IRIS AperTO

UNIVERSITÀ DEGLI STUDI DI TORINO

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Addressing the unmet need in lung cancer: The potential of immuno-oncology

This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/1522518 since 2016-06-10T14:02:29Z

Published version:

DOI:10.1016/j.ctrv.2015.04.001

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

25 April 2024

UNIVERSITÀ DEGLI STUDI DI TORINO

Questa è la versione dell'autore dell'opera:

Addressing the unmet need in lung cancer: The potential of immuno-oncology

Cancer Treatment Reviews Volume 41, Issue 6, June 2015, Pages 465–475

G.V. Scagliotti, P. Bironzo, J.F. Vansteenkiste

La versione definitiva è disponibile alla URL:

http://www.sciencedirect.com/science/article/pii/S0305737215000705

G.V. Scagliotti, P. Bironzo, J.F. Vansteenkiste

Highlights

- We review current and emerging treatment strategies for non-small cell lung cancer.
- Patients typically receive multiple lines of chemotherapy as disease progresses.
- Limited benefits are seen, especially in those receiving later-line chemotherapy.
- Molecular targeted therapies have improved outcomes in subsets of patients only.
- Immuno-oncology may provide durable responses regardless of mutation status.

Abstract

Chemotherapy is currently the standard of care for non-oncogene-driven advanced non-small cell lung cancer (NSCLC). Due to improvements in chemotherapeutic choices and supportive care, patients currently typically undergo multiple lines of chemotherapy as their disease progresses. Although treatments have improved over recent years, limited benefits are seen, especially in patients receiving later-line chemotherapy, as response rates can be low, response duration short and survival poor. Furthermore, only a small percentage of patients derive benefit from later-line therapy, with most experiencing deteriorating quality of life and significant toxicities. More recently, molecular targeted therapies have provided improvements in outcomes. However, these treatments only offer a clear benefit in subsets of tumours harbouring the appropriate genomic alteration (mutation, amplification, translocation). Most of the genomic abnormalities susceptible to therapeutic intervention are detected in adenocarcinoma, mainly in never smokers, while alterations in the genome of other histological subtypes are known but specific agents targeting these alterations have yet to be developed. Thus, the therapeutic management of these subtypes represents an ongoing challenge. Recent advances in immunotherapy have highlighted the potential of immuno-oncology based treatments for NSCLC, offering the potential to provide durable responses and outcomes regardless of histology or mutation status. This review discusses the current unmet medical needs in NSCLC, the limits of current first-line and later-line chemotherapy and targeted agents, and the emergence of new therapeutic strategies.

Keywords

- Immunotherapy;
- NSCLC;
- Immune checkpoint blockade;
- CTLA-4;
- PD-1;
- PD-L1

Introduction

Most newly diagnosed advanced non-small cell lung cancer (NSCLC) patients present with inoperable (~80%) locally advanced (stage IIIB; 22%) or metastatic (stage IV; 56%) disease [1], [2], [3], [4] and [5]. In such patients, systemic treatment options are limited, with a median overall survival (OS) of 8–12 months in the clinical trial setting [6]. Because of the high incidence of NSCLC and the unsatisfactory efficacy of systemic treatment, lung cancer is the most frequent cause of cancer death in men, and is likely to be the most frequent cause of cancer death in women in the near future [7] and [8].

As with many diseases, treatment of NSCLC requires that certain patient groups are considered differently. Elderly patients with NSCLC often present with poor performance status (PS),

comorbidities and a higher level of toxicities, especially when exposed to combination chemotherapies [9]. Thus, for a significant proportion of elderly patients, single-agent chemotherapy is still the preferred treatment [6], [10], [11] and [12]. Patients with PS of 2 also require specific treatment consideration and are typically excluded from clinical trials. For these patients, chemotherapy may improve OS and quality of life (QoL) [13], with single-agent chemotherapy a common option; however, carboplatin-based combination chemotherapy should be considered in eligible patients with PS of 2 [6].

