Immunotherapy in Lung Cancer: From a Minor God to the Olympus

4

Alessandro Russo, Michael G. McCusker, Katherine A. Scilla, Katherine E. Arensmeyer, Ranee Mehra, Vincenzo Adamo, and Christian Rolfo

Abstract

Over the last decade, we have witnessed a paradigm shift in cancer treatment, with the advent of novel therapeutic approaches that target or manipulate the immune system, also known as immunotherapy. Blocking immune checkpoints has emerged as an effective strategy with unprecedented results in several solid tumors, including lung cancer. Since 2012 when PD(L)-1 inhibitors showed first clinical signals of activity in lung cancer, immune checkpoint blockade (ICB) has emerged as a novel effective therapeutic strategy in different settings, determining a dramatic change in the therapeutic landscape of both non-small cell lung cancer (NSCLC) and, more recently, small cell lung cancer (SCLC). Although the benefit from this novel therapeutic approach is undeniable, several open questions still remain unanswered. Herein, we summarize the major breakthroughs in the immunotherapy journey in lung cancer and how it is changing our clinical practice.

Keywords

Non-small cell lung cancer · Small cell lung cancer · Immunotherapy · Programmed death 1 · Programmed death-ligand 1 · Cytotoxic T-lymphocyte antigen-4 · Nivolumab · Pembrolizumab · Atezolizumab · Durvalumab · Tumor mutation burden

A. Russo
University of Maryland Medical Center, Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA

Medical Oncology Unit A.O. Papardo & Department of Human Pathology, University of Messina, Messina, Italy

M. G. McCusker · K. A. Scilla · K. E. Arensmeyer · R. Mehra · C. Rolfo (✉)
University of Maryland Medical Center, Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA
e-mail: Christian.rolfo@umm.edu

V. Adamo
Medical Oncology Unit A.O. Papardo & Department of Human Pathology, University of Messina, Messina, Italy

Introduction

The past decade has witnessed a paradigm shift in cancer treatment, with the advent of novel therapeutic approaches that target or manipulate the immune system (immunotherapy) [1] demonstrating unprecedented results in several solid tumors, including lung cancer. The cancer-immunity cycle refers to the delicate balance between the recognition of self while minimizing toxicities related to autoimmunity [2]. The exploitation of the immune system with agents that

A. Naing, J. Hajjar (eds.), *Immunotherapy*, Advances in Experimental Medicine and Biology 1244,
https://doi.org/10.1007/978-3-030-41008-7_4

stimulate it to react against tumor cells has been extensively studied in oncology and traditionally this strategy has not been effective in lung tumors, with multiple vaccination or immunostimulating strategies failing to prove any significant benefit. Recently, a renewed interest on immunotherapy emerged with the identification of immune checkpoints. Each step of the cancer-immunity cycle requires the coordination of numerous factors that have stimulatory and inhibitory actions [2] and among these, recently, two immune checkpoints have emerged as promising therapeutic targets, CTLA-4 (cytotoxic T-lymphocyte antigen-4) and PD-1 (programmed death 1) (Fig. 4.1).

CTLA4 was the first immune checkpoint receptor to be clinically targeted. It is expressed exclusively on T cells and inhibits the development of an active immune response. CTLA-4 acts at the level of T-cell development and proliferation by counteracting the activity of the T-cell costimulatory receptor CD28 through competing for the binding of the same ligands (CD80 also known as B7.1 and CD86 also known as B7.2) [2, 3]. In contrast to CTLA-4 that is involved in early steps of the cancer-immunity cycle, PD-1 and its ligands have a crucial role in the killing of cancer cells. Physiologically, PD-1/PD-L1 have the task of limiting the activity of T cells in peripheral tissues at the time of an inflammatory response to infection thereby limiting autoimmunity [2, 3]. Similar to CTLA-4, PD-1 is expressed on activated T cells and inhibits T-cell responses by interfering with T-cell receptor signaling. PD-1 has two ligands, PD-L1 (B7-H1) that is expressed on antigen-presenting cells (APCs), macrophages, fibroblasts, and T cells and PD-L2 (B7-DC) that is predominantly expressed on antigen-presenting cells (APCs). PD-L1 is also overexpressed in several solid tumors, while PD-L2 is expressed relatively rarely [4, 5]. The role of CTLA-4 and PD-1/PD-L1 in immune suppression and their expression in solid tumors provided the rationale for their therapeutic exploitation. Moreover, CTLA-4 and PD-1 exert their effects through separate pathways and therefore simultaneous targeting of both pathways has also been evaluated to restore antitumor immunity [6].

Since the first demonstration of activity of PD(L)-1 agents in lung cancer in early clinical trials in 2012 [7, 8], immune checkpoint blockade (ICB) has emerged as a novel effective therapeutic strategy in different clinical settings and determined a dramatic shift in the therapeutic landscape of both NSCLC and SCLC (Fig. 4.2). Several biological prognostic and predictive factors in blood and tissue samples have been identified, but unfortunately no single biomarker can perfectly discriminate between responders and non-responders and PD-L1 still remains the only applicable marker in clinical practice to date [9].

Herein, we summarize the major breakthroughs in the immunotherapy journey in lung cancer and how it is changing our clinical practice.

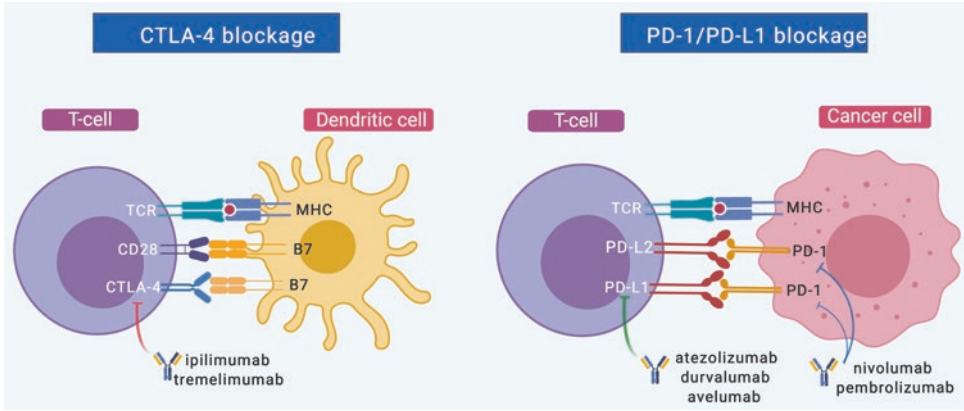

Fig. 4.1 Mechanism of action of CTLA-4 and PD-1/PD-L1 inhibitors. (*Credit: created with BioRender)*

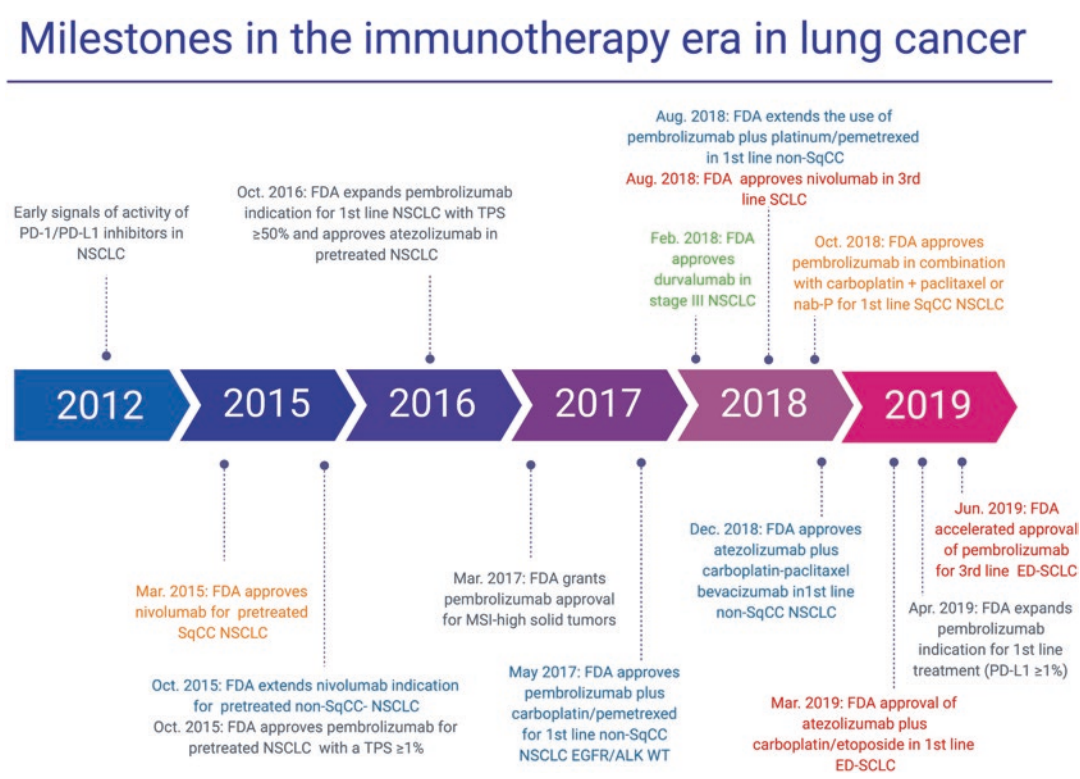

Fig. 4.2 Timeline of major breakthroughs in the immunotherapy era in lung cancer. In orange and in blue FDA approvals in squamous and non-squamous in metastatic NSCLC, respectively; in black data and FDA approvals in metastatic NSCLC independently of histology; in green FDA approval in locally advanced NSCLC; in red FDA approvals in extensive disease SCLC. (*Credit: created with BioRender)*

Early-Stage NSCLC and Locally Advanced NSCLC

Medical treatment of early stage and locally advanced NSCLC has changed little over the last two decades with platinum-based chemotherapy as the cornerstone of treatment either as adjuvant/neo-adjuvant therapy or in association with radiotherapy in inoperable patients. Meta-analyses of randomized phase III trials conducted in 1990s and early 2000s reported an absolute survival benefit at 5 years of 5% from adjuvant/neo-adjuvant approaches in stage IB-IIIA NSCLC compared with surgery alone [10, 11] and 4.5% with concurrent versus sequential chemoradiation in inoperable stage III NSCLC [12]. However, major breakthroughs in molecular biology translated little in early stage NSCLC and no targeted therapies have been approved to date in both early stage and locally advanced NSCLC.

Recently, immune checkpoint blockade has emerged as a new effective therapeutic modality in advanced NSCLC either alone or in combination with platinum-based chemotherapy. The activity and relatively favorable safety profile prompted the evaluation of immune checkpoint inhibitors (ICIs) in earlier lines of treatment, including neo-adjuvant and inoperable stage III NSCLC, leading to the approval of durvalumab as the first in class PD-L1 inhibitor approved as maintenance therapy after concurrent chemoradiation. The role of ICIs as neo-adjuvant therapy has been evaluated in small non-randomized studies with promising results (Table 4.1).

Collectively, single agent PD-1/PD-L1 inhibitors in the palliative setting have been associated with a 7–22% ORR per RECIST. In the neo-adjuvant setting, two to three cycles have resulted

Table 4.1 Clinical studies with immune checkpoint inhibitors in the neo-adjuvant setting

Study name	Resected patients (*n*)	Stage	Drug(s)	Cycles	MPR[a] (%)	ORR (%)
Forde et al. [13]	20	IB-IIIA	Nivolumab	2	45	10
LCM3 [14]	84	IB-IIIB	Atezolizumab	2	18	7
NEOSTAR [15]	23 (arm A) 21 (arm B)	IA-IIIA	Nivolumab Nivolumab + ipilimumab	3 3	17 33	22 19
NADIM [18]	30	IIIA	Nivolumab + carboplatin/paclitaxel	3	80	70
Shu et al. [19]	11	IB-IIIA	Atezolizumab + carboplatin/ nab-paclitaxel	2	64	73

[a]MPR (major pathologic response) defined as <10% residual viable tumor (RVT) in post-therapy specimen

in a major pathological response rate (MPR) of 17–45% in stage I-IIIA NSCLC [13–15]. MPR has been defined as 10% or less residual viable tumor after neo-adjuvant chemotherapy and has been proposed as a surrogate endpoint in neo-adjuvant studies in NSCLC [16]. Recently, immune-related pathologic response criteria (irPRC) have been proposed to better characterize the response of neo-adjuvant ICIs [17]. In contrast, chemo-immunotherapy combos have been associated with higher ORR (70–73%) and MPR (64–80%) [18, 19] and seem to be a more effective strategy in this setting. These data compare favorably with historical controls reporting a MPR of 19–27% [20, 21] and an ORR of approximately 35–50% with platinum-based chemotherapy [22, 23]. Several phase III studies are currently being conducted to evaluate the role of different chemo-immunotherapy combos for three to four courses as neo-adjuvant therapy compared with chemotherapy alone, including CheckMate 816, KEYNOTE-617, IMpower030, and AEGEAN. The results of these trials will provide definitive conclusions on the potential role of ICIs in this therapeutic setting.

