Cancer Immunology, Immunotherapy (2019) 68:341–352
https://doi.org/10.1007/s00262-019-02310-2

REVIEW

Immunotherapy with checkpoint inhibitors in non-small cell lung cancer: insights from long-term survivors

Ernest Nadal[1,2] · Bartomeu Massuti[3] · Manuel Dómine[4] · Rosario García-Campelo[5] · Manuel Cobo[6] · Enriqueta Felip[7]

Received: 3 May 2018 / Accepted: 25 January 2019 / Published online: 6 February 2019

Abstract

Immune checkpoint inhibitors (ICIs) targeting the programmed cell death-1 (PD-1)–programmed cell death ligand-1 (PD-L1) axis have shown promising results in non-small cell lung cancer (NSCLC) patients, some of them with persistent responses to these agents that form a population of long-term survivors. Despite the variable definition of PD-L1 positivity in tumors, an association between expression and response has been reasonably consistent in advanced NSCLC. In addition, the clinical efficacy of ICIs seems to be related to the genomic landscape of the tumor in terms of mutational burden and clonal neoantigens. Furthermore, increasing evidence shows that excessive activation of the immune response elicited by ICIs, leading to immune-related toxicities, might be associated with an improved response to immunotherapy. There are still many unanswered questions about the proper use of these agents to maximize their efficacy, which may be improved through combination with radiation, chemotherapy, targeted therapies, or other immune mediators, including dual checkpoint blockade. To search for clues for addressing these challenges, this review focused on the characteristics and clinical features of long-term NSCLC survivors and the potential biomarkers of response to ICIs.

Keywords Biomarker · Immune checkpoint inhibitors · Immunotherapy · Long-term survival · Non-small cell lung cancer · PD-L1

✉ Ernest Nadal
esnadal@iconcologia.net

[1] Department of Medical Oncology, Catalan Institute of Oncology (ICO), Avda Gran via, 199-203. L'Hospitalet, 08908 Barcelona, Spain

[2] Clinical Research in Solid Tumors (CReST) Group, OncoBell Program, IDIBELL, L'Hospitalet, Barcelona, Spain

[3] Department of Medical Oncology, Hospital Universitario de Alicante, ISABIAL, Alicante, Spain

[4] Department of Medical Oncology, Hospital Universitario Fundación Jiménez Díaz, Oncohealth Institute, Universidad Autónoma de Madrid, Madrid, Spain

[5] Department of Medical Oncology, A Coruña University Hospital, A Coruña, Spain

[6] Medical Oncology Department, Hospital Universitario Málaga Regional y Virgen de la Victoria, IBIMA, Málaga, Spain

[7] Lung Cancer Unit, Hospital Universitari Vall d'Hebron and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Abbreviations

AE	Adverse event
ASCO	American Society of Clinical Oncology
CI	Confidence intervals
HR	Hazard ratio
ICI	Immune checkpoint inhibitor
IHC	Immunohistochemistry
irAE	immune-related adverse event
LDH	Lactate dehydrogenase
LIPI	Lung Immune Prognostic Index
MMR	Mismatch-repair
NLR	Neutrophil to lymphocyte ratio
Non-Sq	Non-squamous
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
PFS	Progression-free survival
Sq	Squamous
TMB	Tumor mutation burden
TME	Tumor microenvironment
TNF	Tumor necrosis factor

Introduction

Lung cancer is the leading cause of cancer death among men and the second cause of cancer death among women worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancers diagnoses, divided by histology into squamous (Sq) and non-squamous (non-Sq) tumors. In advanced disease, which is predominant at presentation, the standard of care is platinum-based chemotherapy and/or targeted therapies in patients harboring *EGFR* or *BRAF* mutations or *ALK*/*ROS1* rearrangements [2]. In patients with high expression of PD-L1 (≥ 50%), front line treatment with pembrolizumab has become the standard of care. Upon progression, until recently, docetaxel-based chemotherapy for patients with a good performance status was the recommended approach, but it was associated with low response rates and short progression-free survival (PFS) at the cost of significant toxicity [3, 4].

In recent years, a new class of treatment that targets the immune system showed promising results in phase II and III studies. Inhibition of the PD-1/PD-L1 immune checkpoint using monoclonal antibodies, such as nivolumab, atezolizumab, pembrolizumab, and durvalumab, prevents the inhibition of effector T-cell function, permitting T-cells to maintain their tumor cell-killing function [5]. Other immune checkpoint inhibitors (ICIs), such as ipilimumab and tremelimumab, prevent activation of CTLA-4 and aid in restoring immune function [6]. Clinical trials with second-line checkpoint inhibitors in previously treated advanced NSCLC have shown durable overall response rates (ORRs) of ~ 20% and an acceptable safety profile [7–10]. Nivolumab, pembrolizumab, and atezolizumab are now approved for previously treated NSCLC; pembrolizumab also received approval for first-line NSCLC treatment in patients with PD-L1 expression > 50%. Recently, durvalumab has been approved for stage III PD-L1-positive patients as consolidation therapy after concurrent chemoradiotherapy [11].

Given the natural adaptability of the immune system response and its capacity to develop durable immune memory, it is conceivable that these agents have the potential to improve long-term survival. However, there are still patients who do not respond or who progress while on immunotherapy. Therefore, there is a need to improve patient selection, to determine the optimal time for integration of ICIs into the lifetime course of NSCLC treatment, and to establish the most effective concurrent or sequential combination therapies in different NSCLC clinical settings. To search for clues for addressing these challenges, this review focused on the characteristics and clinical features of long-term NSCLC survivors and the potential biomarkers of response to ICIs. In addition, the results of current studies of ICIs, either alone or in combination with other therapies, are discussed.

Long-term survival in NSCLC patients treated with ICIs

Several studies have established the definition of long-term survival in advanced NSCLC at more than 2 years from the time of diagnosis [12–16], with rates of survivorship after one or more lines of therapy ranging from 8 to 16%. Currently, an important number of long-term results are available for ICIs (Table 1), including long-term survival data from the phase I CA209-003 study [17]. This study reported a 5-year OS rate of 16% for 129 heavily pretreated patients treated with nivolumab [17]. This rate was nearly four times higher than 5-year survival with metastatic NSCLC (4.5%) reported by the Surveillance, Epidemiology, and End Results Program (SEER) [18]. In the 68 patients with evaluable PD-L1 status, 5-year OS rate was 20% for PD-L1 < 1%, 23% for PD-L1 ≥ 1%, and 43% for PD-L1 ≥ 50%. Of the 16 patients who survived for at least 5 years, nine completed the maximum number of nivolumab cycles per protocol,

Table 1 Long-term results of NSCLC patients treated with ICIs

Study (sample)	Phase	Population	Immune checkpoint inhibitor	OS (time of assessment)
CA209-003 (*N* = 129)	I	Heavily pretreated	Nivolumab	16% (at 5 years)
Checkmate 017 (*N* = 222)	III	Sq NSCLC	Nivolumab	16% (at 3 years)
Checkmate 057 (*N* = 240)	III	Non-Sq NSCLC	Nivolumab	18% (at 3 years)
Keynote 001 (*N* = 550)	I	Treatment-naïve (*N* = 101) Previously treated (*N* = 449)	Pembrolizumab	26.4% (at 3 years) 19% (at 3 years)
Keynote 010 (*N* = 47)	II/III	Previously treated	Pembrolizumab (2 mg/kg) Pembrolizumab (10 mg/kg)	30.1% (at 2 years) 37.5% (at 2 years)
POPLAR (*N* = 144)	II	Previously treated	Atezolizumab	19% (at 3 years)
OAK (*N* = 425)	III	Previously treated	Atezolizumab	28% (at 2 years)
ATLANTIC (*N* = 265)	II	Heavily treated	Durvalumab	22% (at 2 years)

and 12 patients received no further therapy after stopping nivolumab treatment without any evidence of disease progression [17]. With shorter follow-up, Checkmate 017 and Checkmate 057 trials have showed 3-year OS rates of 16% for Sq NSCLC and 18% for non-Sq NSCLC, respectively [19]. Data from the expanded access of nivolumab in Italy presented by Crino at the Annual Meeting of the American Society of Clinical Oncology (ASCO) in 2016, with 371 patients treated with an unlimited number of previous lines, showed a median OS of 9.1 months and slightly more than 30% of patients were alive at 16 months [20].