World Health Organization (WHO) classification for NSCLC includes many histological subtypes and is broadly categorised as squamous (30%) or non-squamous (70%; including adenocarcinoma, NSCLC not otherwise specified, and other cell types) for therapeutic purposes [14] and [15]. In routine clinical practice, a panel of immunohistochemistry markers, including at least cytokeratin 7, cytokeratin 5, thyroid transcription factor-1 and p63, has been shown to increase the likelihood of appropriate subtyping [16].

Advances in our understanding of the molecular biology of NSCLC have led to effective and approved targeted agents for tumours with epidermal growth factor receptor (EGFR) mutations and ALK or ROS1 rearrangements. Additionally, vascular endothelial growth factor (VEGF), heat-shock protein 90 (HSP90), the mammalian target of rapamycin, phosphatidylinositol 3-kinase (PI3 K), BRAF, HER2 and RET translocation have been shown to be additional potential targets of interest [17], [18], [19] and [20]. *EGFR* mutations are detected in approximately 10% of Caucasian and 30–50% of Asian patients with advanced NSCLC, and are generally more frequent among never-smokers [3] and [6]. *ALK* gene rearrangements are detected in 2–7% of patients with advanced NSCLC and are more commonly reported histologically in adenocarcinoma and in never-smokers; *ALK* gene rearrangements are often seen in younger patients [3] and [6].

Targeting oncogenic-driven NSCLC

First-line therapy options

Molecular targeted therapies have improved OS in specific subgroups of NSCLC patients in comparison with historical cohorts [21]. EGFR small molecule tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib and afatinib, and ALK-inhibiting agents such as crizotinib, ceritinib and alectinib, are currently the only truly molecular targeted therapies available for the treatment of advanced NSCLC [22], [23], [24], [25], [26], [27] and [28]. In randomised controlled trials, these agents have dramatically improved response rate, doubled time to progression, reduced tumour associated symptoms and improved QoL, without improving OS versus chemotherapy. This apparent lack of OS benefit is likely to reflect the confounding effects of crossover between treatment arms in the vast majority of patients in all trials [24], [26], [28], [29], [30], [31], [32], [33] and [34]. Furthermore, acquired resistance ultimately develops with all targeted agents.

Squamous cell NSCLC is still treated with cytotoxic chemotherapy alone [3] and [6]. Squamous cell carcinoma of the lung is closely related to smoking and has a distinct and more complex genetic signature compared with non-squamous tumours, including mutations in TP53, P13KCA, SOX2, fibroblast growth factor receptor (FGFR) and PTEN [14], [35] and [36]. However, there is currently insufficient evidence to suggest that blocking these pathways with targeted agents would represent true therapeutic progress.

Second- and further-line therapy options

Second- or further-line use of targeted agents has also shown efficacy in molecularly selected populations, although with some agents, efficacy may be reduced compared with first-line use

[28] and [34]. Thus, current guidelines recommend TKI and ALK-inhibiting therapy for second- or further-line as well as first-line use in patients with tumours expressing EGFR or ALK mutations [3], [6] and [12].

In contrast to the United States (US) where it is approved for first- and second-line treatment of ALK+ NSCLC, crizotinib was only granted approval in Europe for patients with an *ALK* gene rearrangement who have progressed after platinum-based chemotherapy, following a positive study of second-line crizotinib versus chemotherapy [3], [6] and [28]. However, it is noteworthy that crizotinib was superior to standard first-line pemetrexed plus platinum chemotherapy in a recent trial in patients with previously untreated advanced ALK+ NSCLC, which may lead to an extension of crizotinib's European indication in the future [34]. In April 2014, ceritinib received accelerated approval from the US Food and Drug Administration (FDA) for the treatment of patients with ALK+, metastatic NSCLC and disease progression on, or who showed intolerance to, crizotinib [37]. Alectinib was approved for the treatment of ALK+ NSCLC in Japan in July 2014 [38].

