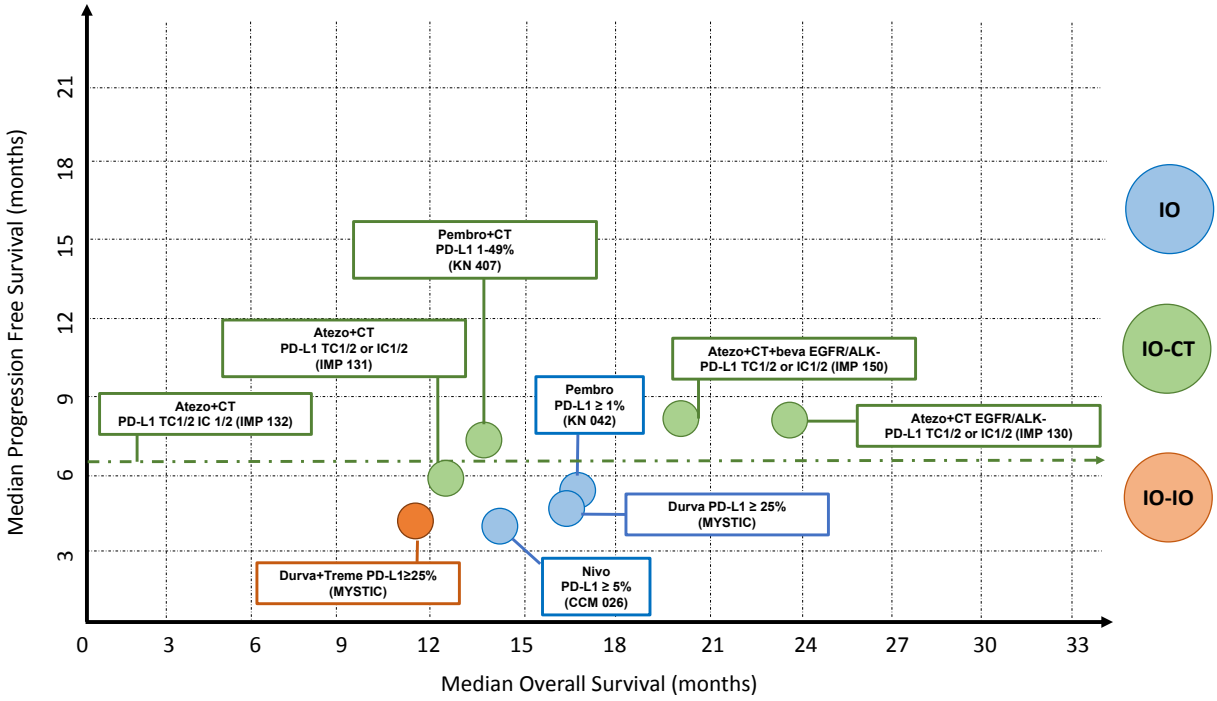

Fig. 2. Survival results from phase III trials exploring PD-(L)-1 inhibitors in "positive" PD-L1 NSCLC patients. Dashed arrows without round are for trials with not available data on progression free or overall survival.

analysis showed an HR of 0.92, (95% CI 0.77–1.11), in patients with PD-L1 TPS 1–49%. Considering that patients were stratified according to PD-L1 expression (≥50% vs 1–49%), before randomization, the OS benefit in the PD-L1 ≥ 1 population was mainly driven by PD-L1 ≥ 50% patients.

No advantages in PFS were reported, however, further follow-up is ongoing. Of note, although maintenance pemetrexed demonstrated a clear survival benefit in non-squamous histology [15], pemetrexed maintenance was optional in Keynote 042 and no data were reported on the exact percentage of patients who receive it in the trial. Pembrolizumab safety profile was consistent with previous reports with a lower frequency of grade 3–4 treatment related adverse events than chemotherapy (17.8% vs 41%) despite longer exposure [14]. This was the first study using OS as primary endpoint that showed an advantage of immunotherapy over chemotherapy. The better toxicity profile may favor the use of pembrolizumab in NSCLC patients PD-L1 positive but the real benefit is evident in the PD-L1 ≥ 50% subgroup so, at the moment, there will be no immediate change in clinical practice. Finally, a recent study addressed the question whether ICI monotherapy may be useful in EGFR mutated patients in first line setting. This phase II single arm trial tested pembrolizumab 200 mg iv every 3 weeks in EGFR mutated NSCLC patients with PD-L1 expression ≥1%. The study was prematurely closed after 11 of 25 planned patients were treated. ORR was 0%, and concerns were raised about pneumonitis in patients exposed to EGFR tyrosine kinase inhibitors (TKIs) after progression to pembrolizumab [16].

Immuotherapy plus chemotherapy

With the same goal of extending immunotherapy to a larger population, the addition of a PD-1/PD-L1 inhibitor to standard chemotherapy has been investigated in NSCLC patients, regardless of PD-L1 expression. Combining immunotherapy to cytotoxic agents may improve the immune system activity through the immunological effects of chemotherapy [17], such as the reduction of T-regulatory cells [18] and myeloid derived suppressor cells activity [19], the increase of the cross-presentation of tumor antigens [20] and the induction of PD-L1 expression on tumor cells [21].

On 10 May 2017 FDA approved pembrolizumab in combination with pemetrexed and carboplatin as first-line treatment in metastatic non-squamous NSCLC, irrespective of PD-L1 expression. This approval was based on the significant increase in ORR and PFS and the minimal worsening in toxicity profile reported in the cohort G of the randomized open label phase II Keynote 021 [22]. In this cohort 123 patients with chemotherapy-naive, stage IIIB or IV, non-squamous NSCLC without EGFR mutations or ALK rearrangements were randomized to receive carboplatin plus pemetrexed with or without pembrolizumab as first-line therapy. The primary endpoint was ORR. Patients were stratified by PD-L1 TPS (< 1% vs ≥ 1%). At the primary analysis, the association of pembrolizumab nearly doubled the ORR compared to chemotherapy alone (55% vs 29%, respectively; p = 0.0016) and significantly improved median PFS (13.0 vs 8.9 months; HR, 0.53; p = 0.0102). Similar OS was reported in the two arms (92% at 6 months for both treatments; 75% and 72% at 1 year, for experimental and control arm respectively). In both groups there were durable responses with 29 out of 33 (88%) responders in the combination group and 14 out of 18 (78%) responders in the chemotherapy alone arm alive without progression at the time of data cutoff. There was a higher proportion of responses in patients with PD-L1 ≥50% but the sample was too small to define a sure relationship between PD-L1 expression levels and efficacy. The toxicity profile was as expected in both treatment groups [22]. Keynote 021 was the first published controlled trial to prospectively report a significant advantage with a manageable and predictable toxicity profile combing an ICI to standard chemotherapy (~40% of grade 3–4 treatment related adverse events). In a subsequent analysis (median follow-up 14.5 months), the HR for OS improved to 0.69 (95% CI, 0.36–1.31) in favor of the combination arm [23]. At 23.9 months of follow up, higher ORR (56.7% versus 30%; p = 0.0016) and PFS (HR, 0.53; 95% CI, 0.33–0.89; p = 0.0049) with median PFS of 24.0 months versus 9.3 months in favor of pembrolizumab-chemotherapy combination were reported. The HR for OS further improved to 0.56 (95% CI, 0.32–0.95; p = 0.0151) with a not reached median OS in the combination arm vs 21.1 months with chemotherapy alone (Table 1) [24].