Another potential neo-adjuvant approach is the concurrent use of ICIs and radiotherapy. This strategy is under evaluation in a pilot phase II study (NCT03237377).

The role of ICIs in the adjuvant setting is unclear and is currently under evaluation in multiple phase III clinical trials (NCT02273375, PEARLS, ANVIL, and IMpower010). Moreover, the phase II study CheckMate 9TN is currently evaluating the role of nivolumab in patients with residual disease after surgery.

The role of ICIs in inoperable stage III NSCLC is much more defined and durvalumab has been FDA and EMA approved as maintenance therapy in non-progressing patients after concomitant chemoradiation. The goal of using ICIs concomitantly with radiation therapy or immediately after is to augment the antitumor responses typically observed with either modality alone, exploiting the synergistic effect observed with both modalities through multiple mechanisms that include the release of signals and chemokines that recruit inflammatory cells into the tumor microenvironment, including antigen-presenting cells that activate cytotoxic T-cell function, release of neoantigens that can evoke the antitumor response, and upregulation of PD-L1 expression on tumor cells [24, 25]. After a decade of failures with alternative strategies to concurrent chemoradiation with platinum-based chemotherapy by adding a targeted agent [26] or replacing the non-platinum agent with a less toxic compound [27], increasing radiation dose [26], or using a tumor-derived vaccine [28], the PACIFIC trial changed the standard of care, adding durvalumab in the therapeutic armamentarium of inoperable locally advanced NSCLC. This randomized phase III trial evaluated durvalumab at the dosage of 10 mg/m^2 I.V. every 2 weeks versus placebo (2:1 randomization) as consolidative therapy in patients with inoperable stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiation [29]. The trial met its two co-primary endpoints, demonstrating a statistically significant improvement in both PFS (17.2 months in the durvalumab group vs. 5.6 months in the placebo group; HR

0.51, 95% CI, 0.41–0.63) and OS (not reached vs. 28.7 months; HR 0.68, 99.73% CI, 0.47–0.997; $p = 0.0025$). Moreover, durvalumab treatment was associated with a higher ORR (28.4% vs. 16.0%; $p < 0.001$) and a longer time to death or distant metastasis (28.3 months vs. 16.2 months in the placebo group; HR 0.53, 95% CI, 0.41–0.68) [29, 30]. Treatment with durvalumab was well tolerated with an incidence of grade 3/4 adverse events of 30.5% in the durvalumab group versus 26.1% in the placebo group. An unplanned post hoc analysis requested by a health authority evaluated the role of pre-treatment PD-L1 status (unknown in 37% of patients) and showed no benefit in terms of OS in PD-L1 <1% patients (HR 1.36) [30]. However, these data should be considered only exploratory and no firm conclusions can be made due to the sample size (only 60 patients). Based on this analysis, it has been concluded that EMA restricted durvalumab use in PD-L1 ≥1% patients only.

The role of nivolumab and pembrolizumab as consolidative therapy after chemoradiation is under evaluation in phase II/III studies (RTOG 3505, MP-LALC, and HCRN LUN14–179).

PACIFIC evaluated durvalumab after concomitant chemoradiation. However, sequential chemoradiation is a valid alternative in patients who are not candidates for concurrent treatment and therefore the role of consolidative immunotherapy in this setting is not known. The phase II study PACIFIC-6 will address this issue.

Furthermore, several studies (PACIFIC-2, RATIONALE001, NICOLAS, DETERRED, and KEYNOTE-799) are evaluating the addition of PD-1/PD-L1 inhibition during concurrent chemoradiation followed by consolidation with immunotherapy.

First Line Metastatic NSCLC

The success of ICI use in pre-treated NSCLC patients prompted the evaluation of these agents in the upfront setting either alone or in combination with platinum-based chemotherapy or other immunotherapeutic agents. The positive results of the KEYNOTE-024, demonstrating the superiority of pembrolizumab compared with platinum-based chemotherapy in strong PD-L1 expressors (TPS ≥50%) of the EGFR/ALK wild type [31, 32], represented a major improvement in non-oncogene-addicted NSCLCs, which were minimally influenced by major therapeutic innovations in the last two decades [33]. The trial reported an impressive median OS of 30 months in the experimental arm with a statistically significant advantage over chemotherapy despite extensive crossover (64.2%) [32] and represented a major shift in the therapeutic landscape of NSCLC, adding a new molecularly defined subgroup of patients with improved outcome after a chemotherapy-free regimen. Subsequent studies tried to extend the benefit of ICB to a higher patient population with different therapeutic strategies, including evaluation of ICIs in PD-L1 ≥1% patients, chemo-immunotherapy combinations in PD-L1 all comers, and dual blockade with PD-1/PD-L1 inhibitors in combination with anti-CTLA4 agents. The results of these trials are summarized in Table 4.2 and contributed to the expanded use of ICIs in chemotherapy-naïve patients.

The KEYNOTE-042 trial aimed to evaluate the role of pembrolizumab in patients with weak and strong PD-L1 expression (TPS ≥1%) compared with standard-of-care platinum-based chemotherapy. The trial met its primary endpoints, with a statistically significant advantage in terms of OS in patients with a TPS of 50% or greater (HR 0.69, 95% CI 0.56–0.85; $p = 0.0003$), 20% or greater (HR 0.77, 95% CI 0.64–0.92; $p = 0.0020$), and 1% or greater (HR 0.81, 95% CI 0.71–0.93; $p = 0.0018$) [34]. However, when restricting the analysis to the subgroup of patients with a TPS 1–49% no differences in OS were observed (HR 0.92, 95% CI 0.77–1.11), suggesting that strong PD-L1 expressors mostly drove the benefit observed in the study population. These data lead to the extension of the FDA approval of pembrolizumab in chemotherapy-naïve EGFR/ALK wild-type NSCLC patients with a TPS ≥1%. The relatively favorable safety profile and activity seen in this trial make the regimen particularly useful in patients who are not candidates or refuse platinum-based chemotherapy.

Table 4.2 Phase III studies with PD-1/PD-L1 inhibitors in first-line NSCLC

Study	*n*	Arms	Population	PD-L1	Treatment BPD	IO duration	Crossover rate	Median FU (mos)	ORR	PFS (mos)	PFS (HR)	OS (mos)	OS (HR)
KEYNOTE-024 [31, 32]	154 vs. 151	Pembrolizumab vs. Platinum-CHT	NSCLC EGFR/ALK WT	≥50%	Allowed	Up to 35 cyles	64.2%	25.2	44.8% vs. 27.8%	10.3 vs. 6.0	0.50	30.0 vs. 14.2	0.63
KEYNOTE-042 [34]	637 vs. 637	Pembrolizumab vs. CP or carbo-pem	NSCLC EGFR/ALK WT	≥1%	Allowed	Up to 35 cyles	N.A.	14.0	27.2% vs. 26.5%	5.4 vs. 6.6	1.05	16.4 vs. 12.1	0.82)
CheckMate 026	271 vs. 270	Nivolumab vs. Platinum-CHT	NSCLC EGFR/ALK WT	≥1%	Allowed	Until PD	60%	13.5	26% vs. 33%	4.2 vs. 5.9[c]	1.15[c]	14.4 vs. 13.2[c]	1.02[c]
KEYNOTE-407 [35]	278 vs. 281	CP or carbo/ nab-P + pembro vs. CP or carbo/nab-P	SqCC	All comers	Allowed	Up to 35 cyles	31.7%	7.8	57.9% vs. 38.4%	6.4 vs. 4.8	0.56	15.9 vs. 11.3	0.64
KEYNOTE-189 [36, 37]	410 vs. 2016	Ccis/carbo-pem + Pembro vs. cis/carbo-pem	Non-SqCC EGFR/ALK WT	All comers	Allowed	Up to 35 cyles	53.9%	18.7	48.0% vs. 19.4%	9.0 vs. 4.9	0.48	22.0 vs. 10.7	0.56
IMpower150 (ARM B vs. C) [38, 39]	400 vs. 400	ABCP vs. BCP	Non-SqCC (EGFR/ALK allowed)	All comers	Allowed	Until PD	N.A.	19.6 19.7	63.5%[a] vs. 48%[a]	8.3[a] vs. 6.8[a]	0.59[b]	19.2[a] vs. 14.7[a]	0.78[a]
IMpower150 (ARM A vs. C) [38, 39]	402 vs. 400	ACP vs. BCP	Non-SqCC (EGFR/ALK allowed)	All comers	Allowed	Until PD	N.A.	19.6 19.7	40.6% vs. 40.2%	N.A.	0.91	19.4[a] vs. 14.7[a]	0.88[a]
IMpower 130 [40]	451 vs. 228	Atezo + carbo/ nab-P vs. Carbo/ nab-P	Non-SqCC (EGFR/ALK allowed)	All comers	Allowed	Until PD	19.3%	18.5 19.2	49.2%[a] vs. 31.9%[a]	7.0[a] vs. 5.5[a]	0.64[a]	18.6[a] vs. 13.9[a]	0.79[a]
IMpower 131 (ARM B vs. C) [41, 42]	343 vs. 340	Atezo + carbo/ nab-P vs. Carbo/ nab-P	SqCC	All comers	Allowed	Until PD	43%	17.1	49% vs. 41%	6.5 vs. 5.6	0.74	14.6 vs. 14.3	0.92
IMpower132 [43]	292 vs. 286	Atezo + cis/carbo + pem vs. Cis/ carbo+ pem	Non-SqCC EGFR/ALK WT	All comers	Allowed	Until PD	37.1%	14.8	47% vs. 32%	7.6 vs. 5.2	0.60	18.1 vs. 13.6	0.81

CheckMate 227 (TMB ≥10) [44]	139 vs. 160	Nivolumab-ipilumumab vs. Platinum-CHT	NSCLC EGFR/ALK WT	All comers	Allowed	Until PD	N.A.	11.2[d]	45.3% vs. 26.9%	7.2 vs. 5.5	0.58	23.03 vs. 16.72	0.77
MYSTIC (ARM A vs. C) [45, 46]	374 vs. 372	Durvalumab vs. Platinum-CHT	NSCLC EGFR/ALK WT	All comers	Allowed	Until PD	39.5%	30.2	35.6%[b] vs. 37.7%[b]	4.7[b] vs. 5.4[b]	0.87[b]	16.3[b] vs. 12.9[b]	0.76[b]
MYSTIC (ARM B vs. C) [45, 46]	372 vs. 372	urvalumab-tremelimumab vs. Platinum-CHT	NSCLC EGFR/ALK WT	All comers	Allowed	Until PD	39.5%	30.2	34.4%[b] vs. 37.7%[b]	3.9[b] vs. 5.4[b]	1.05[b]	11.9[b] vs. 12.9[b]	0.85[b]

[a]*EGFR/ALK WT intention-to-treat (ITT) population;*[b]*ITT population (PD-L1 ≥ 25%);*[c]*ITT population (PD-L1 ≥ 5%);*[d]*minimum follow-up*