Regarding pembrolizumab, 3-year OS data from KEYNOTE-001 were 26.4% in treatment-naïve and 19% in previously treated patients [21]. The updated analysis of the KEYNOTE-010 study that included 47 patients who completed the 2 planned years of treatment showed 2-year OS rates of 14.5% for docetaxel versus 30.1% and 37.5% for pembrolizumab 2 mg/kg and 10 mg/kg every 3 weeks, respectively [22]. With respect to atezolizumab, the randomized phase II POPLAR trial showed a 3-year OS of 19% for atezolizumab and 10% for docetaxel [23]. Similarly, long-term survival data from the phase III OAK study that compared atezolizumab versus docetaxel showed 2-year OS rates of 28% and 20%, respectively [24]. In the BIRCH trial (phase II with atezolizumab monotherapy in PD-L1 positive NSCLC), the cohort of patients who received atezolizumab in front-line achieved a 2-year OS of 50% [25]. The ATLANTIC study was a phase II trial with durvalumab monotherapy in advanced NSCLC treated with two or more lines of treatment. At 24 months, the proportion of long-term survivors was 22% [26].

Characteristics of long-term NSCLC survivors treated with ICIs

With the increased focus on NSCLC survivorship, understanding of this information becomes important for therapeutic decision-making and patient counseling. The results of the studies described above allow investigating potential associations between demographic, pathologic, surgical, and clinical factors and long-term survival with ICI treatment. However, the only study with 5-year follow-up data (nivolumab phase I, CA209-003) showed that the 16 long-term survivors had diverse baseline characteristics, including Sq and non-Sq histology, $\geq 1\%$ and $< 1\%$ PD-L1 tumor expression, one to four prior lines of systemic therapy, 12.5% had *EGFR* mutations, and included one person who had never smoked, three were former smokers and 11 were current smokers [17].

The characteristics of the patients treated with pembrolizumab for 24 months were very similar to those of the global population with respect to sex (trend for a greater effect in men), ethnicity, performance status, smoking habit, and histology [22]. However, differences in PD-L1 expression were observed, since of the 47 patients treated with pembrolizumab during 24 months, 66% of the patients had PD-L1 $\geq 50\%$ compared to 42% of the global population; 89% of the 2-year survivor patients were responders, and 6% were complete responders [22].

In the OAK trial [27], an OS benefit was observed regardless of PD-L1 expression levels and survival outcomes improved in subgroups including all age ranges, never smokers, and patients with baseline brain metastases, with the exception of presence of an EGFR mutation that favored docetaxel. In patients with non-Sq cell carcinoma, median OS was 15.6 months with atezolizumab [Hazard ratio (HR) 0.73; 95% confidence interval (CI) 0.60, 0.89; $p = 0.0015$] and in patients with Sq cell carcinoma, median OS was 8.9 months (HR 0.73; 95% CI 0.54, 0.98; $p = 0.0383$). Of the long-term survivors with atezolizumab at 24 months, 32% had non-Sq carcinoma and 19% had Sq cell carcinoma [24].

The results of cohort 2 ($n = 265$; varied PD-L1 status) and cohort 3 ($n = 68$; PD-L1 expression $\geq 90\%$) included in the ATLANTIC study of durvalumab monotherapy showed that patients from cohort 2 with PD-L1 $\geq 25\%$ had a median OS (95% CI) of 10.9 months (8.6–13.6) and 1-year OS of 47.7%, whereas those with PD-L1 $< 25\%$ had a median OS of 9.3 months (5.9–10.8) and 1-year OS of 34.5%. In cohort 3, the median duration of OS was not reached and the 1-year rate of OS was 50.8% [26].

To date, it has been difficult to identify any clear biomarker or clinical characteristic predicting long-term survival after immunotherapy. As described above, long-term survivors in the CA209-033 study had diverse characteristics in terms of histology, PD-L1 tumor expression, prior lines of systemic therapy, *EGFR* mutations, and smoking history [17]. Over time, the number of patients who survive for prolonged periods after immunotherapy is increasing, and it will become possible to design a case–control study in which the characteristics of long-term survivors are compared with those who survive for shorter periods (e.g., < 1 or 2 years) to identify potential predictors of survival.

Biomarkers and long-term survival

The role of PD-L1 status as a biomarker of response in advanced NSCLC has been investigated in a number of studies [7, 9, 10], including a meta-analysis of 12 studies examining outcomes in relation to PD-L1 expression in patients receiving anti-PD-1/PD-L1 agents [28]. In this meta-analysis, the HR for ORR was 2.18 (95% CI 1.45–3.29; $p = 0.0002$) in patients whose tumors had PD-L1 expression $> 1\%$ compared with those whose tumors had PD-L1 expression $< 1\%$. Regardless of the threshold for

PD-L1 expression used, this analysis showed that more marked response rates were seen in patients with higher versus lower PD-L1 expression. The ORR HR was 2.66 (95% CI 1.74–4.07; $p < 0.00001$) for patients with PD-L1 expression ≥ 5% versus < 5%, 3.38 (95% CI 2.23–5.13; $p < 0.00001$) when PD-L1 expression was ≥ 10% versus < 10%, and 3.99 (95% CI 2.81–5.66; $p < 0.00001$) for tumors with PD-L1 expression ≥ 50% versus < 50% [28]. Similar results were seen in another meta-analysis of 13 studies involving 1979 patients, which found that the likelihood of response was more than two times greater in the PD-L1-positive than -negative patients (HR 2.08; 95% CI 1.49–2.91; $p < 0.01$). In addition, this meta-analysis found a correlation between levels of PD-L1 expression and response to treatment (Pearson's correlation, $r = 0.43$) [29]. These results support the idea that PD-L1 expression identifies tumors with an increased likelihood of response to immune checkpoint blockade; however, it should also be noted that a significant number of patients with PD-L1-negative tumors derive clinical benefit from treatment with PD-1/PD-L1 inhibitors [8, 9]. For example, a post hoc analysis of patients treated with nivolumab in the CA209-903 study who survived for 5 years found that three of ten evaluable patients were PD-L1-negative; the other seven had tumors with PDL1 ≥ 1% expression, and five of these patients had tumors with PD-L1 expression ≥ 50% [30].