Treating NSCLC without driver oncogenes

First-line therapy options

For patients in whom no driver mutation can be identified, platinum-based doublet chemotherapy remains the mainstay of first-line therapy, although all platinum doublets show relatively similar efficacy profiles. Current ESMO guidelines suggest that 4–6 cycles of chemotherapy should be initiated in patients with favourable PS (PS 0 or 1), while for patients with declining PS of 2, mono-chemotherapy remains an option (gemcitabine, vinorelbine or taxanes); carboplatin-based combination chemotherapy should also be considered in eligible patients [6]. Patients with PS 3–4 should be offered best supportive care (BSC) [6].

Traditionally, the histological subtype of NSCLC did not influence the choice of chemotherapy. However, the treatment landscape has recently changed. Patients with non-squamous NSCLC benefited more (in terms of OS) than squamous patients from cisplatin plus pemetrexed in a large phase III non-inferiority study in patients with stage IIIB or IV NSCLC [39] and [40]. Hypothesis generating findings support the superior activity of pemetrexed in non-squamous histology due to the differential expression of thymidylate synthase across different histologies [41]. Indeed, clinical benefits of cisplatin plus pemetrexed versus cisplatin plus gemcitabine were more prominent in patients with less than 10% of tumours expressing thymidylate synthase in a recent phase II trial in patients with NSCLC [42].

Although bevacizumab is an established therapy for NSCLC, its role in the treatment paradigm is less straightforward as predictive factors to select patients for efficacy have not yet been established. Two pivotal phase III trials provided the foundation for using bevacizumab in NSCLC [43], [44] and [45]. Both studies were restricted to non-squamous histology because life threatening or fatal episodes of haemoptysis occurred in patients with squamous histology treated with bevacizumab plus chemotherapy in a phase II randomised clinical study [46].

A growing body of clinical evidence also indicates that maintenance therapy (as continuation or switch therapy) can provide additional long-term benefits, including improved progression-free survival (PFS) and OS [3] and [6]. Two independent studies have established a definitive role for pemetrexed in switch and continuation maintenance therapy [47] and [48]. Other agents already approved for second-line NSCLC, such as docetaxel and erlotinib, have also been tested in this setting [25] and [49]. Furthermore, meta-analyses have consistently demonstrated a benefit, in terms of PFS, for switch and continuation maintenance strategies [50] and [51], while OS may also

be improved without deterioration in QoL [14] and [52]. The decision of whether to implement maintenance therapy should consider the histology, response to platinum-doublet chemotherapy, residual toxicity after first-line chemotherapy, PS and patient preference [6].

Second-line treatment options

Patients progressing after first-line chemotherapy with PS 0–2 should be offered second-line single-agent chemotherapy, as no benefit has been demonstrated with combination regimens [3], [6] and [53]. Approved treatment choices include docetaxel for all NSCLC histologies [54] or pemetrexed for non-squamous NSCLC [55].

In a phase III study in second- and third-line patients who could not tolerate chemotherapy, erlotinib significantly improved median OS (6.7 months versus 4.7 months) and delayed time-to-symptom deterioration (2.2 months versus 1.8 months) versus BSC alone [56]. Extensive information on EGFR mutation status was lacking in this study as the activating EGFR mutation was unknown at the time of recruitment. Consequently, erlotinib has been approved for relapse therapy in patients after one line of previous chemotherapy, irrespective of any biomarker. In a recent meta-analysis, conventional chemotherapy was associated with improved PFS but not OS compared with first-generation EGFR inhibitors in patients expressing wild-type EGFR [57]. Thus, the selection of chemotherapy or erlotinib for second-line treatment should be based on their respective efficacy and safety profiles.

Nintedanib is a triple angiokinase inhibitor that simultaneously acts on vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor and FGFR [58]. In a phase III study, second-line nintedanib plus docetaxel significantly improved PFS, although not OS, versus docetaxel and placebo in patients with advanced NSCLC [59]. Furthermore, in a subgroup analysis, OS was significantly improved in patients with adenocarcinoma histology, representing the first study of second-line therapy in NSCLC to show an OS benefit through combining a targeted agent with chemotherapy [6]. Nintedanib was recently approved in the EU for use in adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology in combination with docetaxel after first-line chemotherapy [60].