N.A. Not Available, *ABCP* atezolizumab + bevacizumab/carboplatin/paclitaxel, *ACP* atezolizumab + carboplatin/paclitaxel, *BCP* bevacizumab/carboplatin/paclitaxel, *Cis* cisplatin, *CP* carboplatin/paclitaxel, *nab-P* nab-paclitaxel, *Platinum-CHT* platinum-based chemotherapy

In contrast, the CheckMate 026, evaluating nivolumab in chemotherapy-naïve NSCLC EGFR/ALK WT with a PD-L1 expression ≥1%, failed to meet its primary endpoint, showing no statistically significant difference between ICB and chemotherapy in terms of PFS in the intention-to-treat (ITT) population (PD-L1 ≥5%) (HR 1.15, 95% CI 0.91–1.45, $p = 0.25$ for PFS). Furthermore, nivolumab was not associated with any differences in terms of OS (HR 1.02, 95% CI 0.80–1.30) and ORR compared with platinum-based chemotherapy (26% vs. 33%, odds ratio 0.70, 95% CI 0.46–1.06) [47]. Moreover, an exploratory subgroup analysis involving patients with a PD-L1 expression level ≥50% showed no differences between the two treatment arms in both PFS (HR 1.07, 95% CI 0.77–1.49) and OS (HR 0.90, 95% CI 0.63–1.29) [47]. Differences in the study design and population included might have contributed to the differences seen with trials evaluating pembrolizumab monotherapy. Similarly, durvalumab monotherapy failed to prolong both PFS (HR 0.87, 95% CI 0.593–1.285; $p = 0.324$) and OS (HR 0.76, 95% CI 0.564–1.019; $p = 0.036$) in the ITT population (PD-L1 ≥25% with SP263 IHC assay) compared with chemotherapy in the phase III MYSTIC trial (arm A vs. B) [45]. However, subgroup analyses of both studies evaluated the predictive role of tumor mutation burden (TMB) with ICIs. In the CheckMate-026 trial, TMB was evaluated in the tissue using a whole exome assay, dividing patients in three tertiles (<100, 100–242, or ≥243 total missense mutations) [47]. Nivolumab in TMB high (≥243 total missense mutations) patients was associated with improved ORR (47% vs. 28%) and PFS (HR 0.62, 95% CI 0.38–1.00) versus chemotherapy, but not OS (HR 1.10), likely secondary to extensive crossover in the control arm (68%). Interestingly, there was no association between TMB and PD-L1 expression, albeit patients with both PD-L1 ≥50% and high TMB seemed to derive the greatest benefit [47]. Whole exome sequencing is impractical in clinical practice and, therefore, smaller targeted-gene next-generation sequencing (NGS) panels have been used to evaluate this potential biomarker with comparable results [48]. However, the impact of the mutational study of different genes on TMB calculation using different NGS platforms (MSK-IMPACT, Foundation Medicine, etc.) has not been analyzed yet [49]. In the MYSTIC trial, a TMB analysis was conducted in both tissue (Foundation Medicine 315-gene panel) and plasma (GuardantOMNI 500-gene panel). Unfortunately, tissue availability for TMB analysis was limited to only 41% of the ITT population. However, despite these limitations high TMB (≥10 mutations/Mb) predicted a better OS with durvalumab compared with chemotherapy (HR 0.70, 95% CI 0.47–1.06). There was a good correlation between tissue and plasma results for TMB in patients with matched specimens (Spearman's rho = 0.6; Pearson's $r = 0.7$) and blood. TMB ≥20 mutations/Mb were associated with improved OS (HR 0.72, 95% CI 0.50–1.05) and PFS (HR 0.77, 95% CI 0.52–1.13) with durvalumab [46]. As reported previously, TMB and PD-L1 were independent predictive factors, suggesting that these biomarkers can be used as complementary tools when selecting patients for immunotherapy treatment. However, standardization of methods used and robust analytical/clinical validation are needed before extensive clinical implementation of this biomarker is implemented [49].

Avelumab is also under clinical development in first-line versus chemotherapy in PD-L1 positive patients in the ongoing randomized phase III study JAVELIN Lung 100.

The addition of chemotherapy to ICIs is based on the rationale that chemotherapy may expose the immune system to high levels of tumor cell antigens through tumor cell killing, induce secretion of cytokines that ultimately enhance T-cell responses, eliminate immunosuppressive cells (i.e., MDSCs and Tregs), and induce tumor PD-L1 overexpression [33]. Several studies have evaluated the safety and efficacy of multiple chemo-immunotherapy regimens. Most of these trials excluded EGFR-mutated and ALK rearranged NSCLCs, due to the lower activity seen in previous studies in pre-treated patients with PD(L)-1 inhibitors in these molecular subgroups [50–53] and included PD-L1 all comers patients.

KEYNOTE-021 was a multi-cohort phase 1/2 study evaluating different chemotherapy regimens in addition to pembrolizumab. One of the most promising chemotherapy combinations was pembrolizumab plus carboplatin-pemetrexed that was further evaluated in the phase II part of the study in a randomized cohort (cohort G). Preliminary efficacy data showed a significant increase in both ORR (55% vs. 29%, $p = 0.0016$) and PFS (13.0 vs. 8.9 months, HR 0.53), but there were no differences in OS (HR 0.90, at a median follow-up of 10.6 months), likely to the extensive use of PD-1/PD-L1 inhibitors as salvage therapy in the chemotherapy arm (74%) [54]. Based on these preliminary results, FDA approved this regimen for first-line treatment of non-squamous NSCLC EGFR/ALK wild-type lung cancer. Final results of the study after a median follow-up of 23.9 months further confirmed the advantage in terms of ORR (56.7% vs. 30.2%, $p = 0.0016$) and PFS (24.0 vs. 9.3 months; HR 0.53, 95% CI 0.33–0.86; $p = 0.0049$). A statistically significant advantage in terms of OS was also reported in the experimental arm (median OS not reached in the chemo-immunotherapy arm vs. 21.1 months; HR 0.56, $p = 0.0151$), despite an extensive crossover (73.3%), with a relatively favorable safety profile (AEs G3–5 41% vs. 27%) [55]. The subsequent phase III randomized trial KEYNOTE-189 evaluated pembrolizumab in association with platinum-pemetrexed chemotherapy in non-squamous NSCLC EGFR/ALK wild type, PD-L1 all comers. At the first interim analysis (median follow-up of 10.5 months), the addition of pembrolizumab was associated with a statistically significant advantage in both of the two co-primary endpoints of the study, OS (N.R. vs. 11.3 months, HR 0.49; $p < 0.001$) and PFS (8.8 vs. 4.9 months, HR 0.52, $p < 0.001$), independent of PD-L1 IHC expression. Higher ORR (47.6% vs. 18.9%, $p < 0.001$) was reported in the chemo-immunotherapy arm, with higher response rates among PD-L1 strongly positive patients (61.4% vs. 22.9% in PD-L1 ≥50%) [36]. The updated survival data of the trial at a median follow-up of 18.7 months continued to show a statistically significant advantage in both 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; $p < 0.00001$) across all PD-L1 TPS groups. Furthermore, chemo-immunotherapy was also associated with a significant prolongation of PFS2 (17.0 vs. 9.0 months; HR 0.49, 95% CI 0.40–0.59; $p < 0.00001$) [37], suggesting that the combinatorial approach is superior to the sequential use of chemotherapy and ICB (crossover rate of 53.9%). In August 2018, the FDA approved an expanded label for pembrolizumab in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of patients with metastatic non-squamous NSCLC with no EGFR or ALK aberrations.

Three phase III trials evaluated atezolizumab in non-squamous NSCLC in association with different platinum-based chemotherapy regimens: carboplatin/paclitaxel with or without bevacizumab (IMpower150), carboplatin/nab-paclitaxel (IMpower130), and cisplatin or carboplatin/pemetrexed (IMpower132).

IMpower150 was a large randomized phase III trial evaluating atezolizumab in association with carboplatin-paclitaxel (ACP – arm A) versus atezolizumab plus bevacizumab/carboplatin/paclitaxel (ABCP – arm B) versus bevacizumab/carboplatin/paclitaxel (BCP – arm C) in all comer chemotherapy-naïve non-squamous NSCLCs. The trial also enrolled EGFR-mutated and ALK rearranged tumors that had previously been treated with appropriate tyrosine kinase inhibitor (TKI) therapy. The two primary endpoints of the study were PFS both among patients in the ITT population (EGFR/ALK wild-type patients) and among patients in the wild-type (WT) population who had high expression of an effector T-cell (Teff) gene signature in the tumor (Teff-high WT population), and overall survival in the WT population. Efficacy and safety results of arm B and C were presented. ABCP was associated with longer PFS than BCP in the entire study population (8.3 vs. 6.8 months; HR 0.62; 95% CI 0.52-–0.74; $p < 0.001$), in the ITT population (WT) (8.3 vs. 6.8 months; HR 0.61; 95% CI 0.52–0.72; $p < 0.001$), and in the Teff-high WT population (11.3 vs. 6.8 months; HR 0.51, 95% CI 0.38–0.68; $p < 0.001$) [38]. At first interim analysis

(median duration of follow-up approximately 20 months), OS was significantly longer in the WT population with ABCP than with BCP (19.2 vs. 14.7 months; HR 0.78, 95% CI 0.64–0.96; $p = 0.02$) [38]. Interestingly, improved OS with ABCP versus BCP was observed in patients with sensitizing EGFR mutations (Not estimable vs. 17.5 months; HR 0.31, 95% CI 0.11–0.83) and in patients with baseline liver metastases (13.3 vs. 9.4 months; HR 0.52, 95% CI 0.33–0.82). The benefit was independent of PD-L1 expression. A synergistic effect between bevacizumab and atezolizumab can be hypothesized, since no OS benefit was observed with the addition of atezolizumab to carboplatin/paclitaxel in both EGFR-positive patients (21.4 vs. 18·7 months; HR 0.93, 95% CI 0.51–1.68) and in patients with liver metastases (8.9 vs. 9.4 months; HR 0.87, 95% CI 0.57–1.32) [39]. These data suggest that ABCP can be a novel treatment option in first-line non-squamous NSCLC. The use in EGFR-mutated patients progressing after an EGFR TKI is promising, but these data should be confirmed prospectively in a larger cohort of patients. In December 2018, the FDA granted approval for ABCP combination as first-line therapy in EGFR/ALK wild-type NSCLC patients.

IMpower130 was a phase III randomized trial evaluating the addition of atezolizumab to carboplatin/nab-paclitaxel in chemotherapy-naïve non-squamous NSCLC patients. Pemetrexed maintenance was permitted after —four to six chemotherapy cycles in the control arm. Co-primary endpoints of the study were PFS and OS in the ITT EGFR/ALK wild-type population. The trial met its co-primary endpoints, showing a statistically significant improvement in both OS (18.6 vs. 13.9 months; HR 0.79, 95% CI 0.64–0.98; $p = 0{\cdot}033$) and PFS (7.0 vs. 5.5 months; HR 0.64, 95% CI 0.54–0.77; $p < 0{\cdot}0001$) in the ITT WT population. The benefit was observed across all PD-L1 subgroups, but no benefit was observed in the EGFR/ALK positive cohort (HR 0.98 for OS and 0.75 for PFS) [40].