These findings indicate that PD-L1 testing can be considered as a valuable tool to identify which patients are the most likely to respond to therapy. However, implementing this test in practice is not without difficulties. PD-L1 expression is not a binary variable, and there are distinct definitions of positivity based on expression levels, as well as differences between assays, and heterogeneous PD-L1 expression within and between tumor sites [31]. For example, one study has shown that PD-L1 expression measured using the SP142 immunochemistry (IHC) assay is lower in lung biopsy specimens than it is in resected surgical tissue [32]. Other studies have shown significant differences between the tumor microenvironment (TME) of paired primary lung cancers and brain metastases [33] and between PD-L1 expression results when using different assays [34]. The available immune checkpoint inhibitors have been developed with their own companion diagnostic test using IHC, but these differ in the thresholds used to define positivity, as well as in the IHC characteristics being assessed [35, 36].

In addition to PD-L1 status, the clinical efficacy of ICIs may be affected by the genomic profile of the tumor. It is known that carcinogens present in cigarette smoke increase the occurrence of somatic mutations and generation of neoantigens [37], which may be ideal targets for tumor-infiltrating lymphocytes. The efficacy of T-cell responses is dependent on the degree of intra-tumoral genetic heterogeneity [38], and seem to be more effective against clonal neoantigens rather than subclonal neoantigens [39]. Accordingly, NSCLC patients harboring tumors with a high frequency of clonal neoantigens showed a favorable response when they received an anti-PD-1 agent compared with those harboring high subclonal neoantigens [39]. In the CheckMate 026 trial comparing nivolumab versus platinum-based chemotherapy in front-line, tumor mutational burden (TMB) was measured in the tumor by exome sequencing and patients were divided into three groups (< 100, 100–242, and ≥ 243 mutations). Patients harboring high TMB achieved longer PFS, but did not have longer OS than patients treated with chemotherapy [40]. Similarly, TMB measured in the blood (bTMB) was assessed in a subset of patients treated in the POPLAR and OAK trials. In the training set (POPLAR), bTMB ≥ 16 predicted benefit from atezolizumab in terms of PFS and OS, however, in the validation set (OAK), high bTMB was only associated with longer PFS (interaction p value = 0.036), but not with OS (interaction p value = 0.75) [41]. Data from the Checkpoint-012 and Checkpoint-227 studies showed that TMB was a significant predictor of response to nivolumab plus ipilimumab [42] and PFS [11], respectively, independent of PD-L1 expression. In Checkpoint-012, TMB was a stronger predictor than PD-L1 expression of response to the combination of nivolumab plus ipilimumab [42]. Checkpoint-227 defined the threshold for high tumor burden as ≥ 10 mutations per megabase in patients receiving nivolumab plus ipilimumab or ≥ 13 mutations per megabase in patients receiving chemotherapy or nivolumab monotherapy [11].

In addition to the IHC-based assays for PD-L1 expression, an exploratory analysis of the POPLAR study with atezolizumab showed that a high T-effector interferon γ-associated gene expression signature assessed on tumor samples was associated with better OS. The T-effector and interferon γ gene signature was defined by CD8A, GZMA, GZMB, IFN-γ, EOMES, CXCL9, CXCL10, and TBX21 genes [10]. It has been also demonstrated that the mismatch repair (MMR) status could effectively predict PD-1 blockade efficacy [43]. This finding is biologically explained as the higher number of mutations not resolved by MMR would render the tumor more immunogenic. Accordingly, additional studies have shown how the mutational burden correlates with greater efficacy of diverse anti PD-L1/PD-1 drugs [44, 45].

The role of the host immune system is a critical factor to consider when dealing with prediction of benefit from ICIs. Low neutrophil to lymphocyte ratio (NLR), as a correlate of the level of inflammation in TME, has been associated with improved OS in patients with stage IIIa/IIIb NSCLC treated with definitive chemoradiation [46]. Other recent studies have evaluated the association between pretreatment NLR and outcomes in patients treated with ICIs, showing a similar pattern: lower NLR at baseline was significantly associated with improved OS and PFS [47–49]. Although it

is unclear if this parameter acts as a predictive or prognostic biomarker, the determination of mediators of inflammation could optimize the selection of patients who can benefit from PD-1/PD-L1 blockade therapy. Finally, specific driver mutations seem to be associated with the absence of benefit from ICIs. The meta-analysis performed by Lee et al. [50] examined the role of nivolumab, pembrolizumab or atezolizumab versus docetaxel as second-line therapy in *EGFR*-mutant advanced NSCLC patients, and showed that treatment with ICIs did not extend OS beyond that achieved with docetaxel. The role of *KRAS* mutations as predictive factors is not well established. A recent analysis of the Italian nivolumab expanded access program for non-Sq NSCLC has shown similar efficacy and safety in patients with *KRAS* mutations to that observed in the overall population and in the CheckMate 057 trial [51].

Biomarkers in development

The information provided from the expression of PD-L1 in the tumor or its neoantigen load is not always sufficient for distinguishing between patients who will respond to therapy and patients who should be offered other treatments. Recent investigations have focused on quantifying and qualifying tumor-infiltrating lymphocytes, and Gettinger and colleagues found that an elevated T-cell infiltration was significantly associated with durable clinical benefit and OS after PD-1 axis blockade in NSCLC [52]. In fact, tumors with high T-cell infiltration but low in situ activation/proliferation show the highest clinical benefit (e.g., Type 2 or "dormant" TIL phenotype) [52]. In addition, some molecular drivers of lack of tumor immune infiltration (immune exclusion) have been identified, offering possible therapeutic targets and the rationale to design treatment strategies for non-responders [53]. The future research directions are searching for other potential biological markers that may predict efficacy of ICIs, such as CD8+ expressed in T-cells or cytokines expressed in tumor samples [54] or in serum [55].

Because of the multifactorial nature of cancer–immune interactions, combinations of biomarker assays are likely to be required [56]. Investigators from eight European academic oncology centers have developed a Lung Immune Prognostic Index (LIPI) to identify patients with worse outcomes with immune checkpoint inhibitors [57]. LIPI is defined by a baseline-derived neutrophil/(leukocytes minus neutrophils) ratio > 3 and a baseline lactate dehydrogenase (LDH) level greater than the upper limit of normal, and correlates with worse OS and PFS in patients receiving immunotherapy, but not in those receiving chemotherapy [57]. Identifying patients who are unlikely to benefit from immunotherapy may be useful for targeting resources towards those most likely to respond.

Similarly, Korean researchers have developed the iSEND model, which incorporates sex, Eastern Cooperative Oncology Group performance status, NLR, and delta NLR into an algorithm that categorizes patients on ICIs into good-, intermediate-, and high-risk categories [58]. Although not yet independently validated, iSEND categories significantly predicted PFS and response to immunotherapy, and could be used to identify extrinsic resistance to immune checkpoint inhibitors. The developers of the iSEND model also note that, once validated, iSEND could be refined to include intrinsic markers of tumor resistance such as genomic or immune-related biomarkers [58].