The results of **Keynote 189**, a phase III placebo-controlled double-

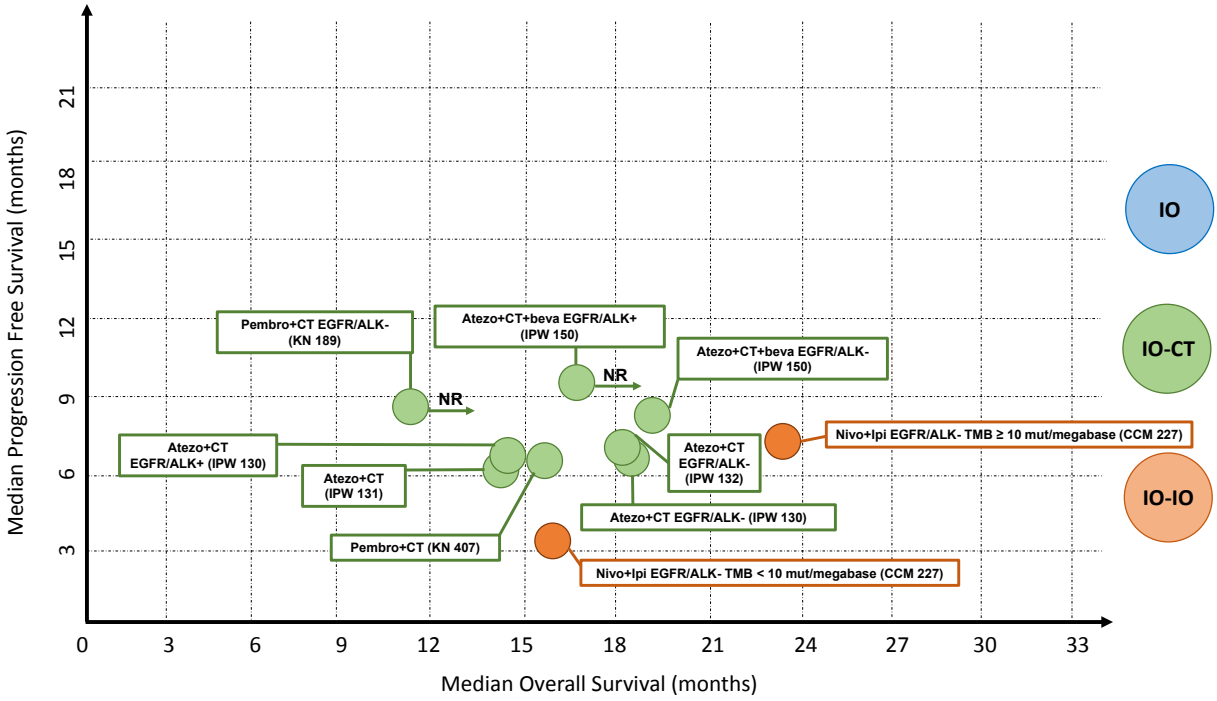

Fig. 3. Survival results from phase III trials exploring PD-(L)-1 inhibitors in NSCLC patients unselected for PD-L1 expression. Arrows indicate trials with not reached overall survival.

blinded trial testing first line platinum-based chemotherapy with or without pembrolizumab in EGFR/ALK wild type non squamous NSCLC patients were recently published [25]. OS and PFS, as assessed by BICR were co-primary endpoints, stratification was based also on PD-L1 TPS (negative or positive). Crossover to pembrolizumab was allowed at disease progression.

After a median follow-up of 10.5 months, RR was 47.6% in the pembrolizumab-combo group vs 18.9% in the placebo-combo group ($p < 0.001$) with a median duration of response of 11.2 and 7.8 months, respectively. Patients treated with pembrolizumab plus chemotherapy showed 51% less likelihood to die compared to patients in the chemotherapy arm: median OS was not reached vs 11.3 months, respectively (HR 0.49; 95% CI, 0.38 to 0.64; $P < 0.001$). Median PFS was 8.8 vs 4.9 months (HR 0.52; 95% CI, 0.43 to 0.64; $p < 0.001$) with and without pembrolizumab (Table 1, Fig. 3). The greatest benefit of the addition of pembrolizumab was evident among patients with PD-L1 TPS of 50% or higher. Despite no significant PFS benefit was evident adding pembrolizumab in patients with PD-L1 TPS < 1%, all evaluated PD-L1 categories, including those with PD-L1 TPS inferior than 1% achieved OS advantage from pembrolizumab combination.

Despite a crossover rate of about 50%, survival benefit was clearly maintained with pembrolizumab addition, highlighting the superiority of the upfront combination therapy over a subsequent use of immunotherapy. As expected, neither an increase of adverse events which usually seem to be associated to chemotherapy nor a higher incidence of immune-mediated adverse events were reported. A significant increase in the rate of nephritis and acute kidney injury (5.2% vs. 0.5%) was the only exception, but it may be both a platinum-based chemotherapy toxicity and an immune mediated effect as reported in the past trials. On the base of Keynote 189 results, on September 2018, EMA approved pembrolizumab in combination with pemetrexed and carboplatin as first-line treatment in metastatic non-squamous NSCLC, irrespective of PD-L1 expression.