KEYNOTE-407 and IMpower131 evaluated the addition of a PD(L)-1 agent to platinum-based chemotherapy (carboplatin/nab-paclitaxel or paclitaxel) in patients with squamous cell carcinoma of the lung. The addition of pembrolizumab to carboplatin/nab-paclitaxel or paclitaxel compared to chemotherapy alone was associated with a statistically significant improvement of both PFS (6.4 vs. 4.8 months; HR 0.56, 95% CI 0.45–0.70; $p < 0.001$) and OS (15.9 vs. 11.3 months; HR 0.64, 95% CI 0.49–0.85; $p < 0.001$), primary endpoints of the KEYNOTE-407 study, independent of PD-L1 status and taxane used [35]. Based on these results, in October 2018 FDA extended first-line pembrolizumab approval in combination with carboplatin/nab-paclitaxel or paclitaxel in chemotherapy-naïve NSCLC with squamous histology. This represented a major improvement in the upfront treatment of squamous NSCLC that had little changed in the last two decades with marginal incremental benefits with the addition of anti-EGFR mAb [56] or the use of novel chemotherapy agents [57]. The IMpower131 trial evaluated the addition of atezolizumab to either carboplatin/paclitaxel (arm A) or carboplatin/nab-paclitaxel (arm B) versus carboplatin/nab-paclitaxel alone (arm C). Preliminary data of arm B versus C were presented at the 2018 ASCO annual meeting. At a median follow-up of 17.1 months, addition of atezolizumab to first-line carboplatin/nab-paclitaxel was associated with a statistically significant improvement in PFS compared with carboplatin/nab-paclitaxel alone (6.3 vs. 5.6 months; HR 0.71, 95% CI 0.60–0.85; $p = 0.0001$), but failed to meet the other co-primary endpoint, with no statistically significant differences in terms of OS (14.0 vs. 13.9 months; HR 0.96, 95% CI 0.78–1.18; $p = 0.6931$) [58]. The definitive results of this trial, including those of arm A, are awaited and could clarify the role of atezolizumab in first-line treatment of squamous NSCLC.

Finally, IMpower132 evaluated atezolizumab in combination with platinum-pemetrexed in chemotherapy-naïve non-squamous NSCLC without EGFR or ALK genetic alterations. The study met one of its two co-primary endpoints with a significant advantage in terms of PFS (7.6 vs. 5.2; HR 0.60, 95% CI 0.49–0.72; $p < 0.0001$), but did not show any statistically significant advantage in terms of OS (18.1 vs. 13.6 months; HR

0.81; 95% CI 0.64–1.03; $p = 0.0797$) at the first interim analysis (median follow-up of 14.8 months), despite a 4.5-month survival gain [43]. A longer follow-up can provide definitive conclusions on the efficacy of this combination.

Another potential strategy is to combine PD(L)-1 inhibitors with other immune checkpoint inhibitors in order to optimize the blockage of immune suppressive signals. One of the most promising combinatorial approaches is to combine PD(L)-1 and CTLA-4 inhibitors. The combination has shown efficacy in metastatic melanoma [59] and renal cell carcinoma [60]. The safety and efficacy of nivolumab-ipilimumab was first tested in NSCLC in the multi-cohort phase 1 CheckMate-012 study. Different schedules were tested and the results of the two arms with nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 12 weeks or every 6 weeks of the randomized part of the study were presented. Dual blockage was associated with a promising clinical activity with ORR of 47% and 38% and median PFS of 8.1 months and 3.9 months, respectively. High PD-L1 expression (≥1%) was associated with higher ORR (57% in both treatment arms). The combination was associated with high frequency of serious adverse events with 37% and 33% of patient experiencing irAEs G3–4 in patients treated with ipilimumab 1 mg/kg every 12 weeks and every 6 weeks, respectively [61]. Moreover, evaluation of tissue TMB through whole exome sequencing showed that this biomarker strongly predicted efficacy with combination PD-1 plus CTLA-4 blockade, independent of PD-L1 expression [62]. Based on these data, nivolumab, 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, was further evaluated in the phase II CheckMate-568 study, with ORR in PD-L1 ≥1% patients as primary endpoint. The combination was associated with increased activity among PD-L1 positive patients (ORR was 41% in PD-L1 ≥1% vs. 15% in PD-L1 <1%). Efficacy on the basis of TMB, evaluated with the FoundationOne CDx assay, was included as a secondary endpoint. TMB ≥10 mut/Mb was identified as the optimal cut-off value for efficacy and was associated with improved ORR (43.7% vs. 23.5% for TMB high and low, respectively) and PFS (7.1 vs. 2.6 months for TMB high and low, respectively), regardless of PD-L1 expression. Safety profile was in line with previous studies, with G3–4 treatment-related AEs seen in 29% of patients [63]. These results were confirmed in the randomized phase III CheckMate-227 study, which met its co-primary endpoints of PFS with the nivolumab-ipilimumab combination versus chemotherapy in first-line advanced NSCLC with high TMB (≥10 mutations/Mb), using the FoundationOne CDx assay, regardless of PD-L1 expression. Among patients with TMB ≥10%, dual blockage was associated with higher ORR (45.3% vs. 26.9%) and longer PFS (7.2 months vs. 5.5 months, HR 0.58; $p < 0.001$) compared with platinum-based chemotherapy. Responses were durable, with 43% of patients progression-free at 1 year and the advantage in PFS was independent of PD-L1 expression (≥1% vs. <1%) compared with 13% with chemotherapy. No differences were observed in terms of PFS in patients with low TBM (<10 Mb) (HR 1.07) [44]. Based on these promising efficacy data, nivolumab-ipilimumab was submitted for FDA approval in July 2018. Unfortunately, in October 2018 updated OS data, the other co-primary endpoint of the trial, for the combination showed no difference in OS between patients whose tumors had TMB ≥10 mut/Mb or <10 mut/Mb compared with chemotherapy (23.03 vs. 16.72 months; HR, 0.77; 95% CI, 0.56–1.06). In January 2019, Bristol-Myers Squibb (BMS) withdrew the application for FDA approval while awaiting the final data from part 1a of the study (nivolumab-ipilimumab vs. chemotherapy in PD-L1 ≥1% patients).

The role of TMB as predictive biomarkers for dual immune checkpoint blockage was also explored in the randomized phase III MYSTIC trial. This was a three arm randomized phase III trial comparing durvalumab (arm A) or durvalumab-tremelimumab (arm B) with chemotherapy in stage IV NSCLC EGFR/ALK wild type, irrespective of PD-L1. Primary endpoints were PFS and OS with durvalumab-tremelimumab versus chemotherapy in PD-L1 ≥25% patients. The trial failed to meet its co-primary endpoints

due to the absence of any statistically significant differences between the two treatment arms in both PFS (3.9 vs. 5.4 months; HR 1.05, 97.54% CI 0.722–1.534; $p = 0.705$) and OS (11.9 vs. 12.9; HR 0.85, 98.77% CI 0.611–1.173; $p = 0.202$) in PD-L1 ≥25% patients. However, an exploratory analysis evaluated TMB in tissue (using FoundationOne CDx assay) and in the blood (using the 500-gene GuardantOMNI panel). TMB in the tissue was evaluable only in 41% of the ITT population and high TMB (≥10 mut/Mb) predicted improved OS with durvalumab-tremelimumab compared to chemotherapy (16.6 vs. 10.9 months; HR 0.72, 95% CI 0.48–1.09). In contrast, in patients with low TMB (<10 mt/Mb), dual blockage was inferior to chemotherapy (8.4 vs. 13.8 months; HR 1.39, 95% CI 1.0–1.32). Blood TMB was assessed in 72.4% and showed a good correlation with tissue in patients with matched tumor samples. Interestingly, increasing blood TMB values correlated with increased OS HR and a TMB ≥20 mut/Mb was selected as the optimal cut-off value. Indeed, patients with high TMB in the blood experienced longer OS (21.9 vs. 10 months; HR 0.49, 95% CI 0.32–074) with durvalumab-tremelimumab compared with chemotherapy, but not in those with low TMB (≤20 mut/Mb) in the blood (median OS 8.5 vs. 11.6 months; HR 1.16, 95% CI 0.93–1.45) [46].

These results are promising and suggest that TMB can be a valid biomarker for patient selection, albeit several open questions still remain unanswered, including optimal cut-off value and standardized detection method. There is an urgent need to overcome the naïve vision of a single biomarker to identify patients who are most likely to respond to ICB therapy, moving to the integration and simultaneous evaluation of multiple clinically relevant biomarkers [64] (Fig. 4.3).

Pre-treated NSCLC

Immune checkpoint inhibitors targeting PD-1/PD-L1 dramatically changed the therapeutic landscape of pre-treated NSCLC.

In 2012, the first in human trial of nivolumab in heavily pre-treated solid tumors, including NSCLC, showed promising activity for this agent with a response rate of 18% and durable responses, exceeding results with historical controls using conventional therapeutic agents [7], proving the activity of ICB in a disease not traditionally considered to be immunogenic. Since the initial study, several PD(L)-1 compounds were tested in second-/third-line NSCLC, demonstrating superiority over the standard of care at that time (docetaxel) and now nivolumab, pembrolizumab, and atezolizumab are approved in this

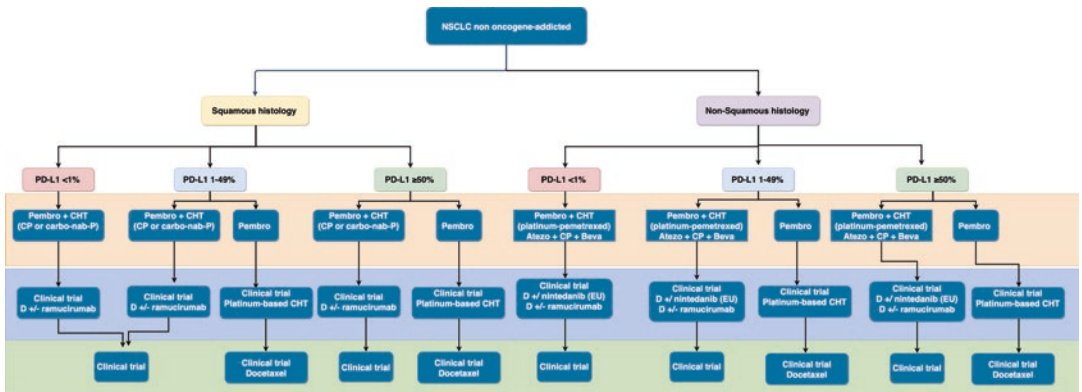

Fig. 4.3 New therapeutic algorithm in advanced/metastatic NSCLC with available therapeutic options. *Legend: Pembro, pembrolizumab; Atezo, atezolizumab; D, docetaxel; CP, carboplatin/paclitaxel; nab-P, nab-paclitaxel; Beva, bevacizumab; EU, approved only by European Medicine Agency; CHT, chemotherapy*

setting. Development of these drugs followed different pathways, since some of them were tested in unselected patient populations (nivolumab, atezolizumab, and avelumab), whereas others followed biomarker-driven development (pembrolizumab).

Nivolumab was evaluated in two large randomized phase III studies with similar designs using docetaxel as the control arm. CheckMate 017 evaluated nivolumab in second-line squamous NSCLC [52], whereas CheckMate 057 addressed second−/third3-line non-squamous NSCLC [53]. PD-L1 IHC expression was retrospectively analyzed using the 28–8 assay. Both studies met the primary endpoints, showing a statistically significant advantage in terms of OS compared with docetaxel in both squamous (9.2 vs. 6.0 months; HR 0.59, 95% CI 0.44–0.79; $p < 0.001$) and non-squamous NSCLC (12.2 vs. 9.4 months; HR 0.73; 96% CI, 0.59–0.89; $p = 0.002$) [52, 53]. Nivolumab was also superior to docetaxel in terms of ORR (19–20% vs. 9–12%) and safety profile (treatment-related AEs G3–4 in 7–10% vs. 54–55%) in both studies, as well as in PFS in squamous histology only (3.5 vs. 2.8 months; HR 0.62, 95% CI 0.47–0.81; $p < 0.001$) [52, 53]. Interestingly, PD-L1 expression as a predictive biomarker produced contrasting results between the two trials, despite similar study designs and the same assessment methods. The different mutational burden of squamous and non-squamous histology, as well as the frequency of oncogene-addicted tumors, might have contributed to this discrepancy. Moreover, a landmark analysis of the CheckMate 057 demonstrated that, excluding patients who had died in the first 3 months, nivolumab was superior to docetaxel in both PD-L1 positive and negative patients [65]. For this reason, nivolumab was approved in both squamous and non-squamous pre-treated NSCLC patients, irrespective of PD-L1 status. Recently, a pooled analysis of both studies showed an encouraging 3-year OS of 17% [66]. These results are noteworthy when compared to conventional chemotherapy. Only 8% of the patients in the docetaxel arm were alive at 3 years, and the plateau in the survival curves suggests a potential long-term benefit.