Relationship between toxicity and benefit of ICIs

Although anti-PD-1 and anti-PD-L1 antibodies show significant clinical benefits, their use can produce immune-related adverse events (irAEs) by boosting immune system function. These autoimmune side effects, frequently grade 1–2, can affect multiple organs including skin, endocrine system, gastrointestinal tract, lungs, kidneys, eyes, pancreas, and others, although they are less frequent and less severe than the toxicities observed with chemotherapy [59]. Usually, treatment of moderate or severe irAEs requires temporary interruption of the ICI and the use of corticoids or, in some cases, TNFα antibody [60]. The impact on overall outcome of steroid use to manage irAEs associated with ICI treatment remains uncertain. Two studies in melanoma [61, 62] and one using pembrolizumab in NSCLC showed that steroids did not affect clinical outcome in terms of response and OS [63]. However, a French study has revealed shorter PFS and OS with the use of doses of prednisone higher than 20 mg/day [64].

The frequency of irAES depends on the treatment employed. The antibodies that block CTLA-4 have shown higher frequency of irAEs compared with antibodies directed against PD-1/PD-L1. Combinations of both anti-CTLA-4 and anti-PD-1/PD-L1 antibodies result in a significant increase in irAEs [65]. The rate of drug discontinuation is < 10% with anti-PD-1/PD-L1, whereas combinations of anti-CTLA4 plus anti-PD-L1 increase the percentage of discontinuations to two or three times that. An updated meta-analysis performed by Pillai and colleagues examined the toxicity profile in 3284 NSCLC patients treated with PD-1 and 2615 NSCLC patients treated with PD-L1 inhibitors [66]. The incidence of overall adverse events (AEs) was similar between both types of agents, whereas rates of irAEs and pneumonitis favored the PD-L1 group. Hypothyroidism was the most frequent irAE reported [66].

The association between the occurrence of irAEs and long-term outcomes with immune checkpoint-blocking

therapy is unclear. Increasing evidence from early studies shows that an excessive activation of the immune response, leading to immune-related toxicities, is associated with an improved response to immunotherapy. This correlation has been demonstrated in patients with melanoma treated with ipilimumab, in whom development of irAEs was significantly associated with the likelihood of response [67]. In a pooled analysis of the CheckMate 067 and 069 studies, patients treated with nivolumab plus ipilimumab who discontinued treatment due to AEs showed a greater benefit in terms of PFS and ORR compared with patients with AEs where treatment discontinuation was not necessary [68]. Another study showed that occurrence of vitiligo, a cutaneous manifestation of immune-related toxicity, was associated with higher rates of objective response to pembrolizumab treatment in patients with melanoma [69]. A retrospective study that included melanoma and NSCLC patients treated with pembrolizumab evaluated the role of cutaneous AEs and response. Patients with macular papular eruption, pruritus, or hypopigmentation (42% of the study patients) all had significantly longer PFS compared with patients with no cutaneous AEs [70]. In patients with advanced NSCLC treated with pembrolizumab as part of the KEYNOTE-001 study ($n=51$), median OS was significantly longer in patients who developed thyroid dysfunction than in those who did not (40 versus 14 months; HR 0.29; 95% CI 0.09–0.94; $p=0.029$) [71]. A recent analysis of the OAK trial has shown higher response rate with an OS trend in favor of atezolizumab-treated patients with versus those without irAEs (HR 0.80; 95% CI 0.60, 1.05; $p=0.11$) [72], whereas a multi-institutional medical records review in patients with advanced or recurrent NSCLC treated with nivolumab showed a superior outcome in patients with irAEs (median PFS 9.2 versus 4.8; $p=0.04$ and median OS not reached versus 11,1; $p=0.01$) [73]. Despite all this evidence, further studies are necessary to elucidate the relationship between irAEs and efficacy of ICIs, especially in NSCLC.

Current and future therapeutic combinations

Most clinical trials have evaluated ICIs as single therapeutic agents; however, a growing amount of evidence suggests that efficacy may be improved through combination with radiation, chemotherapy, targeted therapies, or other immune mediators, including dual checkpoint blockade. Ideally, combinations should modulate TME and favor T-cell activation, with distinct but complementary mechanisms of action [74].

In addition to its direct cytotoxic effects, radiotherapy is known to induce an immunostimulatory form of cell death, called immunogenic cell death, mediated by anti-tumor T-cell and NK cell responses [75]. A number of NSCLC clinical trials are exploring anti-PD-1/PD-L1 antibodies in combination with radiotherapy, most of them phase I or II (ClinicalTrials.gov identifiers: NCT02463994, NCT02608385, NCT02621398, NCT02400814, NCT02407171, NCT02444741, NCT02492568, NCT02658097, and NCT02434081). The only ongoing phase III trial is RTOG 3505, which evaluates concurrent chemoradiation followed by nivolumab therapy or placebo in patients with locally advanced NSCLC in terms of OS, PFS, and toxicity [76]. The results of all these studies are pending.

Chemotherapy has the potential to promote tumor antigen presentation, leading to priming of tumor-specific T-cells, in addition to its direct stimulation of immune effectors and inhibition of immune suppressive factors [77], so there is good rationale to combine it with ICIs. CheckMate 012 (ClinicalTrials.gov identifier: NCT01454102) is a multi-arm phase I study of nivolumab with various anticancer agents or as monotherapy and represents the most mature dataset evaluating anti-PD-1 plus chemotherapy. In the platinum doublet arm, where three platinum-based chemotherapy regimens (cisplatin/gemcitabine; cisplatin/pemetrexed; and carboplatin/paclitaxel) were combined with nivolumab ($n=56$), the ORR was 33–47%, 24-week PFS was 38–71%, and 2-year OS was 25–62%; however, 45% of the patients had grade 3 or 4 toxicity, including pneumonitis [78]. The 3-year update of this trial showed an OS rate of 25%, with no new safety signals observed in patients receiving long-term nivolumab [79].

The KEYNOTE-021 study (cohort G) evaluated the safety and activity of pembrolizumab added to carboplatin and pemetrexed in patients with wild-type *EGFR*/*ALK* advanced non-squamous NSCLC. A total of 123 treatment-naïve patients were enrolled. ORR was 55% in the combination cohort and 18% in the chemotherapy cohort, whereas PFS was 13 versus 8.9 months, respectively. Grade 3–4 treatment-related AEs occurred in 39% of patients in the pembrolizumab plus chemotherapy group and 26% in the chemotherapy alone group [80]. The most recent data presented at the 2017 Congress of the European Society of Medical Oncology, with a median follow-up of 18.7 months, showed longer PFS with pembrolizumab plus chemotherapy (19 months versus 8.9 months; HR 0.54, 95% CI 0.33–0.88; $p=0.0067$). In spite of high cross-over (75% of patients in the chemotherapy arm received subsequent anti-PD1 or anti-PD-L1), patients who received the combination achieved longer OS (not reached versus 20.9 months; HR 0.59, 95% CI 0.34–1.05; $p=0.034$), with higher 18-months OS (70% vs 56%) [81]. The randomized, double-blind KEYNOTE-189 study found a similar benefit of adding pembrolizumab to chemotherapy in patients with advanced, non-squamous, *EGFR*/*ALK*-negative NSCLC [82]. The 12-month OS was 69.2% in the 410 patients receiving pembrolizumab plus

chemotherapy compared with 49.4% in the 206 receiving chemotherapy alone ($p < 0.001$), and PFS was also significantly longer in the group receiving pembrolizumab (median 8.8 versus 4.9 months; HR 0.52; 95% CI 0.43–0.64; $p < 0.001$). The incidence of grade ≥ 3 AEs was similar in the two groups: 67.2% in the pembrolizumab plus chemotherapy group and 65.8% in the chemotherapy group [82].