Recently, the results of a twin phase III study, the open label **Impower 132**, assessing the efficacy and safety of atezolizumab in combination with platinum and pemetrexed chemotherapy compared to chemotherapy alone in non-squamous NSCLC without driver alterations, have been presented. Investigator assessed PFS and OS in the intention to treat (ITT) population were co-primary endpoints. Evaluable tissue was not mandatory for enrollment and it was available only for 60% of patients. The study met its PFS co-primary endpoint with a median PFS of 7.6 months in the atezolizumab plus chemoterapy arm compared to 5.2 months with chemotherapy alone (HR 0.60, 95% CI: 0.49–0.72, $p < 0.0001$) (Table 1, Fig. 3). The PFS advantage was evident in all the key subgroups with better results in females, elderly patients, never smokers and patients without liver metastases. The higher HR in patients with liver metastases compared to patients without liver metastases (HR 0.77, 95% CI 0.47–1.25 vs HR0.56, 95% CI 0.46–069) may be of interest. However, we have to note that the study was not powered to assess PFS benefit in different subgroups and that the presence of liver involvement may be a negative prognostic factor for both arms. At an exploratory analysis that evaluated the PFS by PD-L1 status in biomarker evaluable patients, the benefit of adding atezolizumab was present in all the subgroups (PD-L1 high, low or negative) with better results among patients with higher PD-L1 expression (Table 1, Fig. 1). However, it should be noticed that PD-L1 expression was evaluated for only 60% of patients included in the trial. At this first interim analysis OS data were not mature yet, however it was numerically superior for the combination of atezolizumab and chemotherapy with a median OS of 18.1 months vs 13.6 months in the control arm (HR 0.81; 95% CI 0.64–1.3, $p = 0.0797$) (Table 1, Fig. 3). OS will be further evaluated in the final analysis that is scheduled for 2019. Atezolizumab plus pemetrexed and carboplatin/cisplatin showed a manageable safety profile, consistent with known toxicity profiles of single immunotherapy and chemotherapy; treatment related grade 3–4 adverse events were reported in 58% of patients [26]. Atezolizumab showed a survival benefit in combination with first line platinum-based chemotherapy also in the open label phase III trial **Impower 130.** In this study 723 patients with stage IV non-squamous NSCLC were randomized to receive the combination of atezolizumab and carboplatin plus nab-paclitaxel (Arm A) vs chemotherapy alone (Arm B). In the Arm A, atezolizumab was continued as maintenance treatment until loss of clinical benefit, while best supportive care or pemetrexed were planned as maintenance in Arm B. Patients with EGFR or ALK alterations were

included in the ITT population only after progression to at least one previous targeted agent; overall 679 patients were EGFR wild type and ALK negative in ITT population. The study met its two co-primary endpoints: PFS and OS. The combination treatment resulted in a statistically significant improvement in OS compared with chemotherapy alone with a median OS of 18.6 months vs 13.9 months, respectively (HR 0.79; 95% CI, 0.64–0.98; $p = 0.033$) [27] (Table 1, Fig. 3). At 12 months, 63.1% of patients in the combination group were alive compared with 55.5% in the control arm. Similarly, a significant improvement in PFS was reported with a median PFS of 7.0 months in Arm A vs 5.5 months in Arm B (HR 0.64; 95% CI, 0.54–0.77; $p < 0.0001$) (Table 1, Fig. 3). The PFS and OS improvements occurred although about 20% of patients in the Arm B received pemetrexed as switch maintenance and despite the high crossover rate of 59%. PFS and OS benefits were evident in all PD-L1 subgroups and were consistent across all key subgroups, except in those patients with liver metastases or -EGFR/ALK alterations. Grade 3/4 treatment-related adverse events occurred in 73.2% vs 60.3% of patients in the combination vs chemotherapy arm respectively.

The addition of immunotherapy to the combination of anti-angiogenic agent and chemotherapy has also been investigated. The results of **Impower150,** an open label phase III study combining atezolizumab to the standard first line therapy carboplatin, paclitaxel with or without bevacizumab, in chemo-naïve patients with stage IV non-squamous NSCLC were recently published [28]. PFS in the ITT population with wild-type genotype (WT-ITT population) and among WT ITT population with high expression of an effector T-cell (Teff) gene signature, and OS in the ITT WT population were co-primary endpoints. Cross over was not allowed. The trial met its co-primary endpoints: the four drug combination showed an improvement in PFS in the ITT population (median PFS 8.3 vs 6.8 months; HR 0.62; 95% CI, 0.52 to 0.74; P < 0.001) (Table 1, Fig. 3), in the ITT WT population with high Teff (median PFS 11.3 months vs 6.8 months; HR 0.51, 95% CI, 0.38 to 0.68; P < 0.001) and also in the ITT population including patients with EGFR or ALK alterations, (median PFS 9.7 months vs 6.1 months; HR 0.59, 95% CI, 0.37 to 0.94). Median OS among the patients in the ITT WT population was longer with the four-drug combination compared to the control arm (19.2 months vs 14.7 months; HR 0.78; 95% CI, 0.64 to 0.96; P = 0.02) (Table 1, Fig. 3). According to these results, on December 2018, FDA approved atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin for the first line treatment of patients with metastatic non squamous NSCLC with no EGFR or ALK alterations while, more recently, EMA extended the indication also to EGFR/ALK positive NSCLC patients after targeted therapies. The survival benefit was observed across all subgroups, irrespective of PD-L1 expression levels. Of note, the addition of atezolizumab to bevacizumab plus chemotherapy showed a benefit in key subgroups with potential low benefit from ICI such as patients with EGFR/ALK alterations or with liver metastases (HR 0.54 for both subgroups) [28]. This benefit was not evident for the comparison of atezolizumab plus chemotherapy versus bevacizumab plus chemotherapy (HR 0.85 for patients with liver metastases and HR 0.82 for EGFR/ALK positive patients). In the same analysis the addition of atezolizumab to carboplatin and paclitaxel showed a trend towards an OS benefit in comparison with bevacizumab plus carboplatin and paclitaxel (19.4 vs 14.7 months, HR 0.88, 95% CI 0.72–1.08, p = 0.20), however, data are not mature yet and will be tested again at the time of final analysis. Safety for the atezolizumab, bevacizumab and carboplatin-paclitaxel combination was consistent with the known safety profile of single agents; treatment related grade 3–4 adverse events were reported in 60% of patients. Overall, the four studies in non-squamous NSCLC (Keynote 189, Impower 130, Impower 132, Impower 150) differ in several aspects: two distinct PD-L1 IHC assays were used, Dako 22C3 in the Keynote 189 and Ventana SP142 in the Impower studies, patients with EGFR or ALK rearrangements were excluded in the Keynote 189 and Impower 132, the percentage of PD-L1 negative patients was higher in the Impower 130 and 150 studies (~50%) compared to Keynote 189 (31%) and Impower 132 (23%), crossover was not allowed in Impower 150 while was permitted in Impower 130 (59%), Impower 132 (37%) and in Keynote 189 (41%), follow-up was longer in Impower 150 compared to Keynote 189 (20 vs 10 months). If we indirectly compare Keynote 189 and Impower 150, the incremental effect of immunotherapy seems superior with pembrolizumab and pemetrexed combination compared to atezolizumab and chemotherapy (HR 0.68, 95% CI 0.48 – 0.95). The reasons of the great magnitude of the advantage with pembrolizumab and chemotherapy are unclear: less additive/synergistic effect of paclitaxel compared to pemetrexed, different impact of chemotherapy agents on the activity of ICIs [29], different antidrug-antibody level in response to pembrolizumab or atezolizumab [30], differences in the characteristics of two populations can be hypothesized.