In March 2015, the first immuno-oncology agent, nivolumab, was approved by the FDA for the treatment of patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy [61].

Although there is no clear guidance on the optimal duration of therapy, selection of the most appropriate second-line systemic treatment should depend on a variety of tumour and patient characteristics, including tumour histology, prior treatment, PS and age.

Selected agents in development

Several targeted agents are currently in development. For example, ramucirumab is a human IgG1 monoclonal antibody that targets the extracellular domain of VEGFR-2. In the phase III REVEL study, second-line treatment with docetaxel plus ramucirumab significantly improved median OS (10.5 months with docetaxel plus ramucirumab versus 9.1 months for docetaxel), PFS and overall response rate (ORR) versus docetaxel and placebo in patients with stage IV NSCLC previously treated with one line of platinum-based therapy [62]. Benefits were similar in squamous and non-squamous patients, and no unexpected adverse events (AEs) were identified.

Beyond second-line options

A retrospective review of patients receiving third-line chemotherapy reported a median OS of 5.8–6.5 months and a 1-year survival rate of 25%, with partial responses observed in 8%, stabilisation of disease in 25% and progression in 60% of patients [63] and [64]. An earlier retrospective analysis highlighted that with the sequential use of chemotherapy agents, response rates decreased with each successive line of treatment (Fig. 1) [65].

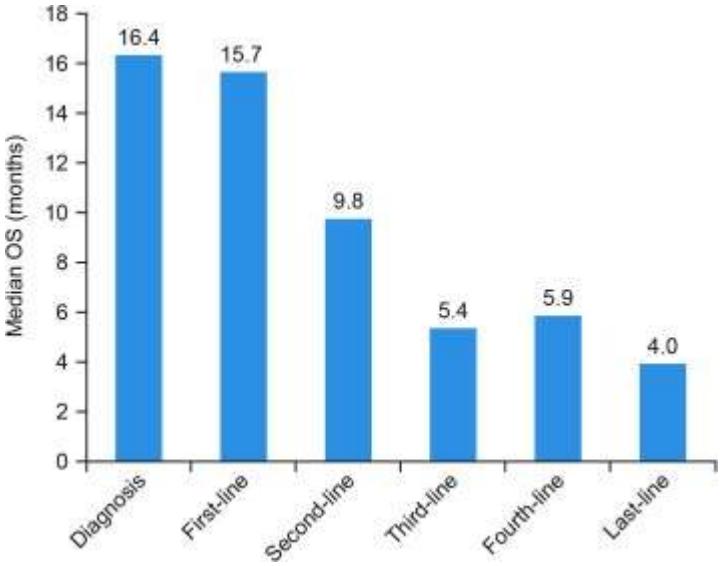

Fig. 1.

Median OS for sequential lines of treatment in patients with NSCLC. *Abbreviations:* NSCLC, non-small cell lung cancer; OS, overall survival [Reprinted from Lung Cancer, 39(1), Massarelli E et al, A retrospective analysis of the outcome of patients who have received two prior chemotherapy regimens including platinum and docetaxel for recurrent non-small-cell lung cancer, pp 55–61, Copyright (2015), with permission from Elsevier [65]].

Figure options

Although several large phase III trials have been conducted, the treatment algorithm beyond second-line therapy remains unclear, especially for patients with a squamous histology. The only available clinical evidence is that erlotinib is better than BSC alone, in a population where the benefit related to EGFR mutated versus EGFR wild-type tumours was unclear [56].

The need for new treatment approaches

New therapies and treatment strategies are required to improve outcomes in patients with NSCLC. Some patients, for example those with poor PS, brain metastases or squamous histology, have restricted treatment options. Furthermore, some agents are associated with poor tolerability. Acquired resistance to targeted therapies is also a clinical challenge, with treatment options for patients who progress on TKI therapy remaining limited [66] and [67].