Similar results were seen in the second interim analysis of the KEYNOTE-407 study (NCT02775435), which was presented at the 2018 Annual Meeting of ASCO [83]. This randomized, double-blind study found that compared with chemotherapy alone, the addition of pembrolizumab to paclitaxel/nab-paclitaxel significantly improved response (58.4% vs 35.0%) and increased PFS (median 6.4 versus 4.8 months; HR 0.56; 95% CI 0.45, 0.70; $p < 0.0001$), regardless of PD-L1 expression [83]. The overall rate of AEs, including grade ≥ 3, was similar in the two groups.

Atezolizumab in combination with platinum-based doublet chemotherapy as first-line therapy has also shown promising clinical activity with well-tolerated toxicities. Combined ORR was 67% in the 37 patients evaluated, showing better results with pemetrexed (RR = 75%). The safety profile was as predicted, with no unexpected toxicities. Major grade 3–4 drug-related toxicities were anemia (7%), neutropenia (7–13%), and thrombocytopenia (7%), while only one grade 5 AE of candidemia was observed [84].

The combination with other immune modulatory agents is also promising. For example, the anti-PD-1 and anti-CTLA-4 combination was initially tested and approved in melanoma patients [85] and it is being explored in NSCLC in the first- and second-line settings. Various treatment arms of the CheckMate 012 evaluated the safety and efficacy of nivolumab in combination with ipilimumab as first-line therapy in patients with advanced NSCLC [86]. The trial included four treatment groups, with doses varying from 1 to 3 mg/kg for both nivolumab and ipilimumab. The groups selected for further exploration were nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 or 12 weeks. In these groups ($n = 77$), grade 3–4 treatment-related AEs occurred in 14 (37%) patients in the ipilimumab every 12 weeks cohort and 13 (33%) patients in the every 6 weeks cohort. After a median follow-up of 12.8 months, ORR was 47% and 38%, respectively, improving the clinical benefit compared with anti-PD-1 monotherapy in patients with NSCLC [86]. With 2 years of follow-up, pooled results from both cohorts showed continued clinical benefit with nivolumab plus ipilimumab in all patients and those with ≥ 1% and ≥ 50% tumor PD-L1 expression (2-year OS of 49%, 58%, and 62%, respectively), regardless of histology, smoking status, or EGFR status [87]. An additional phase III study of nivolumab plus ipilimumab versus standard chemotherapy (Checkmate 227; NCT02477826) will further define the role for first-line immune checkpoint blockade in advanced NSCLC.

Regarding pembrolizumab, the KEYNOTE-021 study also included cohorts evaluating pembrolizumab in combination with ipilimumab for patients with pretreated NSCLC (cohorts D and H). The updated efficacy data ($n = 51$; median follow-up of 7 months) demonstrated a significant toxicity profile and an ORR (24%) similar to that of pembrolizumab alone [88]. Similarly, durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA4) have been studied in a combination phase I dose escalation trial in patients with advanced NSCLC, showing anti-tumor activity regardless of PD-L1 status. In the combined durvalumab 10 to 20 mg/kg every 4 weeks or every 2 weeks plus tremelimumab 1 mg/kg patient cohort, 30% of patients had grade 3–4 drug-related AEs, and 16% discontinued treatment owing to drug-related AEs. Confirmed ORR was six of 26 (23%): two of nine (22%) patients with PD-L1-positive tumors and four of 14 (29%) patients with PD-L1-negative tumors (< 25% staining). In the subset of patients with PD-L1-negative tumors who had 0% staining, confirmed ORR was four of 10 (40%), underlining the ability of the combination treatment to overcome negative PD-L1 [89]. From these data, the durvalumab 20 mg/kg plus tremelimumab 1 mg/kg dose was selected for phase III studies [90]. The ongoing phase III studies of anti-PD-L1/PD-1 therapies and different combinations in first- and second-line NSCLC are shown in Table 2.

Concluding remarks

The landscape of NSCLC treatment has completely changed due to the recent approval of different ICIs. Although the determination PD-L1 expression has many limitations, high PD-L1 has been consistently associated with greater response rate and longer PFS across different clinical trials and therefore should be considered as a predictive marker of the benefit from ICI treatment. ICI treatment is effective in a subset of long-term survivors, but current predictive factors are not reliable. Therefore, the identification and development of robust predictive biomarkers for long-term benefit with ICIs is required. The extensive list of ongoing clinical trials involving checkpoint blockade outlines the large number of unmet needs and raises questions about the optimal use of these agents in the treatment of patients with lung cancer. The results of these studies testing combination with chemotherapy, other immunotherapy agents, and radiotherapy are eagerly awaited to determine the best therapeutic sequence and to characterize patients with durable responses.

Table 2 Ongoing phase III studies of anti-PD-L1/PD-1 therapies and different combinations in NSCLC

Study name	Estimated sample	Description	Treatment course	Treatment arms
CheckMate 227 (NCT02477826)	2220	Nivolumab, or nivolumab plus ipilimumab, or nivolumab plus platinum-doublet chemotherapy versus chemotherapy alone in patients with advanced NSCLC	First line	Nivolumab Nivolumab + ipilimumab Nivolumab + platinum doublet chemotherapy Platinum doublet chemotherapy
CheckMate 955 (NCT03048136)	124	Nivolumab in combination with ipilimumab in chemotherapy-naive stage IV or recurrent NSCLC	First line	Nivolumab flat dose + ipilimumab Nivolumab weight-based dose + ipilimumab
CheckMate 9LA (NCT03215706)	420	Nivolumab plus ipilimumab in combination with chemotherapy compared with chemotherapy alone in stage IV NSCLC	First line	Nivolumab + ipilimumab + chemotherapy Chemotherapy
NCT02869789	1000	Nivolumab in combination with ipilimumab in NSCLC	First line	Nivolumab + ipilimumab
CheckMate 722 (NCT02864251)	465	Nivolumab plus chemotherapy or nivolumab plus ipilimumab versus chemotherapy in patients with EGFR mutation, T790M-negative NSCLC	Second line	Nivolumab + platinum doublet chemotherapy Nivolumab + ipilimumab Platinum doublet chemotherapy
CheckMate 816 (NCT02998528)	326	Nivolumab and ipilimumab versus platinum doublet chemotherapy in early-stage NSCLC	Neoadjuvant	Nivolumab + ipilimumab Platinum doublet chemotherapy
NCT02869789	1000	Nivolumab in combination with ipilimumab in NSCLC	First line	Nivolumab + ipilimumab
IMpower130 (NCT02367781)	724	Atezolizumab in combination with carboplatin plus nab-paclitaxel compared with carboplatin plus nab-paclitaxel in non-squamous NSCLC	First line	Atezolizumab + nab-paclitaxel + carboplatin Nab-paclitaxel + carboplatin
IMpower131 (NCT 02367794)	1025	Atezolizumab in combination with carboplatin plus paclitaxel or carboplatin plus nab-paclitaxel compared with carboplatin plus nab-paclitaxel in stage IV squamous NSCLC	First line	Atezolizumab + paclitaxel + carboplatin Atezolizumab + nab-paclitaxel + carboplatin Nab-paclitaxel + carboplatin
IMpower132 (NCT02657434)	568	Atezolizumab in combination with carboplatin or cisplatin plus pemetrexed compared with carboplatin or cisplatin plus pemetrexed in stage IV non-squamous NSCLC	First line	Atezolizumab + carboplatin or cisplatin + pemetrexed Carboplatin or cisplatin + pemetrexed
IMpower150 (NCT02366143)	1202	Atezolizumab in combination with carboplatin plus paclitaxel with or without bevacizumab compared with carboplatin plus paclitaxel plus bevacizumab in stage IV non-squamous NSCLC	First line	Atezolizumab + paclitaxel + carboplatin Atezolizumab + bevacizumab + paclitaxel + carboplatin Bevacizumab + paclitaxel + carboplatin
MYSTIC (NCT02453282)	1118	Durvalumab in combination with tremelimumab therapy or durvalumab monotherapy versus platinum-based chemotherapy in advanced or metastatic NSCLC	First line	Durvalumab Durvalumab + tremelimumab Platinum-based chemotherapy
NEPTUNE (NCT02542293)	960	Durvalumab in combination with tremelimumab therapy versus platinum-based chemotherapy in advanced or metastatic NSCLC	First line	Durvalumab + tremelimumab Platinum-based chemotherapy
POSEIDON (NCT03164616)	801	Durvalumab or durvalumab and tremelimumab in combination with platinum-based chemotherapy in metastatic NSCLC	First line	Durvalumab + tremelimumab + platinum-based chemotherapy Durvalumab + platinum-based chemotherapy Platinum-based chemotherapy