In the Keynote 189 and the Impower 132 the same chemotherapy regimen, including platinum and pemetrexed, was used, so ICI, pembrolizumab and atezolizumab, respectively, was the only difference in treatment. Both studies reached the PFS co-primary endpoint, however atezolizumab reduced the risk of progression by 40% while with pembrolizumab the corresponding risk reduction was by 48%. Comparing to the Keynote 189, the Impower 132 failed at the first OS interim analysis, showing only a not statistically significant numerically improvement in OS. The lack of statistical significance in the Impower 132 might be explained by the high number of patients who received second-line immunotherapy in the control arm (22.4% patients received nivolumab and 9.4% pembrolizumab). Moreover, the effect of atezolizumab was higher than pembolizumab in PD-L1 negative patients with an improvement in median PFS of 3.6 months vs 1 month and a 55% vs 25% reduction in risk of progression, respectively. We don't know if the different results may be attributable to the ICI class PD-1 vs PD-L1 inhibitor. Few data in the literature on this topic exist and no direct comparisons have been made between different ICI classes. It is noteworthy that, in contrast with anti PD-1, the PD-L1 inhibitors do not block the interaction of PD-L2, another PD-1 ligand, to the receptor and that this binding affects the immune response generating inhibitory signals. Moreover, the PD-L2 may also regulate respiratory immunity binding to repulsive guidance molecule b (RGMb) [31]. No apparent difference regarding efficacy emerged between PD-1 and PD-L1 inhibitors [32]. However, toxicity profiles of the two classes appeared comparable with the exception of a higher incidence of pneumonitis in patients receiving PD-1 inhibitors compared to those who were given PD-L1 inhibitors (4% vs. 2%; p = 0.01). This may be explained by the effect on respiratory system due to PD-L2 [33].

The association of immunotherapy and chemotherapy was also explored in squamous histology.

The double-blinded placebo controlled phase III trial **Keynote 407** randomized stage IV untreated squamous NSCLC to receive carboplatin and paclitaxel or nab-paclitaxel plus pembrolizumab or placebo [34]. The primary endpoints were PFS by BICR and OS in the ITT. Patients were stratified according to PD-L1 expression (TPS < 1% or ≥1%), choice of taxane (paclitaxel vs nab-paclitaxel), geographic region (East Asia vs rest of the world). Adding pembrolizumab to standard chemotherapy significantly improved OS over chemotherapy alone: median OS was 15.9 vs 11.3 months, respectively (HR 0.64, 95% CI 0.49–0.85, p = 0.0008) despite a cross over rate of 31.7% (Table 1, Fig. 3). The advantage was evident in all the subgroups regardless of PD-L1 expression levels (HR 0.61 for TPS < 1%, HR 0.57 for TPS 1–49%, HR 0.64 for TPS ≥ 50%) (Table 1). PFS was also improved with pembrolizumab with a median PFS of 6.4 vs 4.8 months (HR 0.56, 95% CI 0.45–0.60) (Table 1, Fig. 3) and the ORR was almost doubled (58.4% vs 35.0%, p = 0.0004). Pembrolizumab plus chemotherapy showed again a tolerable safety profile and frequency and severity of toxicities were similar to chemotherapy alone (69.8% vs 68.2%) [34]. This combination received FDA and EMA approval.

Finally, **Impower 131**, an open label phase III study, showed a benefit of the combination of atezolizumab and chemotherapy as

compared to chemotherapy alone in patients with stage IV squamous NSCLC, regardless of tumor PD-L1 expression level. 1021 patients were randomly assigned to the combination of atezolizumab with carboplatin and paclitaxel (Arm A) or to atezolizumab plus carboplatin and nab-paclitaxel (Arm B) or to carboplatin and nab-paclitaxel alone (Arm C) [35]. PFS and OS were co-primary endpoints. The outcomes of groups B and C were presented. The study met the PFS endpoint: median PFS was 6.3 vs 5.6 months in Arm B and Arm C respectively (HR 0.71, 95% CI 0.60–0.85, p = 0.0001) (Table 1, Fig. 3) with a reduced risk of disease progression or death in 29% of patients treated with atezolizumab combo compared to those receiving chemotherapy alone and a doubling of PFS benefit with immunotherapy combination: 12 months PFS rate was 24.7% in patients receiving immunotherapy vs 12% in those receiving chemotherapy alone. The benefit was consistent among all PD-L1 subgroups, including those with PD-L1–negative tumors and liver metastases, with better results in patients with higher PD-L1 levels. At this interim analysis no survival benefit was observed with the addition of atezolizumab: median OS was 14 months for atezolizumab plus chemotherapy vs 13.9 months for chemotherapy alone (Table 1, Fig. 3). The rate of severe side effects was higher with the combined-modality treatment than with chemotherapy alone (69% vs 58%), but the safety profile was generally manageable and consistent with known toxicities of each agent.

Immunotherapy combinations

Several recent trials addressed the question whether combining different immunotherapies may improve outcomes in some patients.

The open label randomized multicohort phase I Checkmate 012 trial showed an improved efficacy of the combination of nivolumab and the anti-CTLA4 ipilimumab, as respect to nivolumab monotherapy in all PD-L1 expression cohorts, with better results in those patients with higher PD-L1 levels. The adverse events were more frequent with the combination but still acceptable with 33% of treatment related grade 3–4 adverse event with the schedule nivolumab every 2 weeks (3 mg/kg or 1 mg/kg) and ipilimumab at 1 mg/kg every 6 weeks [36]. A retrospective analysis of Checkmate 012 showed that patients with higher TMB assessed by WES had also higher ORR and longer PFS upon nivolumab and ipilimumab. Moreover, at the multivariate analysis, TMB was independent of PD-L1 expression and was associated to efficacy of immunotherapy combination. These data supported the idea that TMB may be a predictive factor for nivolumab and ipilimumab treatment [37].