In recent decades, systemic treatment options for patients with lung cancer have evolved from chemotherapy through targeted therapies to the more recent immuno-oncology agents, which will be the focus of the remainder of this review.

Targeting the immune system in NSCLC

Immuno-oncology is a novel therapeutic strategy currently being evaluated for the treatment of lung cancer. This approach differs from traditional modalities, which target the tumour directly or

aim to disrupt the tumour blood supply, as it is designed to potentiate the patient's immune response to tumour cells [68], [69], [70] and [71]. Limited success was achieved with early immunotherapy approaches, such as interleukin-2 and interferon; however, in theory, by targeting the immune system rather than the tumour directly, immuno-oncology agents have the potential to achieve clinical benefit in NSCLC regardless of phenotype, genotype, histology or mutational status [68], [69], [70], [71] and [72].

Through immune surveillance the immune system can recognise tumour-specific or associated antigens as abnormal and generate an antitumour response, eradicating or controlling tumours [68], [69], [70] and [71]. Immune surveillance involves both the innate and the adaptive immune response (Fig. 2) [68], [69], [70], [71] and [73]. The altered cytokine profiles observed in NSCLC tumours suggest that despite a host-mounted antitumour immune response, growth and progression continue [68], [69], [70], [71] and [73]. Tumours are able to evade detection by the host immune system through several mechanisms, some of which have been recognised in lung cancers [70] and [72]. These include inhibition of tumour antigen presentation, recruitment of immune suppressor cells and inhibition of antitumour immunity by checkpoint pathway engagement [70] and [72].