Table 2 (continued)

Study name	Estimated sample	Description	Treatment course	Treatment arms
ARCTIC (NCT02352948)	597	Durvalumab monotherapy or in combination with tremelimumab determined by PD-L1 expression versus standard of care in locally advanced or metastatic NSCLC	Third line	Durvalumab for PD-L1-positive tumors Standard of care for PD-L1-positive tumors Durvalumab + tremelimumab for PD-L1-negative tumors Standard of care for PD-L1-negative tumors Durvalumab for PD-L1-negative tumors Tremelimumab for PD-L1-negative tumors

Acknowledgements The authors would like to thank Anabel Herrero, on behalf of Springer Healthcare, for assistance in the preparation of the manuscript, and Catherine Rees, of Springer Healthcare communications, for revising the manuscript based on peer review comments.

Author contributions EN drafted the manuscript, coordinated the different contributions, reviewed evidence and wrote the first draft of the section "Biomarkers and long-term survival". BM reviewed evidence and wrote the first draft of the section "Characteristics of long-term NSCLC survivors treated with ICIs". MD reviewed evidence and wrote the first draft of the section "Relationship between toxicity and benefit of ICIs". RGC reviewed evidence and wrote the first draft of the section "Current and future therapeutic combinations". MC reviewed evidence and wrote the first draft of the section "Long-term survival in NSCLC patients treated with ICIs". EF coordinated the "Introduction" and "Concluding remarks", as well as the different authors' contributions with EN. All authors reviewed and approved the final manuscript version.

Funding Medical writing assistance was funded by Bristol-Myers Squibb. Ernest Nadal has received a grant from the Department of Health of the Generalitat de Catalunya (SLT006/17/00127). The authors would like to thank CERCA Programme/Generalitat de Catalunya for institutional support.

Compliance with ethical standards

Conflict of interest Ernest Nadal has received honoraria for participating in advisory boards and speaking honorarium from Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Pfizer, Takeda, Boehringer Ingelheim and AstraZeneca. Bartomeu Massuti has received honoraria for participation in advisory boards and speaking from Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Merck Serono, Merck Sharp & Dohme, Pfizer, and Roche. Manuel Dómine declares that he has no conflict of interest. Rosario García-Campelo has received honoraria for participation in advisory boards and speaking from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, Novartis, Pfizer, Roche/Genentech, and Takeda. Manuel Cobo has received speaker honorarium from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, and Roche. Enriqueta Felip has received honoraria for participation in advisory boards and speaking from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, GuardantHealth, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Takeda.

References

1. Torre LA, Siegel RL, Jemal A (2016) Lung cancer statistics. Adv Exp Med Biol 893:1–19
2. Novello S, Barlesi F, Califano R et al (2016) Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 27:v1–v27
3. Carnio S, Novello S, Mele T, Levra MG, Scagliotti GV (2014) Extending survival of stage IV non-small cell lung cancer. Semin Oncol 41:69–92
4. Melosky B (2014) Treatment algorithms for patients with metastatic non-small cell, non-squamous lung cancer. Front Oncol 4:256
5. Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X (2015) Human cancer immunotherapy with antibodies to the PD-1 and PD-L1 pathway. Trends Mol Med 21:24–33