The open label phase III Checkmate 227 evaluated the efficacy of nivolumab monotherapy or nivolumab based combinations (nivolumab plus chemotherapy or nivolumab plus ipilimumab) as first line therapy in chemo-naive stage IV or recurrent NSCLC patients, randomized according to PD-L1 expression levels (≥1% or < 1%). The study was emended ongoing and two co-primary endpoints were established: PFS (assessed by BICR) with nivolumab plus ipilimumab versus chemotherapy in a TMB selected population and OS with nivolumab plus ipilimumab versus chemotherapy in a PD-L1 selected population [38].

A TMB of at least 10 mutations per megabase (10 mut/Mb), evaluated using The FoundationOne CDx (Foundation Medicine, Cambridge, MA) platform, was chosen as cutoff for selecting patients according to the results of the Checkmate 568 trial, a phase 2 trial of nivolumab plus ipilimumab in NSCLC. In this trial a TMB ≥ 10 mut/Mb was associated with improved response and prolonged PFS, irrespective of PD-L1 expression level. However, in the same study high PD-L1 (cut off 1%) correlated with an improvement in RR and PFS similar to the benefit observed according to TMB analysis [39].

In Checkmate 227, RR and PFS were significantly improved with nivolumab plus ipilimumab compared to chemotherapy among patients with a high TMB (≥10 mutations per megabase) regardless of PD-L1 levels: RR was 45.3% vs 26.9% and median PFS 7.2 vs 5.5 months (HR 0.58; 97.5% CI, 0.41–0.81; P < 0.001) (Table 1, Fig. 3), with 43% vs 13% of patients being progression-free at 1 year. A subgroup analysis among patients with a high TMB showed longer PFS with nivolumab plus ipilimumab among both patients with a PD-L1 expression level of at least 1% and those with a level of less than 1% irrespective of histology (squamous vs non-squamous). At the same analysis the nivolumab plus ipilimumab combination showed better results than nivolumab monotherapy in patients with high TMB, underlining the positive impact of a dual immune checkpoint blockade in this subset of patients. The safety of nivolumab plus ipilimumab were consistent with Checkmate 012 trial and grade 3–4 adverse event were reported in 31.2% of patients treated with nivolumab plus ipilimumab. An analysis on the efficacy and safety of nivolumab plus ipilimumab and nivolumab plus chemotherapy vs chemotherapy alone in patients with < 1% PD-L1 expression were recently presented. PFS in nivolumab plus chemotherapy vs chemotherapy alone in patients with < 1% PD-L1 expression level was one of the secondary endpoints [40]. Compared to chemotherapy alone, the chemo-immunotherapy combination showed longer median PFS 5.6 vs 4.7 (HR 0.74, 95% CI 0.58–0.94), higher ORR (36.7 vs 23.1) and longer duration of responses (7.2 vs 4.7 months) (Table 1, Fig. 4). The PFS benefit was enhanced according to TMB and patients with low TMB (< 10mut/Mb) did not show any advantage by the combination of nivolumab either with chemotherapy or ipilimumab. Nivolumab plus ipilimumab showed higher PFS (1-year PFS rates: 45% vs 27% vs 8%) and more durable responses (1-year DOR 93% vs 33% vs not-calculated) in patients with high TMB and < 1% PD-L1 expression level as compared to nivolumab plus chemotherapy and chemotherapy alone. Of note, no clear benefit was evident with combination strategies (nivolumab plus ipilimumab or chemotherapy) in those patients with < 1% PD-L1 expression level and TMB < 10 mut/Mb.

More recently, in an unpublished updated exploratory analysis the combination nivolumab plus ipilimumab showed a HR for OS of 0.77 (95% CI: 0.56–1.06) compared to chemotherapy in patients with TMB ≥10 mut/Mb, similarly to what observed in patients with TMB < 10 mut/Mb (HR 0.78; 95% CI: 0.61–1.00) [41]. The median OS in patients with TMB ≥10 mut/Mb was 23.0 months in the combination arm vs 16.7 months in the chemotherapy arm; the same difference was evident also in patients with TMB < 10 mut/Mb: median OS 16.2 months vs 12.4 months in the combination and chemotherapy arms, respectively (Table 1, Fig. 3).

Double immune checkpoint blockade was also tested in the MYSTIC trial, a phase III study comparing durvalumab monotherapy or durvalumab and tremelimumab, an anti-CTLA4 antibody, vs platinum-based chemotherapy in treatment naive metastatic NSCLC [42]. MYSTIC did not meet primary endpoints of OS and PFS in patients with PD-L1 TC ≥25%. In particular, at the primary analysis of patients with PD-L1 expression of 25% or more, durvalumab monotherapy demonstrated clinical activity but did not achieve a statistically significant improvement in OS (HR 0.76; 97.54% CI 0.564–1.019; p = 0.036, p level for significance = 0.03) [42]. According to these results, durvalumab activity as monotherapy is consistent with that of first line pembrolizumab in PDL-1 TPS ≥20% NSCLC patients from Keynote 042 [14]. In MYSTIC, the combination of durvalumab plus tremelimumab did not meet the PFS (HR = 1.05; 99.5% CI 0.722–1.534; p = 0.705) or OS primary endpoints (HR 0.85; 98.77% CI 0.611–1.173; p = 0.202) (Table 1, Fig. 2). An exploratory analysis showed that high blood TMB (≥16 mut/Mb) was associated with better OS for durvalumab plus tremelimumab vs chemotherapy (HR 0.62, 95% CI 0.45–0.85, 2 years OS: 39% vs 18%). The safety profiles both for monotherapy and combination were consistent with previous experience with 40.4% of grade 3 or 4 AEs vs 47.7% vs 46.0% with monotherapy, combination and chemotherapy, respectively.

PD-1/PD-L1 inhibitors plus targeted therapy

The role of ICIs in oncogene-addicted NSCLC is still unclear.