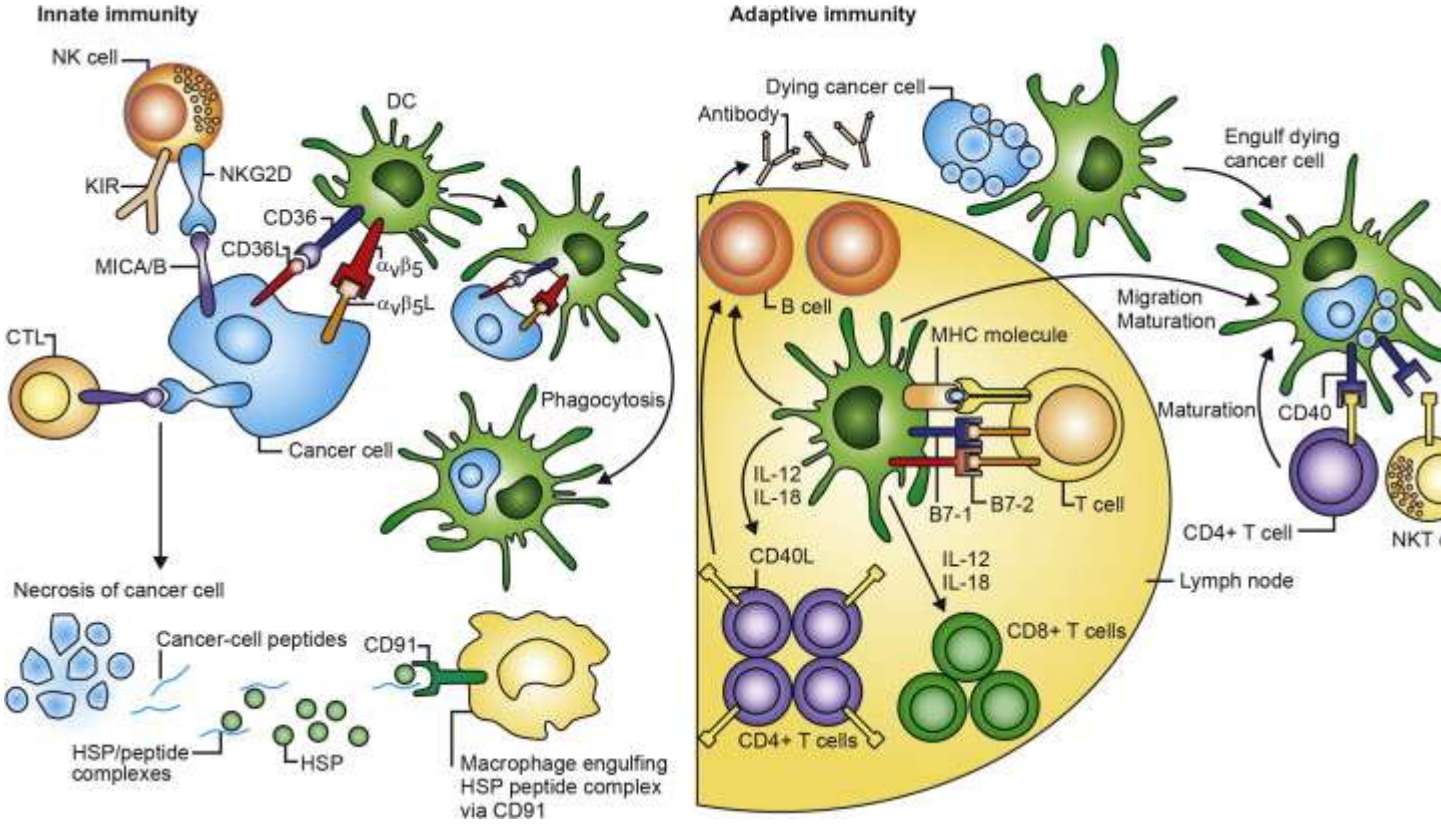

Fig. 2.

Signalling pathways involved in the crosstalk between immune cells and cancer cells in the innate and adaptive immune systems. *Abbreviations*: CTL, cytotoxic T-lymphocyte; DC, dendritic cell; HSP, heat shock protein; KIR, killer-cell immunoglobulin-like receptor; NK, natural killer; NKT, natural killer T cell. [Zielinski C et al, Rationale for targeting the immune system through checkpoint molecule blockade in the treatment of non-small-cell lung cancer, Annals of Oncology, 2013, 24(5), 1170–1179, by permission of the European Society for Medical Oncology [73]].

Figure options

As part of the host immune defence against tumours, T cells activated in the lymph nodes migrate to the tumour site where they recognise and eliminate tumour cells [68], [69], [70] and [71]. Several checkpoint receptors expressed on T cells modulate the immune response as part of normal physiological processes to maintain self-tolerance, prevent autoimmunity, suppress inappropriate responses to host antigens and protect non-tumour tissues from damage [71]. Tumours can exploit these pathways to evade the immune response. Two such pathways with the potential for therapeutic targeting include programmed death-1 receptor (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) [68], [69], [70] and [71]. In the context of tumour immunology, CTLA-4 signalling serves to limit the initiation of a T-cell response in the lymph nodes, while PD-1 expression is more prominent in limiting T-cell activity in the tumour microenvironment (Fig. 3) [74] and [75]. Blockade of these checkpoint pathways differs from antigen-specific immunotherapeutic approaches as an anticancer strategy because it targets the entire immune system [76] and [77]. Table 1 provides a summary of clinical data for immuno-oncology regimens in NSCLC [78], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88] and [89].