6. Pardoll DM (2012) The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 12:252–264
7. Borghaei H, Paz-Ares L, Horn L et al (2015) Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373:1627–1639
8. Brahmer J, Reckamp KL, Baas P et al (2015) Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373:123–135
9. Garon EB, Rizvi NA, Hui R et al (2015) Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 372:2018–2028
10. Fehrenbacher L, Spira A, Ballinger M et al (2016) Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 387:1837–1846
11. Hellmann MD, Ciuleanu TE, Pluzanski A et al (2018) Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 378:2093–2104
12. Okamoto T, Maruyama R, Shoji F, Asoh H, Ikeda J, Miyamoto T, Nakamura T, Miyake T, Ichinose Y (2005) Long-term survivors in stage IV non-small cell lung cancer. Lung Cancer 47:85–91
13. Satoh H, Ishikawa H, Ohara G, Kagohashi K, Kurishima K, Ohtsuka M, Hizawa N (2007) Long-term survivors after chemotherapy in advanced non-small cell lung cancer. Anticancer Res 27:4457–4460
14. Dujon C, Azarian R, Petitpretz P (2009) Long-term survivors of advanced non-small-cell lung cancer: characterisation and prognostic factors in a retrospective study. Rev Mal Respir 26:952–960
15. Giroux Leprieur E, Lavole A, Ruppert AM, Gounant V, Wislez M, Cadranel J, Milleron B (2012) Factors associated with long-term survival of patients with advanced non-small cell lung cancer. Respirology 17:134–142
16. Van Damme V, Govaerts E, Nackaerts K, Dooms C, Wauters I, Vansteenkiste J (2013) Clinical factors predictive of long-term survival in advanced non-small cell lung cancer. Lung Cancer 79:73–76
17. Gettinger S, Horn L, Jackman D et al (2018) Five-year follow-up of nivolumab in previously treated advanced non-small-cell lung cancer: results from the CA209-003 study. J Clin Oncol 36:1675–1684
18. National Cancer Institute (2017) Cancer Stat facts: lung and bronchus cancer. https://seer.cancer.gov/statfacts/html/lungb.html. Accessed 13 June 2017
19. Vokes EE, Ready N, Felip E et al (2018) 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 29(4):959–965
20. Crino L, Bidoli P, Delmonte A et al (2016) Italian cohort of nivolumab Expanded Access Programme (EAP): preliminary data from a real-world population. J Clin Oncol 34:3067-
21. Leighl NB, Hellmann MD, Hui R, Carcereny E, Felip E, Ahn MJ, Eder JP (2017) KEYNOTE-001: 3-year overall survival for patients with advanced NSCLC treated with pembrolizumab. J Clin Oncol 35:abst 9011
22. Herbst R, Garon E, Kim D-W et al (2017) KEYNOTE-010: durable clinical benefit in patients with previously treated, PD-L1-expressing NSCLC who completed pembrolizumab. J Thorac Oncol 12:S254–S255
23. Park K, Lewanski C, Gadgeel S et al. 3-year survival and duration of response in randomized phase ii study of atezolizumab vs docetaxel in 2L/3L NSCLC (POPLAR). J Thorac Oncol 12:S1840
24. Gadgeel S, Ciardiello F, Rittmeyer A et al (2017) OAK, a randomized Ph III study of atezolizumab vs docetaxel in patients with advanced NSCLC: results from subgroup analyses. J Thorac Oncol 12:S9–S10
25. Garassino M, Rizvi N, Besse B et al (2017) Atezolizumab as 1L therapy for advanced NSCLC in PD-L1—selected patients: updated ORR, PFS and OS data from the BIRCH study. J Thorac Oncol 12:S251–S252
26. Garassino MC, Cho BC, Kim JH et al (2018) 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 19:521–536
27. Rittmeyer A, Barlesi F, Waterkamp D et al (2017) Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 389:255–265
28. Abdel-Rahman O (2016) Correlation between PD-L1 expression and outcome of NSCLC patients treated with anti-PD-1/PD-L1 agents: a meta-analysis. Crit Rev Oncol Hematol 101:75–85
29. Aguiar PN Jr, Santoro IL, Tadokoro H, de Lima Lopes G, Filardi BA, Oliveira P, Mountzios G, de Mello RA (2016) The role of PD-L1 expression as a predictive biomarker in advanced non-small-cell lung cancer: a network meta-analysis. Immunotherapy 8:479–488
30. Brahmer J, Horn L, Jackman D, Spigel D, Scott A, Hellmann M, Powderly J (2017) Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced non-small cell lung cancer (NSCLC): clinical characteristics of long-term survivors. http://www.abstractsonline.com/pp8/#!/4292/presentation/12343 . Accessed 13 June 2017
31. Mansfield AS, Dong H (2016) Implications of programmed cell death 1 ligand 1 heterogeneity in the selection of patients with non-small cell lung cancer to receive immunotherapy. Clin Pharmacol Ther 100:220–222
32. Ilie M, Long-Mira E, Bence C et al (2016) Comparative study of the PD-L1 status between surgically resected specimens and matched biopsies of NSCLC patients reveal major discordances: a potential issue for anti-PD-L1 therapeutic strategies. Ann Oncol 27:147–153
33. Mansfield AS, Aubry MC, Moser JC, Harrington SM, Dronca RS, Park SS, Dong H (2016) Temporal and spatial discordance of programmed cell death-ligand 1 expression and lymphocyte tumor infiltration between paired primary lesions and brain metastases in lung cancer. Ann Oncol 27:1953–1958
34. McLaughlin J, Han G, Schalper KA et al (2016) Quantitative assessment of the heterogeneity of PD-L1 expression in non-small-cell lung cancer. JAMA Oncol 2:46–54
35. Teixido C, Karachaliou N, Gonzalez-Cao M, Morales-Espinosa D, Rosell R (2015) Assays for predicting and monitoring responses to lung cancer immunotherapy. Cancer Biol Med 12:87–95
36. Kumar R, Collins D, Dolly S, McDonald F, O'Brien MER, Yap TA (2017) Targeting the PD-1/PD-L1 axis in non-small cell lung cancer. Curr Probl Cancer 41:111–124
37. Govindan R, Ding L, Griffith M et al (2012) Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell 150:1121–1134
38. de Bruin EC, McGranahan N, Mitter R et al (2014) Spatial and temporal diversity in genomic instability processes defines lung cancer evolution. Science 346:251–256
39. McGranahan N, Furness AJ, Rosenthal R et al (2016) Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science 351:1463–1469
40. Carbone DP, Reck M, Paz-Ares L et al (2017) First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 376:2415–2426
41. Gandara DR, Kowanetz M, Mok TSK et al (2017) Blood-based biomarkers for cancer immunotherapy: tumor mutational burden in blood (bTMB) is associated with improved atezolizumab (atezo) efficacy in 2L + NSCLC (POPLAR and OAK). Ann Oncol 28:1295O