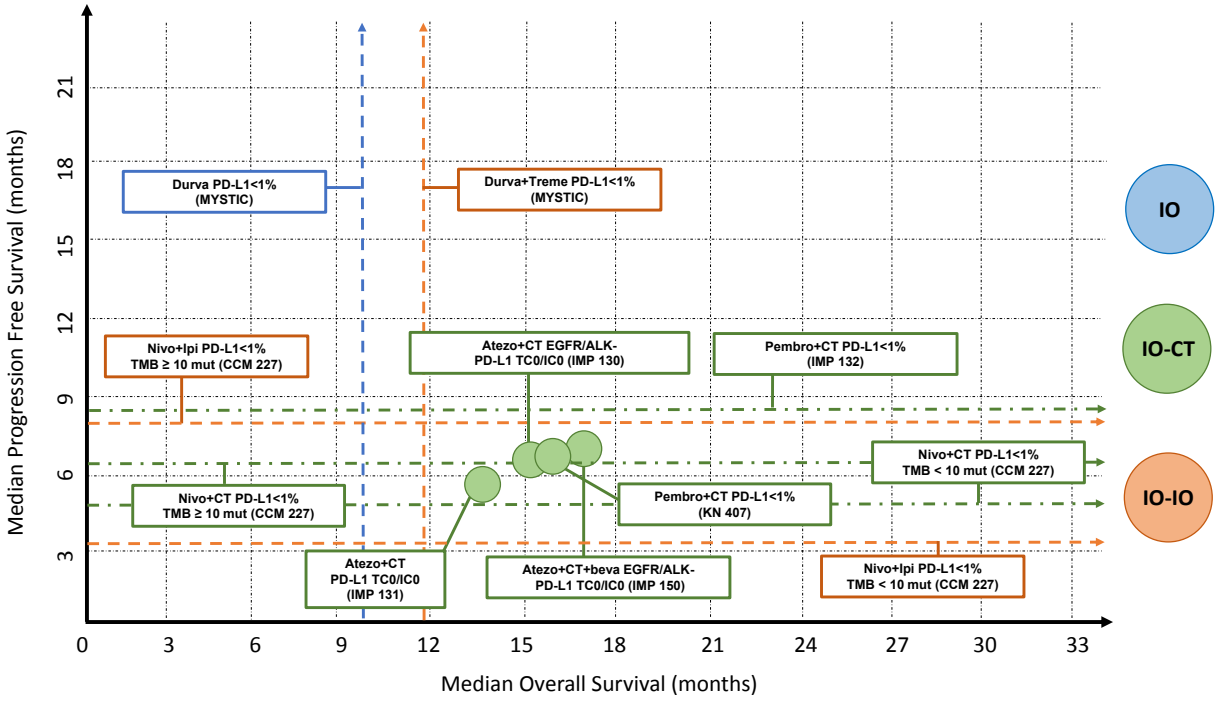

Fig. 4. Survival results from phase III trials exploring PD-(L)-1 inhibitors in "negative" PD-L1 NSCLC patients. Dashed arrows without round are for trials with not available data on progression free or overall survival.

Currently, TKIs represent the standard treatment in patients with NSCLC associated with EGFR mutations or ALK and ROS1 rearrangements. Targeted therapy can cause the release of new antigen able to boost the immune response [43], from here the idea of combining immunotherapy to targeted therapy to improve clinical outcomes. To date, toxicities issues have hampered the development of combinations of ICIs and of EGFR or ALK TKIs. The phase Ib TATTON study testing osimertinib and nivolumab was early closed due to the occurrence of interstitial lung disease in 38% of patients [44]. Due to this safety concerns, the recruitment in the CAURAL phase III trial evaluating the combination of osimertinib and durvalumab vs osimertinib alone in EGFR T790M positive patients after failure of a previous EGFR TKI was prematurely stopped.

The combination of nivolumab and erlotinib showed grade 3–4 toxicities rate of 25% and an ORR of 15% in 21 EGFR mutant NSCLC (20 pretreated with an EGFR TKI) [45]. Similar safety results were reported in EGFR TKI naïve patients with the combination of erlotinib and atezolizumab (grade 3–4 toxicities 39%) [46] or gefitinib and durvalumab (grade 3–4 toxicities 20%) [47], in both studies the ORR was ~75%, apparently comparable to the ORR with single agent EGFR TKI in this setting. In ALK rearranged NSCLC patients, the phase I/II CheckMate 370 showed severe hepatic toxicities in 38% of patients treated with nivolumab and crizotinib [48]. However, the combination of alectinib and atezolizumab had an acceptable safety profile and the main grade 3–4 toxicity was skin rash, reported in 18.9% of patients [49]. Due to the high incidence of high-grade toxicities with combination of TKI and immunotherapy, further development of this approach remains controversial and should be investigational.

Perspectives and patients' selection

Although immunotherapy has widely changed the treatment paradigm in NSCLC, the best first line therapy in advanced NSCLC patients is still a matter of debate. A possible treatment algorithm is proposed in Fig. 5.

To date, PD-L1 expression by immunohistochemistry (IHC) is the only approved marker to select patients for immunotherapy but its role as biomarker is not yet completely clear.

To define the PD-L1 expression level, companies used distinct PD-L1 IHC assays (Dako 28-8, Dako 22C3, Ventana SP142, Ventana SP263 assay for nivolumab, pembrolizumab, atezolizumab and durvalumab, respectively) such as different methods of interpretation and cut offs. Despite patients with higher PD-L1 expression level show higher likelihood of response to ICIs, about 10% of patients with negative PD-L1 respond to anti PD1/PD-L1 ICIs as well as some PD-L1 highly positive patients do not respond [5,9,10,34,35]. Intratumoral heterogeneity, interobserver variability, technological limits and dynamic nature of the PD-L1 may also be the reason of absence of concordance between responses and the reported PD-L1 value. Moreover, biopsy is often not representative of the tumoral PD-L1 real expression [50].