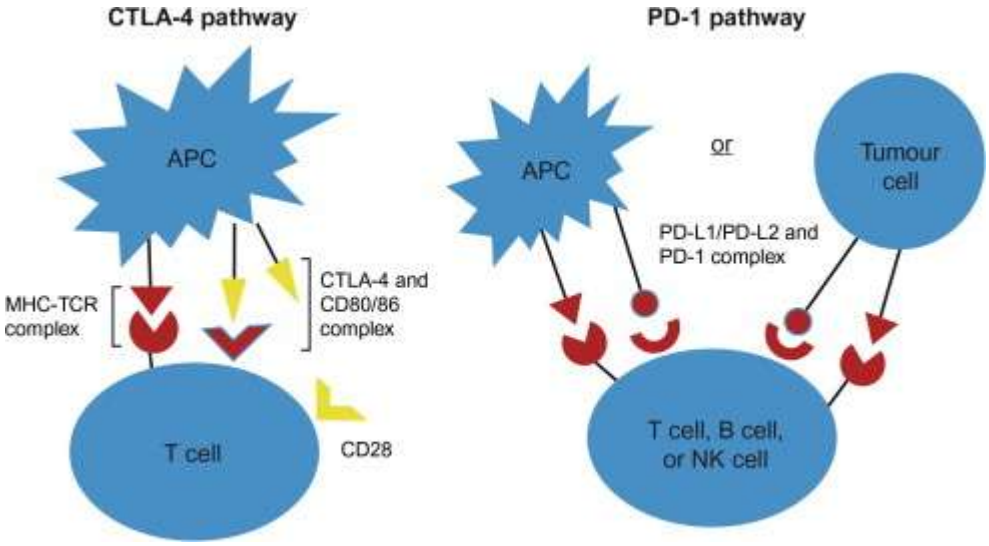

Fig. 3.

CTLA-4 and PD-1 inhibitory checkpoint pathways. *Abbreviations:* APC, antigen presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC-TCR, major histocompatibility complex-T cell receptor; NK, natural killer; PD-1, programmed death-1 receptor; PD-L1, programmed death-1 ligand; PD-L2, programmed death-2 ligand [Originally published by the American Society of Clinical Oncology. [Brahmer JR: 31 (8), 2013: 1021–1028] [75]].

Figure options

Table 1.

Immuno-oncology regimens for NSCLC: clinical trial data summary.

Refs.	Regimen[a]	Phase/setting (N)	ORR (%)	Median PFS	Median OS	1-/2-year OS (%)	Summary
Lynch [78]	Ipilimumab + carboplatin/paclitaxel (phased)	II/first line (*N* = 68)	32	5.1 months irPFS 5.7 months	12.2 months	42/16	Significantly improved irPFS (primary

Refs.	Regimen[a]	Phase/setting (N)	ORR (%)	Median PFS	Median OS	1-/2-year OS (%)	Summary
							endpoint)
							Most irAEs were grade 1–2 and manageable
							No impact of ipilimumab on toxicities seen with paclitaxel and carboplatin
	Ipilimumab + carboplatin/paclitaxel (concurrent)	II/first line (*N* = 70)	21	4.1 months irPFS 5.5 months	9.7 months	50/18	No significant improvement in irPFS
							Similar safety profile to phased regimen
Zatloukal [79]	Tremelimumab after ⩾4 cycles first-line platinum-based chemotherapy	II/maintenance (*N* = 44)	4.8	NR (21% progression-free at 3 months)	NR	NR	PFS analysis did not show superiority of tremelimumab over BSC
Gettinger [80]	Nivolumab	I/pretreated (*N* = 129)	17	2.3 months	9.9 months	42/24	Encouraging survival profile and clinical activity
							Manageable safety

Refs.	Regimen[a]	Phase/setting (N)	ORR (%)	Median PFS	Median OS	1-/2-year OS (%)	Summary
							profile (most irAEs low grade)
Rizvi [81]	Nivolumab	I/first line (*N* = 52)	21	15.6 weeks	98.3 weeks	NR	Durable responses observed regardless of tumour histology
							Tolerable safety profile
Ramalingham [82]	Nivolumab	II/pretreated (*N* = 117)	15	2 months	8.2 months	41/NR	Durable responses observed regardless of tumour histology
							Tolerable safety profile
Garon [83]	Pembrolizumab	I/naive (*N* = 38)	26	27 weeks	NR	NR	Durable objective responses
							Well tolerated
	Pembrolizumab	I/pretreated (*N* = 217)	20	10 weeks	8.2 months	NR	Durable objective responses
							Well tolerated
Soria [84]	MPDL3280A	I/pretreated[b] (*N* = 37)	24	NR (24-week PFS 45%)	NR	NR	Rapid and durable responses
							PD-L1 tumour status correlated with response
							Well