Atezolizumab was compared with docetaxel in pre-treated NSCLC in phase II (POPLAR) and phase III randomized studies (OAK), showing improved OS across all PD-L1 expression levels with incremental efficacy results at the increase of PD-L1 IHC expression in tumor cells (TC) or tumor-infiltrating immune cells (IC) using the SP142 assay [51, 67]. However, this IHC assay reported in some harmonization study lower tumor cell staining than other tests [68, 69] and is not FDA approved for lung cancer patients. An exploratory analysis was conducted in plasma samples collected in both trials to evaluate blood TMB using the FoundationOne CDx NGS assay, using POPLAR samples as training sets and validating the optimal cut-off value with the OAK samples. Blood TMB ≥16 mut/Mb (27% of the blood evaluable population of the OAK trial) was clearly predictive of improved PFS, showing a good correlation with tissue TMB values and no association with strong PD-L1 expression [70]. Based on the results of the OAK trial, in October 2018, FDA granted atezolizumab approval for pre-treated NSCLC, irrespective of PD-L1 status.

The development of pembrolizumab in NSCLC started with the phase 1 multi-cohort study KEYNOTE-001, which evaluated the safety and activity of this compound, and also validated the companion diagnostic 22C3 IHC assay for PD-L1 expression. Pembrolizumab was well tolerated with few treatment-related AEs of grade 3 or more (9.5% of the patients) and showed good clinical activity with an ORR of 19.4%, a median PFS of 3.7 months, and a median OS of 12.0 months in the overall population. No significant differences in efficacy or side-effect profile were reported with different schedules used (2 mg/kg or 10 mg/kg every 3 weeks) and a PD-L1 TPS ≥50% was associated with a higher response rate and longer PFS and OS [71]. In October 2015, the U.S. FDA granted accelerated approval for pembrolizumab for NSCLC patients whose disease had progressed after other treatments and with tumor expression of PD-L1, assessed with the companion diagnostic PD-L1 IHC 22C3 pharmDx test. The subsequent randomized phase II/III study KEYNOTE-010

compared pembrolizumab at two different dosages (2 mg/kg or 10 mg/kg every 3 weeks) to docetaxel in pre-treated NSCLC patients, PD-L1 positive (TPS ≥1%). The trial met its primary endpoint, reporting a statistically significant advantage in OS in both pembrolizumab arms (10.4 vs. 8.5 months and 12.7 vs. 8.5 months, respectively, for pembrolizumab 2 mg/kg and 10 mg/kg, with a HR of 0.71 and 0.61). Similarly to previous immunotherapy studies in pre-treated NSCLC, no differences were observed in PFS curves between the three treatment arms. Patients with strong PD-L1 expression (TPS ≥50%) derived the greatest OS benefit with both pembrolizumab 2 mg/kg (14.9 vs. 8.2 months; HR 0.54, 95% CI 0.38–0.77; p = 0·0002) and 10 mg/kg schedules (17.3 vs. 8.2 months; HR 0.50, 95% CI 0.36–0.70; $p < 0.0001$) [50].

Avelumab was evaluated in the phase III randomized study JAVELIN Lung 200, which compared this PD-L1 inhibitor with docetaxel in pre-treated NSCLC, independent of PD-L1 expression. The study failed to meet its primary endpoint, showing no statistically significant differences in terms of OS between the two treatment arms in the overall study population (10.5 vs. 9.9 months; HR 0.90, 96% CI, 0.75–1.08; p = 0.12) and in PD-L1 positive patients (≥1%) (11.4 vs. 10.3; HR 0.90, 96% CI 0.72–1.12; p = 0.16) [72]. The lack of OS benefit might be attributable to the better performance of the control arm than expected on similar randomized trials of anti–PD-1/PD-L1 agents (8.5–9.6 months) [50, 51], likely due to the subsequent use of ICIs. Exploratory subgroup analyses showed an increasing clinical activity with avelumab in patients with higher PD-L1 expression (HR 0.67 and HR 0.59 with ≥50% and ≥80% PD-L1 expression) [72], consistent with other PD(L)-1 inhibitors in NSCLC.

Durvalumab was evaluated as third-line option in the single-arm phase II study ATLANTIC. The trial included three cohorts of patients: EGFR+/ALK+ NSCLC with PD-L1 expression ≥25% (cohort 1), EGFR/ALK wild-type NSCLC with PD-L1 expression ≥25% (cohort 2), and PD-L1 ≥90% (cohort 3). The clinical activity and safety profile of durvalumab were consistent with those of other PD(L)-1 inhibitors. Responses were higher in EGFR/ALK wild-type patients and increased with higher PD-L1 expression levels (30.9% in PD-L1 ≥90% and 16.4% in PD-L1 ≥25% among EGFR/ALK wild-type patients) [73]. The 12.2% ORR reported among EGFR/ALK positive patients suggests that a subgroup of oncogene-addicted NSCLCs can derive benefit from ICB and supports further evaluation of this strategy in these patients.

Neither durvalumab nor avelumab is approved in stage IV NSCLC.

ICIs and SCLC

Treatment of extensive small cell lung cancer (ED-SCLC) has not changed over the last three decades with platinum-etoposide as the standard-of-care first-line option and topotecan or cyclophosphamide, doxorubicin, and vincristine (CAV) mostly used in subsequent treatment lines [74]. Several attempts to improve outcomes of ED-SCLC patients by incorporating novel chemotherapy agents (irinotecan, pemetrexed) or using targeted therapies (bevacizumab) failed to show any significant survival benefits [75–77]. As a consequence, survival of ED-SCLC patients enrolled in phase III trials did not improve significantly over the years [78].

The use of ICIs is attractive in SCLC due to the high number of somatic mutations seen in this tumor type that is one of the highest reported across human solid tumors [79].

The first ICI tested in ED-SCLC was the anti-CTLA4 agent ipilimumab. A phase II study evaluated the addition of ipilimumab to carboplatin/paclitaxel as first-line treatment in two alternative regimens, concurrent ipilimumab (ipilimumab + paclitaxel/carboplatin followed by placebo + paclitaxel/carboplatin) or phased ipilimumab (placebo + paclitaxel/carboplatin followed by ipilimumab + paclitaxel/carboplatin). Phased ipilimumab was associated with a non-statistically significant longer median OS compared with paclitaxel/carboplatin alone (12.9 vs. 9.9 months; HR, 0.75, 95% CI 0.46–1.23; p = 0.13) and a statistically significant improvement of immune-

related PFS (HR, 0.64, 95% CI 0.40–1.02; $p = 0.03$) [80]. Based on these promising results, a subsequent randomized phase III trial evaluated the addition of phased ipilimumab to platinum-etoposide versus platinum-etoposide alone. The trial failed to show a significant improvement in OS (11.0 vs. 10.9 months; HR 0.94; 95% CI, 0.81–1.09; $p = 0.3775$), the primary endpoint of the study, and in PFS (4.6 vs. 4.4 months; HR 0.85; 95% CI, 0.75–0.97) with the addition of phased ipilimumab [81].

The positive results of PD(L)-1 inhibitors in NSCLC prompted the evaluation of these compounds in SCLC in multiple clinical settings, including upfront treatment, maintenance therapy in non-progressing patients after standard platinum-etoposide chemotherapy, and in subsequent lines of therapy (Table 4.3).

Nivolumab was evaluated in pre-treated ED-SCLC in a phase I/II study (CheckMate 032) in monotherapy or in combination with ipilimumab. The trial initially evaluated nivolumab monotherapy at the dosage of 3 mg/kg ($n = 98$) and the combination nivolumab 1 mg/kg plus ipilimumab 3 mg/kg ($n = 61$), or nivolumab 3 mg/kg plus ipilimumab 1 mg/kg ($n = 54$). Nivolumab monotherapy was associated with an ORR of 11%, whereas the combination achieved a 23% ORR in patients treated with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and a 19% ORR in those receiving nivolumab 3 mg/kg plus ipilimumab 1 mg/kg. Tumor responses occurred in patients, irrespective of PD-L1 expression. Durable responses were observed, with a promising 1-year and 2-year OS rate of 27% and 14% for nivolumab 3 mg/kg and 40% and 26% for nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, respectively [82, 83]. Based on these data, a randomized phase II part of the study was launched, comparing nivolumab 3 mg/kg ($n = 147$) and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg ($n = 95$). ORR was in line with those of the non-randomized part of the study (12% for nivolumab and 21% for nivolumab-ipilimumab), regardless of platinum sensitivity, line of therapy, and PD-L1 status [83]. An exploratory analysis evaluated the predictive value of TMB assessed through whole exome sequencing in both patients of the non-randomized and randomized parts of the study. Patients with TMB high (≥248 total missense mutations) were associated with the highest ORR with both nivolumab (4.8% with TMB low, 6.8% with TMB intermediate, and 21.3% with TMB high) and nivolumab-ipilimumab (22.2% with TMB low, 16.0% with TMB intermediate, and 46.2% with TMB high). Furthermore, patients with TMB high experienced the highest OS with both nivolumab (1-year OS rate of 22.1% with TMB low, 26.0% with TMB intermediate, and 35.2% with TMB high) and nivolumab-ipilimumab (23.4% with TMB low, 19.6% with TMB intermediate, and 62.4% with TMB high) [84], further confirming the potential role of TMB as a biomarker for immunotherapy across lung cancers. Based on these preliminary results, in August 2018, FDA approved nivolumab as third-line option in ED-SCLC. Nivolumab is currently being compared with second-line chemotherapy (topotecan or amrubicin) in the phase III randomized trial CheckMate 331 in PD-L1 all comers patents. Primary endpoint of the study is OS.

Similarly, pembrolizumab demonstrated efficacy in pre-treated SCLC in the phase II KEYNOTE-158 study, with 19% ORR and durable activity (6-month PFS rate: 38.9% in PDL1+ and 14.3% in PDL1- patients; 1-year OS rate: 53.1% in PDL1+ and 30.7% in PDL1- patients) [85]. In June 2019, FDA granted accelerated approval of pembrolizumab for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy, based on tumor response rate and durability of response.

Nivolumab 240 mg every 2 weeks and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks versus placebo were also evaluated as a maintenance strategy in ED-SCLC non-progressing patients after platinum-etoposide in the phase III trial CheckMate 451. The trial did not meet the primary endpoint, without showing a statistically significant advantage in terms of OS with the dual ICB versus placebo (HR 0.92, $p = 0.37$) [86]. PFS and ORR with both nivolumab-ipilimumab and nivolumab alone

Table 4.3 Clinical activity of immune checkpoint inhibitors in phase I-III studies in ED-SCLC

Study	Phase	*n*	Population	Arm(s)	ORR	PFS (mos)	6-mo PFS	OS (mos)	1-yr OS
First-line studies									
Reck et al. [80]	2	130	ED-SCLC	Carboplatin/paclitaxel Carboplatin/paclitaxel + concurrent ipilimumab Carboplatin/paclitaxel + phased ipilimumab	49% 32% 57%	5.2 3.9 5.2	N.A. N.A. N.A.	9.9 9.1 12.9	N.A. N.A. N.A.
Reck et al. [81]	3	954	ED-SCLC	Carboplatin/etoposide + phased ipilimumab Carboplatin/etoposide	62% 62%	4.6 4.4	N.A.	11.0 10.9	40% 40%
IMpower133 [88]	3	403	ED-SCLC	Atezolizumab 1200 mg + carboplatin/etoposide Carboplatin/etoposide	60.2% 64.4%	5.2 4.3	30.9% 22.4%	12.3 10.3	51.7% 38.2%
Maintenance studies									
Gadgeel et al. [87]	2	45	ED-SCLC	Pembrolizumab 200 mg	14.7%	1.4	20%	9.6	37%
CheckMate 451 [86]	3	834	ED-SCLC	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg Nivolumab 240 mg Placebo	N.A. N.A. N.A.	1.7 1.9 1.4	20% 21% 10%	9.2 10.4 9.6	41% 44% 40%
≥2 line studies									
KEYNOTE-028 [90]	1b	24	PD-L1+, ED-SCLC	Pembrolizumab 10 mg/kg	33.3%	1.9	28.6%	9.7	37.7%
KEYNOTE-158 [85]	2	107	ED-SCLC	Pembrolizumab 200 mg	19%	2.0	38.9% (PDL1+) 14.3% (PDL1-)	9.1	53.1% (PDL1+) 30.7% (PDL1-)
CheckMate 032 (non-rand.) [82–84]	1/2	98 61	ED-SCLC	Nivolumab 3 mg/kg Nivolumab 1 mg/kg + ipilimumab 3 mg/kg	11% 23%	N.A. N.A.	N.A. N.A.	4.1 7.8	27% 40%
CheckMate 032 (randomized) [82–84]	1/2	147 95	ED-SCLC	Nivolumab 3 mg/kg Nivolumab 1 mg/kg + ipilimumab 3 mg/kg	12% 21%	N.A. N.A.	N.A. N.A.	N.A. N.A.	N.A. N.A.
Study 1108 [91]	2	21	ED-SCLC	Durvalumab 10 mg/kg	9.5%	1.5	14%	4.8	27.6%
Study 10 (NCT02261220) [92]	1	30	ED-SCLC	Durvalumab 20 mg/kg + tremelimumab 1 mg/kg	13.3%	1.8	16.3%	7.9	41.7%

were modest and in line with the results of a phase II study with pembrolizumab in the same setting [87], suggesting a modest activity of ICIs in the maintenance setting in unselected patients.