42. Hellmann MD, Nathanson T, Rizvi H et al (2018) Genomic features of response to combination immunotherapy in patients with advanced non-small-cell lung cancer. Cancer Cell 33:843 e4–852 e4
43. Le DT, Uram JN, Wang H et al (2015) PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 372:2509–2520
44. Rizvi NA, Hellmann MD, Snyder A et al (2015) Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 348:124–128
45. Schrock A, Sharma N, Peled N et al (2017) Updated dataset assessing tumor mutation burden (TMB) as a biomarker for response to PD-1/PD-L1 targeted therapies in lung cancer (LC). J Thorac Oncol 12:S422
46. Scilla KA, Bentzen SM, Lam VK et al (2017) Neutrophil-lymphocyte ratio is a prognostic marker in patients with locally advanced (Stage IIIA and IIIB) non-small cell lung cancer treated with combined modality therapy. Oncologist 22:737–742
47. Labomascus S, Fughhi I, Bonomi P, Fidler MJ, Borgia JA, Basu S, Hoch MA, Batus M (2017) Neutrophil to lymphocyte ratio as predictive of prolonged progression free survival (PFS) and overall survival (OS) in patients with metastatic non-small cell lung cancer (NSCLC) treated with second-line PD-1 immune checkpoint inhibitors. J Clin Oncol 35:e14530-e
48. Bagley SJ, Kothari S, Aggarwal C et al (2017) Pretreatment neutrophil-to-lymphocyte ratio as a marker of outcomes in nivolumab-treated patients with advanced non-small-cell lung cancer. Lung Cancer 106:1–7
49. Zer A, Sung MR, Walia P et al (2018) Correlation of neutrophil to lymphocyte ratio and absolute neutrophil count with outcomes with PD-1 axis inhibitors in patients with advanced non-small-cell lung cancer. Clin Lung Cancer 19(5):426–434. e1. https://doi.org/10.1016/j.cllc.2018.04.008
50. Lee CK, Man J, Lord S, Links M, Gebski V, Mok T, Yang JC (2017) Checkpoint inhibitors in metastatic EGFR-mutated non-small cell lung cancer—a meta-analysis. J Thorac Oncol 12:403–407
51. Ardizzoni A, Bidoli P, Chiari R et al (2017) Nivolumab in advanced non-squamous NSCLC patients with KRAS mutations: results from the italian expanded access program (EAP). J Thorac Oncol 12:S1804
52. Gettinger S, Choi J, Mani N et al (2017) Predictive value of measuring somatic mutations and tumor infiltrating lymphocytes for PD-1 axis therapy in non-small cell lung cancer (NSCLC). J Thorac Oncol 12:S430–S431
53. Olugbile S, Bao R, Hensing T, Nakamura Y, Vokes E (2017) Molecular determinants of lack of tumor immune infiltration in NSCLC. J Thorac Oncol 12:S431–S432
54. Tumeh PC, Harview CL, Yearley JH et al (2014) PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 515:568–571
55. Sanmamed MF, Perez-Gracia JL, Schalper KA et al (2017) Changes in serum interleukin-8 (IL-8) levels reflect and predict response to anti-PD-1 treatment in melanoma and non-small cell lung cancer patients. Ann Oncol 28:1988–1995
56. Blank CU, Haanen JB, Ribas A, Schumacher TN (2016) Cancer Immunology. The "cancer immunogram". Science 352:658–660
57. Mezquita L, Auclin E, Ferrara R et al (2018) Association of the lung immune prognostic index with immune checkpoint inhibitor outcomes in patients with advanced non-small cell lung cancer. JAMA Oncol 4:351–357
58. Park W, Kwon D, Saravia D et al (2018) Developing a predictive model for clinical outcomes of advanced non-small cell lung cancer patients treated with nivolumab. Clin Lung Cancer 19:280–288 e4
59. Costa R, Carneiro BA, Agulnik M, Rademaker AW, Pai SG, Villaflor VM, Cristofanilli M, Sosman JA, Giles FJ (2017) Toxicity profile of approved anti-PD-1 monoclonal antibodies in solid tumors: a systematic review and meta-analysis of randomized clinical trials. Oncotarget 8:8910–8920
60. Cousin S, Italiano A (2016) Molecular pathways: immune checkpoint antibodies and their toxicities. Clin Cancer Res 22:4550–4555
61. Horvat TZ, Adel NG, Dang TO et al (2015) Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at memorial sloan kettering cancer center. J Clin Oncol 33:3193–3198
62. Weber JS, Hodi FS, Wolchok JD et al (2017) Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol 35:785–792
63. Leighl N, Gandhi L, Hellmann M et al (2015) Pembrolizumab for NSCLC: immune-mediated adverse events and corticosteroid use. J Thorac Oncol 10:S233
64. Martínez Bernal G, Mezquita L, Auclin E et al (2017) Baseline corticosteroids (CS) could be associated with absence of benefit to immune checkpoint inhibitors (ICI) in advanced non-small cell lung cancer (NSCLC) patients. Ann Oncol 28:1323
65. Zhang T, Xie J, Arai S et al (2016) The efficacy and safety of anti-PD-1/PD-L1 antibodies for treatment of advanced or refractory cancers: a meta-analysis. Oncotarget 7:73068–73079
66. Pillai R, Behera M, Owonikoko T, Kamphorst A, Pakkala S, Belani C, Khuri F, Ahmed R, Ramalingam S (2017) Evaluation of toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer (NSCLC). J Thorac Oncol 12:S253–S254
67. Downey SG, Klapper JA, Smith FO et al (2007) Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. Clin Cancer Res 13:6681–6688
68. Schadendorf D, Larkin J, Postow M, Chiarion-Sileni V, Gonzalez R, Rutkowski P (2016) Efficacy and safety outcomes in patients with advanced melanoma (MEL) who discontinued treatment with nivolumab (NIVO) plus ipilimumab (IPI) due to toxicity. In: 12th Congress of the European Association of Dermato Oncology, August 31-September 3, 2016; Vienna, Austria
69. Hua C, Boussemart L, Mateus C et al (2016) Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. JAMA Dermatol 152:45–51
70. Sanlorenzo M, Vujic I, Daud A et al (2015) Pembrolizumab cutaneous adverse events and their association with disease progression. JAMA Dermatol 151:1206–1212
71. Osorio JC, Ni A, Chaft JE et al (2017) Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. Ann Oncol 28:583–589
72. von Pawel J, Syrigos K, Mazieres J et al (2017) Association between immune-related adverse events (irAEs) and atezolizumab efficacy in advanced NSCLC: analyses from the phase III study OAK. Ann Oncol 28:1314P
73. Haratani K, Hayashi H, Chiba Y et al (2017) Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. JAMA Oncol
74. Melero I, Berman DM, Aznar MA, Korman AJ, Perez Gracia JL, Haanen J (2015) Evolving synergistic combinations of targeted immunotherapies to combat cancer. Nat Rev Cancer 15:457–472
75. Marshall R, Popple A, Kordbacheh T, Honeychurch J, Faivre-Finn C, Illidge T (2017) Immune checkpoint inhibitors in lung cancer—an unheralded opportunity? Clin Oncol (R Coll Radiol) 29:207–217
76. Gerber DE, Urbanic JJ, Langer C et al (2017) Treatment design and rationale for a randomized trial of cisplatin and etoposide plus thoracic radiotherapy followed by nivolumab or placebo for locally advanced non-small-cell lung cancer (RTOG 3505). Clin Lung Cancer 18:333–339

77. Zitvogel L, Kepp O, Kroemer G (2011) Immune parameters affecting the efficacy of chemotherapeutic regimens. Nat Rev Clin Oncol 8:151–160
78. Rizvi NA, Hellmann MD, Brahmer JR et al (2016) Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 34:2969–2979
79. Juergens R, Hellmann M, Brahmer J et al (2017) First-line nivolumab plus platinum-based doublet chemotherapy for advanced NSCLC: checkmate 012 3-year update. J Thorac Oncol 12:S1792–S1793
80. Langer CJ, Gadgeel SM, Borghaei H et al (2016) 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 17:1497–1508
81. Borghaei H, Langer CJ, Gadgeel S et al (2017) Updated results from KEYNOTE-021 cohort G: a randomized, phase 2 study of pemetrexed and carboplatin (PC) with or without pembrolizumab (pembro) as first-line therapy for advanced nonsquamous NSCLC. Ann Oncol 28:LBA49
82. Gandhi L, Rodriguez-Abreu D, Gadgeel S et al (2018) Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 378:2078–2092
83. Paz-Ares LG, Luft A, Tafreshi A et al (2018) Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel (Chemo) with or without pembrolizumab (Pembro) for patients (Pts) with metastatic squamous (Sq) nonsmall cell lung cancer (NSCLC). American Society of Clinical Oncology, Chicago
84. Liu SV, Powderly JD, Camidge DR et al (2015) Safety and efficacy of MPDL3280A (anti-PDL1) in combination with platinum-based doublet chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). J Clin Oncol 33:8030-
85. Larkin J, Chiarion-Sileni V, Gonzalez R et al (2015) Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 373:23–34
86. Hellmann MD, Rizvi NA, Goldman JW et al (2017) 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 18:31–41
87. Goldman JW, Antonia S, Gettinger S et al (2017) Nivolumab plus ipilimumab as first-line treatment for advanced NSCLC: 2-year overall survival and long-term outcomes from checkmate 012. J Clin Oncol 35:Abstr 9093
88. Gubens MA, Sequist LV, Stevenson J et al (2016) Phase I/II study of pembrolizumab (pembro) plus ipilimumab (ipi) as second-line therapy for NSCLC: KEYNOTE-021 cohorts D and H. J Clin Oncol 34:9027-
89. Antonia S, Goldberg SB, Balmanoukian A et al (2016) Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. Lancet Oncol 17:299–308
90. Planchard D, Yokoi T, McCleod MJ, Fischer JR, Kim YC, Ballas M, Shi K, Soria JC (2016) A phase III study of durvalumab (MEDI4736) with or without tremelimumab for previously treated patients with advanced NSCLC: rationale and protocol design of the ARCTIC study. Clin Lung Cancer 17:232–236.e1