PD-L1 on its own may not be informative enough for the correct selection of patients. According to the PFS results of Checkmate 026 [12] and 227 [32], TMB was considered as a potential new and independent biomarker and the nivolumab plus ipilimumab combination could represent the treatment of choice for high TMB patients, irrespective of PD-L1 expression level. Nivolumab plus ipilimumab combination has not be formally compared with ICI-chemotherapy combinations, although an exploratory analysis reported a PFS benefit in favor of nivolumab plus ipilimumab in patients with high TMB and PDL-1 < 1% (Fig. 5). Furthermore, considering the reported advantage in patients with higher TMB (≥10 mut/Mb), TMB testing may be also clinically useful to select patients for the chemotherapy plus immunotherapy combinations. Those patients with low TMB (< 10 mut/Mb), that did not show any benefit from nivolumab combination neither with chemotherapy or ipilimumab, may be excluded from both these combinations. Nevertheless, both TMB feasibility and predictive value remains highly questionable. Regarding TMB feasibility, in Checkmate 227, only 57.7% of the collected samples were adequate for TMB analysis, and TMB positive patients were only 10.3% and 17.1% of the screened and enrolled patients respectively [36]. Recently blood TMB was evaluated in pretreated NSCLC patients from OAK and POPLAR studies [51] and in treatment naïve NSCLC patients from the

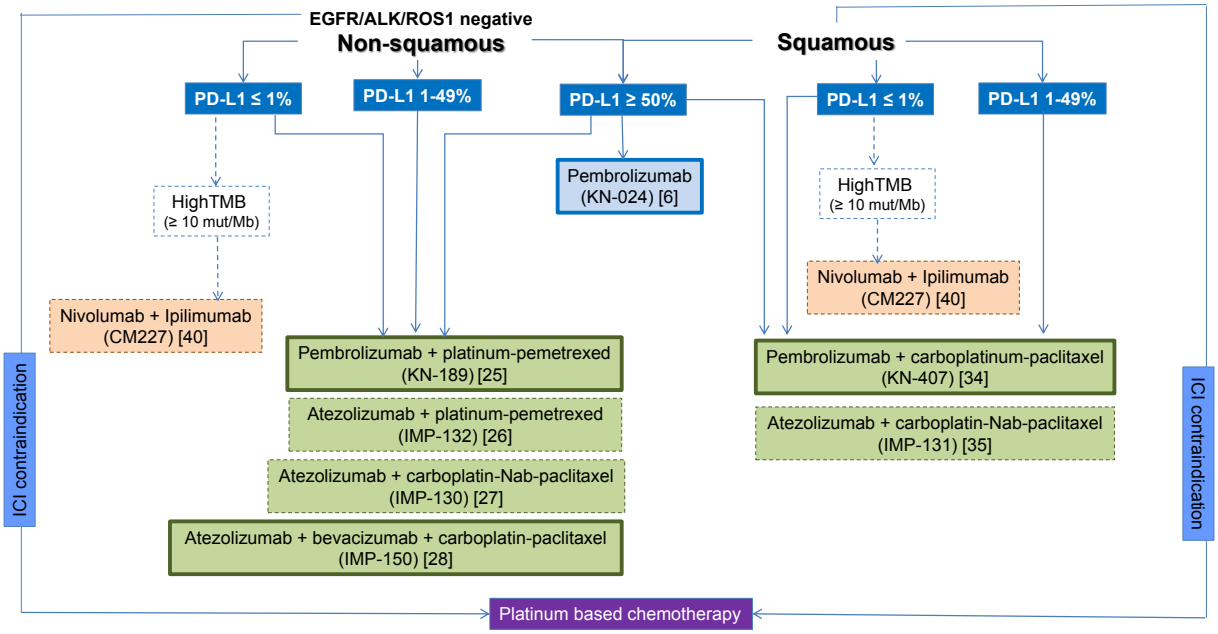

Fig. 5. First line treatment algorithm. Dashed lines are for treatments that did not receive approval from regulatory agencies so far. Continuous lines indicate treatments who received approval from regulatory agencies.

single arm phase II study B-F1RST receiving atezolizumab [52] and in patients treated with first line durvalumab or durvalumab plus tremelimumab from MYSTIC trial [42]. In these studies, TMB was feasible in 72–78% of patients and the rate of positive TMB (≥10 mut/Mb) ranged between 23% and 30%, suggesting that TMB may be more easily tested on blood rather than on tumor biopsies. Recent evidence from LACE-BIO II study including 908 resected stage II-III NSCLC patients showed a better OS and disease-free survival in patients with TMB > 8 Mb, suggesting a prognostic rather than a predictive value for this biomarker [53]. Furthermore, although TMB on tissue (cut off 10 mut/Mb) or blood (cut off 16 mut/Mb) significantly correlated with a PFS benefit upon nivolumab in Checkmate 026 [12], atezolizumab in the pooled analysis of OAK and POPLAR studies [51] and an OS benefit upon durvalumab plus tremelimumab [40], absence of significant association between blood TMB and PFS upon atezolizumab was observed in the B-F1RST study [52]. In this regard, the OS preliminary data from Checkmate 227 [41] support TMB as a prognostic factor, suggesting caution on its use in patient selection for treatment with a combination of nivolumab with ipilimumab. Due to the need of further evidence on the relationship between TMB and PD-L1 and the impact of nivolumab plus ipilimumab on OS in first-line NSCLC patients, the request for FDA evaluation of this combination in TMB high NSCLC has been withdrawn.

Overall, as PD-L1, TMB is a dynamic biomarker and it may change over the time; intra-tumoral heterogeneity may condition NGS results; an accepted definition such as a universally defined cut-point to determine “high” TMB is currently lacking, there is not sufficient ability to reproduce results using different platforms/assays, and, finally, costs are not well established and biopsy specimens are not often big enough to obtain good quality DNA for assessment [54].

A better characterization of patients with poor outcome during first line immunotherapy remains an unmet need. Both in patients treated with nivolumab single agent (Checkmate 026) or in combination with ipilimumab (Checkmate 227), the progression rate is higher in the immunotherapy arm (27% vs 10% in Checkmate 026 and 15.8% vs 11.9% in Checkmate 227) [12,36]. Furthermore, the crossings of the Kaplan Meier curves in studies both with single agent ICIs in first (Keynote 042 [14] and Checkmate 026 [12]) or further lines (Checkmate 057 [10]) and with double immune checkpoint combination (Checkmate 227 [36]) suggests that a variable percentage of NSCLC patients (ranging from 14% [55] to 26% [56]) may have a clear worse prognosis when treated with immunotherapy compared to chemotherapy. This could be due to hyperprogressive disease (HPD), an acceleration of tumor growth during immunotherapy recently described in previously treated NSCLC patients and in different cancer types [57]. HPD could also explain the lower access to subsequent treatments in patients discontinuing single agent nivolumab (44% vs 64% in Checkmate 026) or nivolumab plus ipilimumab (34.4% vs 49.2% in Checkmate 227) for reasons other than toxicities. Finally, a better characterization of the benefit of first-line ICI in challenging populations is of paramount. In this regard, steroids use (≥10 mg/die of prednisone-equivalent) was associated with worse outcome in NSCLC patients treated with anti-PD-1/PD-L1 agents [58]. Furthermore, in patients with EGFR/ALK alterations or with liver metastases the addition of atezolizumab to chemotherapy doublet did not significantly improve survival [27], however, in these same populations the quadruple treatment with chemotherapy, bevacizumab and atezolizumab provided a clear benefit [28], suggesting a potential role of anti-angiogenetic drugs in these settings. The benefit of single agent immunotherapy in elderly patients is still a matter of debate [59], and a subgroup analysis from Impower 132 raised the same question for immunotherapy and chemotherapy combinations due to a similar magnitude of PFS benefit in patients older or younger than 65 (HR 0.55 vs 0.63), but a greater OS advantage for patients older than 65 (HR 0.71 vs 0.89) with atezolizumab and platinum-pemetrexed [60]. It’s likely that immunosenescence, a measure of the immunological age might play a more relevant role rather than chronological age itself to select patients who do not benefit from immune checkpoint blockade [61,62].