The role of ICIs in combination with chemotherapy is being explored in multiple randomized phase III trials, including CASPIAN (durvalumab ± tremelimumab + platinum-etoposide vs. platinum-etoposide), KEYNOTE-604 (platinum-etoposide ± pembrolizumab), and IMpower133 (carboplatin-etoposide ± atezolizumab). The preliminary results of IMpower133 were recently presented and showed, at a median follow-up of 13.9 months, an OS (12.3 vs. 10.3 months; HR 0.70, 95% CI, 0.54–0.91; $p = 0.0069$) and PFS (5.2 vs. 4.3 months; HR 0.77, 95% CI, 0.62–0.96; $p = 0.017$) advantage for chemo-immunotherapy combination. This 2-month OS advantage with addition of atezolizumab was associated with a 13% higher 1-year OS compared with carboplatin-etoposide alone (51.7% vs. 38.2%). The toxicity of atezolizumab plus carboplatin and etoposide was relatively favorable, with no new findings and in line with the safety profile of chemotherapy and atezolizumab alone. Interestingly, an exploratory analysis evaluating the predictive role of blood TMB, assessed through the FoundationOne CDx assay, showed a consistent OS and PFS benefit above and below the prespecified cut-offs of 10 and 16 mutations per megabase [88], questioning the role of TMB as a predictive biomarker to immunotherapy response in SCLC. This is the first trial showing a survival advantage in first-line treatment of ED-SCLC compared with platinum-etoposide after three decades of unsuccessful therapeutic efforts. However, the overall survival benefit is at the moment narrow (only 2 months of absolute OS increase) and it is still unclear whether a combinatorial approach is superior to a sequential strategy, although it is now clear that a maintenance strategy is not effective, at least in unselected patient populations. Furthermore, this schedule seems to be cost-ineffective [89]. The results of ongoing phase III studies with chemo-immunotherapy combinations and CheckMate 331 in second-line versus standard-of-care chemotherapy can provide definitive conclusions on the exact place in therapy of ICIs in ED-SCLC. Moreover, the identification of reliable predictive biomarkers is crucial to overcome the limits of PD-L1 expression (uncertain predictive value, lower expression in SCLC than observed in other solid tumors, including NSCLC) and TMB (conflicting results, tissue availability, and methods' standardization) in this aggressive disease.

On June 27, 2019, AstraZeneca announced that CASPIAN met its primary endpoint, showing a statistically significant and clinically meaningful improvement in OS in combination with etoposide and platinum-based chemotherapy as upfront therapy in patients with ED-SCLC. The full results of the study have not been presented yet and are eagerly awaited.

Conclusions and Future Perspectives

Immunotherapy represented a major breakthrough in lung cancer management and today represents a backbone of treatment in several settings. Although the benefit from this novel therapeutic approach is undeniable, several open questions still remain unanswered. Future clinical trials should define the optimal treatment duration (elective discontinuation after 2 years? Until progression?), efficacy and safety in special populations that are often excluded (patients with viral chronic infections, autoimmune disease, ECOG performance status ≥2, and active brain metastases) or underrepresented in clinical trials (elderly, racial minorities), and novel predictive biomarkers that can better select candidates for immunotherapy. The role of TMB in tissue and/or in liquid biopsy is promising, but is still far from an immediate application in clinical practice. Furthermore, the use of plasma-cell-free-DNA and other circulating biomarkers (exosomes, circulating tumor cells, and cytokines) on liquid biopsy is under active evaluation and might provide useful information that can integrate PD-L1 in the decision-making process. Finally, longer follow-up of clinical trials reported so far and post-approval studies will

provide further details on the long-term safety of ICIs either as single agent or in combination with chemotherapy.

Conflict of Interest Disclosures Dr. Rolfo reports personal fees from Novartis, personal fees from MSD, non-financial support from OncoDNA, personal fees and non-financial support from GuardantHealth, outside the submitted work. Dr. Mehra reports research funding from AstraZeneca and consultation for Genentech. All other authors have no conflicts of interest to report.

References

1. Pauken KE, Wherry EJ. Overcoming T cell exhaustion in infection and cancer. Trends Immunol. 2015;36(4):265–76.
2. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013;39(1):1–10.
3. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252–64.
4. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. Cell. 2015;161(2):205–14.
5. Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations. Sci Transl Med. 2016;8(328):328rv4.
6. Pico de Coaña Y, Choudhury A, Kiessling R. Checkpoint blockade for cancer therapy: revitalizing a suppressed immune system. Trends Mol Med. 2015;21(8):482–91.
7. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Horn L, Drake CG, Pardoll DM, Chen L, Sharfman WH, Anders RA, Taube JM, McMiller TL, Xu H, Korman AJ, Jure-Kunkel M, Agrawal S, McDonald D, Kollia GD, Gupta A, Wigginton JM, Sznol M. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443–54.
8. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, Pitot HC, Hamid O, Bhatia S, Martins R, Eaton K, Chen S, Salay TM, Alaparthy S, Grosso JF, Korman AJ, Parker SM, Agrawal S, Goldberg SM, Pardoll DM, Gupta A, Wigginton JM. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366(26):2455–65.
9. Fujii T, Naing A, Rolfo C, Hajjar J. Biomarkers of response to immune checkpoint blockade in cancer treatment. Crit Rev Oncol Hematol. 2018;130:108–20.
10. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet. 2014;383(9928):1561–71.
11. Burdett SS, Stewart LA, Rydzewska L. Chemotherapy and surgery versus surgery alone in non-small cell lung cancer. Cochrane Database Syst Rev. 2007;3:CD006157.
12. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, Belderbos J, Clamon G, Ulutin HC, Paulus R, Yamanaka T, Bozonnat MC, Uitterhoeve A, Wang X, Stewart L, Arriagada R, Burdett S, Pignon JP. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(13):2181–90.
13. Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, Zahurak M, Yang SC, Jones DR, Broderick S, Battafarano RJ, Velez MJ, Rekhtman N, Olah Z, Naidoo J, Marrone KA, Verde F, Guo H, Zhang J, Caushi JX, Chan HY, Sidhom JW, Scharpf RB, White J, Gabrielson E, Wang H, Rosner GL, Rusch V, Wolchok JD, Merghoub T, Taube JM, Velculescu VE, Topalian SL, Brahmer JR, Pardoll DM. Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med. 2018;378(21):1976–86.
14. Kwiatkowski DJ, Rusch VW, Chaft JE, Johnson BE, Nicholas A, Wistuba II, et al. Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Interim analysis and biomarker data from a multicenter study (LCMC3). J Clin Oncol. 2019;37(15_suppl):8503.
15. Cascone T, William WN, Weissferdt A, Lin HY, Leung CH, Carter BW, et al. Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): Clinical and correlative results from the NEOSTAR study. J Clin Oncol. 2019;37(15_suppl):8504.
16. Hellmann MD, Chaft JE, William WN Jr, Rusch V, Pisters KM, Kalhor N, Pataer A, Travis WD, Swisher SG, Kris MG, University of Texas MD Anderson Lung Cancer Collaborative Group. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. Lancet Oncol. 2014;15(1):e42–50.
17. Cottrell TR, Thompson ED, Forde PM, Stein JE, Duffield AS, Anagnostou V, Rekhtman N, Anders RA, Cuda JD, Illei PB, Gabrielson E, Askin FB, Niknafs N, Smith KN, Velez MJ, Sauter JL, Isbell JM, Jones DR, Battafarano RJ, Yang SC, Danilova L, Wolchok JD, Topalian SL, Velculescu VE, Pardoll DM, Brahmer JR, Hellmann MD, Chaft JE, Cimino-Mathews A, Taube JM. Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: a proposal for quantitative immune-related pathologic response criteria (irPRC). Ann Oncol. 2018;29(8):1853–60.
18. Provencio M, Nadal E, Insa A, García Campelo R, Huidobro G, Domine M, et al. OA01.05 phase II study of neo-adjuvant chemo/immunotherapy for resectable

stages IIIA non-small cell lung cancer-nadim study-SLCG. J Thorac Oncol. 2018;13(10):S320.
19. Shu CA, Grigg C, Chiuzan C, Garofano RF, Patel V, Hernandez S, et al. Neoadjuvant atezolizumab + chemotherapy in resectable non-small cell lung cancer (NSCLC). J Clin Oncol. 2018;36(15_suppl):8532.
20. Chaft JE, Rusch V, Ginsberg MS, Paik PK, Finley DJ, Kris MG, Price KA, Azzoli CG, Fury MG, Riely GJ, Krug LM, Downey RJ, Bains MS, Sima CS, Rizk N, Travis WD, Rizvi NA. Phase II trial of neoadjuvant bevacizumab plus chemotherapy and adjuvant bevacizumab in patients with resectable nonsquamous non-small-cell lung cancers. J Thorac Oncol. 2013;8(8):1084–90.
21. Pataer A, Kalhor N, Correa AM, Raso MG, Erasmus JJ, Kim ES, Behrens C, Lee JJ, Roth JA, Stewart DJ, Vaporciyan AA, Wistuba II, Swisher SG, University of Texas M. D. Anderson Lung Cancer Collaborative Research Group. Histopathologic response criteria predict survival of patients with resected lung cancer after neoadjuvant chemotherapy. J Thorac Oncol. 2012;7(5):825–32.
22. Scagliotti GV, Pastorino U, Vansteenkiste JF, Spaggiari L, Facciolo F, Orlowski TM, Maiorino L, Hetzel M, Leschinger M, Visseren-Grul C, Torri V. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. J Clin Oncol. 2012;30(2):172–8.
23. Westeel V, Quoix E, Puyraveau M, Lavolé A, Braun D, Laporte S, Bigay-Game L, Pujol JL, Ozenne G, Rivière A, Douillard JY, Lebeau B, Debieuvre D, Poudenx M, David P, Molinier O, Zalcman G, Lemarié E, Morin F, Depierre A, Milleron B, Intergroupe Francophone de Cancérologie Thoracique. A randomised trial comparing preoperative to perioperative chemotherapy in early-stage non-small-cell lung cancer (IFCT 0002 trial). Eur J Cancer. 2013;49(12):2654–64.
24. Hwang WL, Pike LRG, Royce TJ, Mahal BA, Loeffler JS. Safety of combining radiotherapy with immune-checkpoint inhibition. Nat Rev Clin Oncol. 2018;15(8):477–94.
25. Weichselbaum RR, Liang H, Deng L, Fu YX. Radiotherapy and immunotherapy: a beneficial liaison? Nat Rev Clin Oncol. 2017;14(6):365–79.
26. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, Bogart J, Hu C, Forster K, Magliocco A, Kavadi V, Garces YI, Narayan S, Iyengar P, Robinson C, Wynn RB, Koprowski C, Meng J, Beitler J, Gaur R, Curran W Jr, Choy H. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16(2):187–99.
27. Senan S, Brade A, Wang LH, Vansteenkiste J, Dakhil S, Biesma B, Martinez Aguillo M, Aerts J, Govindan R, Rubio-Viqueira B, Lewanski C, Gandara D, Choy H, Mok T, Hossain A, Iscoe N, Treat J, Koustenis A, San Antonio B, Chouaki N, Vokes E. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. J Clin Oncol. 2016;34(9):953–62.
28. Butts C, Socinski MA, Mitchell PL, Thatcher N, Havel L, Krzakowski M, Nawrocki S, Ciuleanu TE, Bosquée L, Trigo JM, Spira A, Tremblay L, Nyman J, Ramlau R, Wickart-Johansson G, Ellis P, Gladkov O, Pereira JR, Eberhardt WE, Helwig C, Schröder A, Shepherd FA, START trial team. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2014;15(1):59–68.
29. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim YC, Karapetis CS, Hiret S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro CJ, Wadsworth C, Melillo G, Jiang H, Huang Y, Dennis PA, Özgüroğlu M, PACIFIC Investigators. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med. 2017;377(20):1919–29.
30. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Kurata T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim YC, Karapetis CS, Hiret S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Faivre-Finn C, Reck M, Vansteenkiste J, Spigel DR, Wadsworth C, Melillo G, Taboada M, Dennis PA, Özgüroğlu M, PACIFIC Investigators. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med. 2018;379(24):2342–50.
31. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR, KEYNOTE-024 Investigators. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375(19):1823–33.
32. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Vandormael K, Riccio A, Yang J, Pietanza MC, Brahmer JR. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol. 2019;37(7):537–46.
33. Russo A, Franchina T, Ricciardi GRR, Toscano G, Schifano S, Lo Certo G, Battaglia A, Pantò E, Scaffidi Fonti M, Adamo V. The changing scenario of 1st line therapy in non-oncogene addicted NSCLCs in the era of immunotherapy. Crit Rev Oncol Hematol. 2018;130:1–12.

34. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Castro G Jr, Srimuninnimit V, Laktionov KK, Bondarenko I, Kubota K, Lubiniecki GM, Zhang J, Kush D, Lopes G, KEYNOTE-042 Investigators. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393(10183):1819–30.
35. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, Hermes B, Çay Şenler F, Csőszi T, Fülöp A, Rodríguez-Cid J, Wilson J, Sugawara S, Kato T, Lee KH, Cheng Y, Novello S, Halmos B, Li X, Lubiniecki GM, Piperdi B, Kowalski DM, KEYNOTE-407 Investigators. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med. 2018;379(21):2040–51.
36. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC, KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018;378(22):2078–92.
37. Gadgeel SM, Garassino MC, Esteban E, Speranza G, Felip E, Hochmair MJ, et al. KEYNOTE-189: updated OS and progression after the next line of therapy (PFS2) with pembrolizumab (pembro) plus chemo with pemetrexed and platinum vs placebo plus chemo for metastatic nonsquamous NSCLC. J Clin Oncol. 2019;37(15_suppl):9013.
38. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Rodríguez-Abreu D, Moro-Sibilot D, Thomas CA, Barlesi F, Finley G, Kelsch C, Lee A, Coleman S, Deng Y, Shen Y, Kowanetz M, Lopez-Chavez A, Sandler A, Reck M, IMpower150 Study Group. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378(24):2288–301.
39. Reck M, TSK M, Nishio M, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Rodríguez-Abreu D, Moro-Sibilot D, Thomas CA, Barlesi F, Finley G, Lee A, Coleman S, Deng Y, Kowanetz M, Shankar G, Lin W, Socinski MA, IMpower150 Study Group. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Lancet Respir Med. 2019;7(5):387–401.
40. West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, Kopp HG, Daniel D, McCune S, Mekhail T, Zer A, Reinmuth N, Sadiq A, Sandler A, Lin W, Ochi Lohmann T, Archer V, Wang L, Kowanetz M, Cappuzzo F. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019. pii: S1470-2045(19)30167-6.
41. Jotte RM, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Rodriguez Abreu D, Hussein MA, Soo RA, Conter HJ, Kozuki T, Silva C, Graupner V, Sun S, Lin RS, Kelsch C, Kowanetz M, Hoang T, Sandler A, Socinski MA. IMpower131: primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. J Clin Oncol. 2018;O 36:LBA9000. https://doi.org/10.1200/JCO.2018.36.18_suppl.LBA9000.
42. Socinski MA, Rittmeyer A, Shapovalov D, Orlandi F, McCleod M, Soo RA, Palmero R, Kozuki T, Migliorino MR, Koynov KD, Berard H, Hughes BG, Yu W, Graupner V, Sun SW, Kowanetz M, Hoang T, Lin W, Jotte RM. LBA65IMpower131: progression-free survival (PFS) and overall survival (OS) analysis of a randomised phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel in 1L advanced squamous NSCLC. Ann Oncol. 2018;29 https://doi.org/10.1093/annonc/mdy424.077.
43. Barlesi F, Nishio M, Cobo M, Steele N, Paramonov V, Parente B, et al. LBA54IMpower132: efficacy of atezolizumab (atezo) + carboplatin (carbo)/cisplatin (cis) + pemetrexed (pem) as 1L treatment in key subgroups with stage IV non-squamous non-small cell lung cancer (NSCLC). Ann Oncol. 2018;29(suppl_8).
44. Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, Minenza E, Linardou H, Burgers S, Salman P, Borghaei H, Ramalingam SS, Brahmer J, Reck M, O'Byrne KJ, Geese WJ, Green G, Chang H, Szustakowski J, Bhagavatheeswaran P, Healey D, Fu Y, Nathan F, Paz-Ares L. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med. 2018;378(22):2093–104.
45. Rizvi NA, Chul Cho B, Reinmuth N, Lee KH, Ahn M-J, Luft A, et al. LBA6Durvalumab with or without tremelimumab vs platinum-based chemotherapy as first-line treatment for metastatic non-small cell lung cancer: MYSTIC. Ann Oncol. 2018;29(suppl_10).
46. Peters S, Cho BC, Reinmuth N, et al. Tumor mutational burden (TMB) as a biomarker of survival in metastatic non-small cell lung cancer (mNSCLC): Blood and tissue TMB analysis from MYSTIC, a Phase III study of first-line durvalumab ± tremelimumab vs chemotherapy. Presented at: 2019 AACR Annual Meeting; March 29–April 3, 2019; Atlanta, GA. Abstract CT074.
47. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, Felip E, van den Heuvel MM, Ciuleanu TE, Badin F, Ready N, Hiltermann TJN, Nair S, Juergens R, Peters S, Minenza E, Wrangle JM, Rodriguez-Abreu D, Borghaei H, Blumenschein GR Jr, Villaruz LC, Havel L, Krejci J, Corral Jaime J, Chang H, Geese WJ, Bhagavatheeswaran P, Chen AC, Socinski MA,

CheckMate 026 Investigators. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med. 2017;376(25):2415–26.
48. Rizvi H, Sanchez-Vega F, La K, Chatila W, Jonsson P, Halpenny D, Plodkowski A, Long N, Sauter JL, Rekhtman N, Hollmann T, Schalper KA, Gainor JF, Shen R, Ni A, Arbour KC, Merghoub T, Wolchok J, Snyder A, Chaft JE, Kris MG, Rudin CM, Socci ND, Berger MF, Taylor BS, Zehir A, Solit DB, Arcila ME, Ladanyi M, Riely GJ, Schultz N, Hellmann MD. Molecular determinants of response to anti-programmed cell death (PD)-1 and anti-programmed death-ligand 1 (PD-L1) blockade in patients with non-small-cell lung cancer profiled with targeted next-generation sequencing. J Clin Oncol. 2018;36(7):633–41.
49. Meléndez B, Van Campenhout C, Rorive S, Remmelink M, Salmon I, D'Haene N. Methods of measurement for tumor mutational burden in tumor tissue. Transl Lung Cancer Res. 2018;7(6):661–7. https://doi.org/10.21037/tlcr.2018.08.02.
50. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, Majem M, Fidler MJ, de Castro G Jr, Garrido M, Lubiniecki GM, Shentu Y, Im E, Dolled-Filhart M, Garon EB. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540–50.
51. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols MC, Cortinovis DL, Leach J, Polikoff J, Barrios C, Kabbinavar F, Frontera OA, De Marinis F, Turna H, Lee JS, Ballinger M, Kowanetz M, He P, Chen DS, Sandler A, Gandara DR, OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255–65.
52. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Arén Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373(2):123–35.
53. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhäufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crinò L, Blumenschein GR Jr, Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F, Brahmer JR. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627–39.
54. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Jalal SI, Panwalkar A, Yang JC, Gubens M, Sequist LV, Awad MM, Fiore J, Ge Y, Raftopoulos H, Gandhi L, KEYNOTE-021 investigators. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016;17(11):1497–508.
55. Borghaei H, Langer CJ, Gadgeel S, Papadimitrakopoulou VA, Patnaik A, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Jalal SI, Panwalkar A, Yang JC, Gubens M, Sequist LV, Awad MM, Fiore J, Saraf S, Keller SM, Gandhi L. 24-month overall survival from KEYNOTE-021 Cohort G: pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced nonsquamous non-small cell lung cancer. J Thorac Oncol. 2019;14(1):124–9.
56. Thatcher N, Hirsch FR, Luft AV, Szczesna A, Ciuleanu TE, Dediu M, Ramlau R, Galiulin RK, Bálint B, Losonczy G, Kazarnowicz A, Park K, Schumann C, Reck M, Depenbrock H, Nanda S, Kruljac-Letunic A, Kurek R, Paz-Ares L, Socinski MA, SQUIRE Investigators. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. Lancet Oncol. 2015;16(7):763–74.
57. Socinski MA, Bondarenko I, Karaseva NA, Makhson AM, Vynnychenko I, Okamoto I, Hon JK, Hirsh V, Bhar P, Zhang H, Iglesias JL, Renschler MF. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol. 2012;30(17):2055–62.
58. Jotte RM, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Rodriguez Abreu D, Hussein MA, et al. IMpower131: primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. J Clin Oncol. 2018;36(18_suppl):LBA9000.
59. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, Lao CD, Wagstaff J, Schadendorf D, Ferrucci PF, Smylie M, Dummer R, Hill A, Hogg D, Haanen J, Carlino MS, Bechter O, Maio M, Marquez-Rodas I, Guidoboni M, McArthur G, Lebbé C, Ascierto PA, Long GV, Cebon J, Sosman J, Postow MA, Callahan MK, Walker D, Rollin L, Bhore R, Hodi FS, Larkin J. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017;377(14):1345–56.
60. Motzer RJ, Tannir NM, DF MD, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm MO, Bracarda S, Barrios CH, Tomita Y, Castellano D, Rini BI, Chen AC, Mekan S, MB MH, Wind-Rotolo M, Doan J,

Sharma P, Hammers HJ, Escudier B, CheckMate 214 Investigators. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378(14):1277–90.
61. Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, Ready NE, Gerber DE, Chow LQ, Juergens RA, Shepherd FA, Laurie SA, Geese WJ, Agrawal S, Young TC, Li X, Antonia SJ. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017;18(1):31–41.
62. Hellmann MD, Nathanson T, Rizvi H, Creelan BC, Sanchez-Vega F, Ahuja A, Ni A, Novik JB, LMB M, Abu-Akeel M, Liu C, Sauter JL, Rekhtman N, Chang E, Callahan MK, Chaft JE, Voss MH, Tenet M, Li XM, Covello K, Renninger A, Vitazka P, Geese WJ, Borghaei H, Rudin CM, Antonia SJ, Swanton C, Hammerbacher J, Merghoub T, McGranahan N, Snyder A, Wolchok JD. Genomic features of response to combination immunotherapy in patients with advanced non-small-cell lung cancer. Cancer Cell. 2018;33(5):843–852.e4.
63. Ready N, Hellmann MD, Awad MM, Otterson GA, Gutierrez M, Gainor JF, Borghaei H, Jolivet J, Horn L, Mates M, Brahmer J, Rabinowitz I, Reddy PS, Chesney J, Orcutt J, Spigel DR, Reck M, O'Byrne KJ, Paz-Ares L, Hu W, Zerba K, Li X, Lestini B, Geese WJ, Szustakowski JD, Green G, Chang H, Ramalingam SS. First-line nivolumab plus ipilimumab in advanced non-small-cell lung cancer (CheckMate 568): outcomes by programmed death ligand 1 and tumor mutational burden as biomarkers. J Clin Oncol. 2019;37(12):992–1000.
64. Signorelli D, Giannatempo P, Grazia G, Aiello MM, Bertolini F, Mirabile A, Buti S, Vasile E, Scotti V, Pisapia P, Cona MS, Rolfo C, Malapelle U, Group IY. Patients selection for immunotherapy in solid tumors: overcome the naïve vision of a single biomarker. Biomed Res Int. 2019;2019:9056417.
65. Peters S, Cappuzzo F, Horn L, Paz-Ares L, Borghaei H, Barlesi F, Steins M, Felip E, Spigel D, Dorange C, Lu H, Healey D, Kong Sanchez T, Bhagavatheeswaran P, Novotny J Jr, Lestini B, Brahmer J. OA03.05 analysis of early survival in patients with advanced non-squamous NSCLC treated with nivolumab vs docetaxel in CheckMate 057. J Thorac Oncol. 2017;12:S253. https://doi.org/10.1016/j.jtho.2016.11.241.
66. Vokes EE, Ready N, Felip E, Horn L, Burgio MA, Antonia SJ, Arén Frontera O, Gettinger S, Holgado E, Spigel D, Waterhouse D, Domine M, Garassino M, LQM C, Blumenschein G Jr, Barlesi F, Coudert B, Gainor J, Arrieta O, Brahmer J, Butts C, Steins M, Geese WJ, Li A, Healey D, Crinò L. Nivolumab versus docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases. Ann Oncol. 2018;29(4):959–65.
67. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, Park K, Smith D, Artal-Cortes A, Lewanski C, Braiteh F, Waterkamp D, He P, Zou W, Chen DS, Yi J, Sandler A, Rittmeyer A, POPLAR Study Group. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016;387(10030):1837–46.
68. Hirsch FR, McElhinny A, Stanforth D, Ranger-Moore J, Jansson M, Kulangara K, Richardson W, Towne P, Hanks D, Vennapusa B, Mistry A, Kalamegham R, Averbuch S, Novotny J, Rubin E, Emancipator K, McCaffery I, Williams JA, Walker J, Longshore J, Tsao MS, Kerr KM. PD-L1 immunohistochemistry assays for lung cancer: results from phase 1 of the blueprint PD-L1 IHC assay comparison project. J Thorac Oncol. 2017;12(2):208–22.
69. Rimm DL, Han G, Taube JM, Yi ES, Bridge JA, Flieder DB, Homer R, West WW, Wu H, Roden AC, Fujimoto J, Yu H, Anders R, Kowalewski A, Rivard C, Rehman J, Batenchuk C, Burns V, Hirsch FR, Wistuba II. A prospective, multi-institutional, pathologist-based assessment of 4 immunohistochemistry assays for PD-L1 expression in non-small cell lung cancer. JAMA Oncol. 2017;3(8):1051–8.
70. Gandara DR, Paul SM, Kowanetz M, Schleifman E, Zou W, Li Y, Rittmeyer A, Fehrenbacher L, Otto G, Malboeuf C, Lieber DS, Lipson D, Silterra J, Amler L, Riehl T, Cummings CA, Hegde PS, Sandler A, Ballinger M, Fabrizio D, Mok T, Shames DS. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. Nat Med. 2018;24(9):1441–8.
71. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, Carcereny E, Ahn MJ, Felip E, Lee JS, Hellmann MD, Hamid O, Goldman JW, Soria JC, Dolled-Filhart M, Rutledge RZ, Zhang J, Lunceford JK, Rangwala R, Lubiniecki GM, Roach C, Emancipator K, Gandhi L, KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372(21):2018–28.
72. Barlesi F, Vansteenkiste J, Spigel D, Ishii H, Garassino M, de Marinis F, Özgüroğlu M, Szczesna A, Polychronis A, Uslu R, Krzakowski M, Lee JS, Calabrò L, Arén Frontera O, Ellers-Lenz B, Bajars M, Ruisi M, Park K. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. Lancet Oncol. 2018;19(11):1468–79.
73. Garassino MC, Cho BC, Kim JH, Mazières J, Vansteenkiste J, Lena H, Corral Jaime J, Gray JE, Powderly J, Chouaid C, Bidoli P, Wheatley-Price P, Park K, Soo RA, Huang Y, Wadsworth C, Dennis PA, Rizvi NA, ATLANTIC Investigators. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. Lancet Oncol. 2018;19(4):521–36.

74. Johnson DH, Schiller JH, Bunn PA Jr. Recent clinical advances in lung cancer management. J Clin Oncol. 2014;32(10):973–82.
75. Lara PN Jr, Natale R, Crowley J, Lenz HJ, Redman MW, Carleton JE, Jett J, Langer CJ, Kuebler JP, Dakhil SR, Chansky K, Gandara DR. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol. 2009;27(15):2530–5.
76. Socinski MA, Smit EF, Lorigan P, Konduri K, Reck M, Szczesna A, Blakely J, Serwatowski P, Karaseva NA, Ciuleanu T, Jassem J, Dediu M, Hong S, Visseren-Grul C, Hanauske AR, Obasaju CK, Guba SC, Thatcher N. Phase III study of pemetrexed plus carboplatin compared with etoposide plus carboplatin in chemotherapy-naive patients with extensive-stage small-cell lung cancer. J Clin Oncol. 2009;27(28):4787–92.
77. Tiseo M, Boni L, Ambrosio F, Camerini A, Baldini E, Cinieri S, Brighenti M, Zanelli F, Defraia E, Chiari R, Dazzi C, Tibaldi C, Turolla GM, D'Alessandro V, Zilembo N, Trolese AR, Grossi F, Riccardi F, Ardizzoni A. Italian, multicenter, phase III, randomized study of cisplatin plus etoposide with or without bevacizumab as first-line treatment in extensive-disease small-cell lung cancer: the GOIRC-AIFA FARM6PMFJM trial. J Clin Oncol. 2017;35(12):1281–7.
78. Oze I, Hotta K, Kiura K, Ochi N, Takigawa N, Fujiwara Y, Tabata M, Tanimoto M. Twenty-seven years of phase III trials for patients with extensive disease small-cell lung cancer: disappointing results. PLoS One. 2009;4(11):e7835.
79. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, Børresen-Dale AL, Boyault S, Burkhardt B, Butler AP, Caldas C, Davies HR, Desmedt C, Eils R, Eyfjörd JE, Foekens JA, Greaves M, Hosoda F, Hutter B, Ilicic T, Imbeaud S, Imielinski M, Jäger N, Jones DT, Jones D, Knappskog S, Kool M, Lakhani SR, López-Otín C, Martin S, Munshi NC, Nakamura H, Northcott PA, Pajic M, Papaemmanuil E, Paradiso A, Pearson JV, Puente XS, Raine K, Ramakrishna M, Richardson AL, Richter J, Rosenstiel P, Schlesner M, Schumacher TN, Span PN, Teague JW, Totoki Y, Tutt AN, Valdés-Mas R, van Buuren MM, van't Veer L, Vincent-Salomon A, Waddell N, Yates LR, Australian Pancreatic Cancer Genome Initiative, ICGC Breast Cancer Consortium, ICGC MMML-Seq Consortium, ICGC PedBrain, Zucman-Rossi J, Futreal PA, McDermott U, Lichter P, Meyerson M, Grimmond SM, Siebert R, Campo E, Shibata T, Pfister SM, Campbell PJ, Stratton MR. Signatures of mutational processes in human cancer. Nature. 2013;500(7463):415–21.
80. Reck M, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, Sebastian M, Lu H, Cuillerot JM, Lynch TJ. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol. 2013;24(1):75–83.
81. Reck M, Luft A, Szczesna A, Havel L, Kim SW, Akerley W, Pietanza MC, Wu YL, Zielinski C, Thomas M, Felip E, Gold K, Horn L, Aerts J, Nakagawa K, Lorigan P, Pieters A, Kong Sanchez T, Fairchild J, Spigel D. Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. J Clin Oncol. 2016;34(31):3740–8.
82. Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, Jäger D, Pietanza MC, Le DT, de Braud F, Morse MA, Ascierto PA, Horn L, Amin A, Pillai RN, Evans J, Chau I, Bono P, Atmaca A, Sharma P, Harbison CT, Lin CS, Christensen O, Calvo E. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016;17(7):883–95.
83. Ready N, Farago AF, de Braud F, Atmaca A, Hellmann MD, Schneider JG, Spigel DR, Moreno V, Chau I, Hann CL, Eder JP, Steele NL, Pieters A, Fairchild J, Antonia SJ. Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. J Thorac Oncol. 2019;14(2):237–44.
84. Hellmann MD, Callahan MK, Awad MM, Calvo E, Ascierto PA, Atmaca A, Rizvi NA, Hirsch FR, Selvaggi G, Szustakowski JD, Sasson A, Golhar R, Vitazka P, Chang H, Geese WJ, Antonia SJ. Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in small-cell lung cancer. Cancer Cell. 2018;33(5):853–861.e4.
85. Chung HC, Lopez-Martin JA, Kao SC, Miller WH, Ros W, Gao B, Marabelle A, Gottfried M, Zer A, Delord JP, Penel N, Jalal SI, Xu L, Zeigenfuss S, Pruitt SK, Piha-Paul SA. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158. J Clin Oncol. 2018;36:8506.
86. Owonikoko T, Ready N, Postmus P, Reck M, Peters S, Pieters A, et al. PS01.58: a phase 3 trial of nivolumab, nivolumab plus ipilimumab, or placebo maintenance for extensive-stage SCLC after first-line chemotherapy: topic: medical oncology. J Thorac Oncol. 2016;11(11):S306–7.
87. Gadgeel SM, Pennell NA, Fidler MJ, Halmos B, Bonomi P, Stevenson J, Schneider B, Sukari A, Ventimiglia J, Chen W, Galasso C, Wozniak A, Boerner J, Kalemkerian GP. Phase II study of maintenance pembrolizumab in patients with extensive-stage small cell lung cancer (SCLC). J Thorac Oncol. 2018;13(9):1393–9.
88. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, Huemer F, Losonczy G, Johnson ML, Nishio M, Reck M, Mok T, Lam S, Shames DS, Liu J, Ding B, Lopez-Chavez A, Kabbinavar F, Lin W, Sandler A, Liu SV, IMpower133 Study Group. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379(23):2220–9.

89. Zhou K, Zhou J, Huang J, Zhang N, Bai L, Yang Y, Li Q. Cost-effectiveness analysis of atezolizumab plus chemotherapy in the first-line treatment of extensive-stage small-cell lung cancer. Lung Cancer. 2019;130:1–4.
90. Ott PA, Elez E, Hiret S, Kim DW, Morosky A, Saraf S, Piperdi B, Mehnert JM. Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the phase Ib KEYNOTE-028 study. J Clin Oncol. 2017;35(34):3823–9.
91. Goldman JW, Dowlati A, Antonia SJ, Nemunaitis JJ, Butler MO, Segal NH, et al. Safety and antitumor activity of durvalumab monotherapy in patients with pretreated extensive disease small-cell lung cancer (ED-SCLC). J Clin Oncol. 2018;36(15_suppl):8518.
92. Cho DC, Mahipal A, Dowlati A, Chow WA, Segal NH, Chung KY, Schneider BJ, Nemunaitis JJ, Abdul Razak AR, Tsai FY, Balmanoukian AS, Bazhenova L, Xiao F, Angra N, Abdullah SE, Luke JJ. Safety and clinical activity of durvalumab in combination with tremelimumab in extensive disease small-cell lung cancer (ED-SCLC). J Clin Oncol. 2018;36:8517. https://doi.org/10.1200/JCO.2018.36.15_suppl.8517.