In contrast with chemotherapy that has often limited access through the blood brain barrier, ICI, by the activation of immune system against cancer cells, may be potentially effective on brain metastases. Some evidences suggest that brain lesions from NSCLC are characterized by a higher expression of PD-L1 than the primary site [63] and that the presence of tumor infiltrating lymphocytes in brain metastases is related to a better prognosis [64]. CNS involvement is associated with poor prognosis and for this reason patients with untreated, symptomatic or unstable brain lesions are often excluded from clinical trials [63]. However, most of the data for immunotherapy in NSCLC patients,

coming from pretreated patients included in Expanded Access Programs [65] or in large retrospective multicentric studies [66], confirmed efficacy and safety of ICI in pretreated NSCLC patients with brain metastases, despite their poor prognosis. Interestingly, intracranial ORR, including patients with active brain metastases not previously treated with local therapy before ICI, was 27.3% [66].

Recent data reported that intestinal microbiota may influence the antitumor activity of immunotherapy: the intestinal bacterial flora would be able to regulate the activation of immune cells and so the global activity of immunotherapy [67–70]. Interestingly NSCLC patients treated with antibiotics within 30 days from the beginning of ICI had shorter PFS (1.9 vs 3.8 months, HR 1.5, p = 0.03) compared to patients who did not receive any antibiotics [71]. Furthermore, in one recent study including 100 cancer patients (60 NSCLC) *Akkermansia muciniphila* was significantly enriched in responders compared to progressing patients (69% vs 34% p = 0.007) and correlated with enhanced Th-1 cytokine (i.e. IL-12) production and increased intratumoral CD4/Foxp3 ratio [67]. These data suggest that the negative impact of antibiotics on patients' outcome upon immune checkpoint blockade are likely related to the modification of the intestinal microbiota.

Finally, a review and metanalysis of 20 randomized controlled trials of ICIs (including NSCLC trials), showed that the magnitude of OS benefit with ICIs may be sex-dependent, favoring men respect to women with a statistically significant difference (p = 0.0019). According with this result sex should be taken into account in the evaluation risk vs benefit and different approaches may be explored in women or men [72].

Researcher who are involved in clinical trials should develop original and high-quality study designs, such as adaptive or basket biomarker enriched clinical trials, included in large collaborative platforms with multiple active sites and cross-sector collaboration, to better clarify the role and the impact of different factors in the effectiveness of immunotherapy [73]. Considering the high cost of ICI, the estimated total annual cost for first line pembrolizumab in USA is more than 3 milliards [74], a better patients' stratification is of paramount significance for a sustainable cancer care. Furthermore, a clever treatment schedule could help to avoid drug wastage and to optimize economic resources [75]. For pembrolizumab, as an example, the use of a personalized pro kilo dose would have led to save 0.82 billion annually compared to fixed dose of 200 mg every 3 weeks [74]. Cost effectiveness analysis could offer a deepen insight on this subject [76].

New biomarkers able to select patients who could benefit or not from ICIs are an urgent need to significantly improve immunotherapy efficacy and reduce costs. In this regard, recently a three levels plasma microRNA signature classifier (MSC), has shown promising results for treatment selection. The MSC, composed by 24 circulating miRNAs, reflecting an immunosuppressive profile of immune cell subsets, can early identify patients characterized by worse prognosis after ICI treatment, irrespective of PD-L1 expression levels [77].

Together with the identification of new biomarkers, also cognitive, psychological and social factors should be taken in account to personalize immunotherapies maximizing patient's outcomes and further research is needed to implement patients' participation to the clinical decision-making process [78,79].

Conclusions

In conclusion, immune checkpoint blockade has broadly revolutionized the first line treatment of advanced NSCLC patients with no oncogenic drivers. While the combination of anti-PD1/PD-L1 agents and chemotherapy was associated with significant benefit regardless of PD-L1 expression, first-line single-agent immunotherapy prolonged survival only in high PD-L1 selected patients. TMB is emerging as a novel marker, and non-invasive measurement of bTMB could represent a future more feasible tool. To date, TMB positive patients are the best candidate for double immune checkpoint blockade, while platinum-based chemotherapy may represent still the only first line option for patients with no PD-L1 expression and low TMB. Nevertheless, the predictive value of TMB should be further investigated in future randomized trials.

In EGFR mutated NSCLC no activity signals were reported with single-agent pembrolizumab in an early study, however, the combination of first-line chemo-bevacizumab plus immunotherapy produced positive results in oncogene addicted NSCLC patients progressing to previous tyrosine kinase inhibitors. The addition of antiagiogenetics may be also a promising option for patients with liver metastases who seem to have a worse survival outcome upon immunotherapy and chemotherapy combinations. The validation of PD-L1 expression, TMB and other biomarkers in order to identify patients who can mostly benefit from ICIs, the characterization of hyperprogressive disease and of the mechanistic bases explaining the negative impact of corticosteroids, antibiotics use, immunological aging and female sex on patients' outcome upon ICIs represent the tough challenges for future research in this field of cancer treatment.

Conflict of interest

We wish to confirm that there are no significant conflicts of interest associated with this publication that could have influenced its outcome. Marina Chiara Garassino declares consultancies from Astra Zeneca, Roche, Boehringer Ingelheim, BMS, MSD, Eli Lilly, Novartis, Bayer, Pfizer, Sanofy, Italfarmaco. All the other Authors have not conflict of interest to declare (financial, professional or personal).

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