Refs.	Regimen[a]	Phase/setting (N)	ORR (%)	Median PFS	Median OS	1-/2-year OS (%)	Summary
							tolerated
Brahmer [85]	MEDI-4736	I/first line and pretreated (*N* = 13)	23	NR	NR	NR	Durable remissions were achieved Acceptable safety profile
Antonia [86]	Nivolumab (1 mg/kg) + ipilimumab (3 mg/kg)	I/first line (*N* = 24)	13	NR (44% at 24 weeks)	NR	65/NR	Combination is feasible with antitumour activity in PD-L1+ and PD-L1− patients
	Nivolumab (3 mg/kg) + ipilimumab (1 mg/kg)	I/first line (*N* = 25)	20	NR (33% at 24 weeks)	NR	44/NR	Combination is feasible with antitumour activity in PD-L1+ and PD-L1− patients
Antonia [87]	Nivolumab + platinum doublet chemotherapy	I/first line (*N* = 25)	33–47	NR	51–83 weeks	NR (18-month OS = 33–86%)	Manageable safety profile ORR similar to chemotherapy alone Encouraging OS rates
Rizvi [88]	Nivolumab + bevacizumab	I/second line (*N* = 12)	8	37.1	NR	75/NR	PFS similar to other agents approved for

Refs.	Regimen[a]	Phase/setting (N)	ORR (%)	Median PFS	Median OS	1-/2-year OS (%)	Summary
							maintenance therapy after second-line chemotherapy
							Encouraging safety profile
Gettinger [89]	Nivolumab + erlotinib	I/first line (*N* = 21)	19	29.4	NR	NR (18-month OS = 33–64%)	Encouraging response duration
							Consistent responses across EGFR mutation subtypes
							Manageable safety profile

Abbreviations: BSC, best supportive care; EGFR, epidermal growth factor receptor; irAE, immune-related adverse event; irPFS, immune-related progression-free survival; NR, not reached; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-1 ligand; PD-L1−, programmed death-1 ligand negative; PD-L1+, programmed death-1 ligand positive; PFS, progression-free survival.

aResults cannot be directly compared.
b98% of patients received prior systemic therapy.
Table options

Anti-CTLA-4 agents

Preclinical findings, together with the emerging profile of NSCLC as an immunological disease, have provided the rationale for the clinical development of CTLA-4 antibodies [76] and [77]. Clinical data with the anti-CTLA-4 monoclonal antibody ipilimumab, which facilitates stimulation of T-cell activity by inhibiting CTLA-4, has demonstrated enhanced activated T-cell antitumour responses in patients with metastatic melanoma [90]. The clinical activity of ipilimumab was subsequently demonstrated in two phase III trials, in which improved OS benefits were observed in patients with previously-treated and untreated metastatic melanoma [91] and [92]. Thus, ipilimumab is currently licensed for use in patients with advanced (unresectable or metastatic)

melanoma and is actively being evaluated in patients with other tumour types, including NSCLC and small cell lung cancer (SCLC).

In a phase II trial in patients with advanced (stage IIIB or IV) NSCLC, first-line chemotherapy (carboplatin and paclitaxel) plus concurrent (four doses of ipilimumab plus paclitaxel and carboplatin followed by two doses of placebo plus paclitaxel and carboplatin) and phased (two doses of placebo plus paclitaxel and carboplatin followed by four doses of ipilimumab plus paclitaxel and carboplatin) ipilimumab significantly improved median immune-related PFS (irPFS), defined as the time from randomisation to immune-related progressive disease or death [93] and [94], compared with placebo plus concomitant carboplatin and paclitaxel (phased ipilimumab = 5.7 months [hazard ratio (HR) = 0.72, p = 0.05]; concurrent ipilimumab = 5.5 months [HR = 0.81, p = 0.13]; chemotherapy = 4.6 months) [78]. Although no significant differences in OS were detected between the arms (p = 0.104), median OS for the phased ipilimumab group was 12.2 months versus 8.3 months for the chemotherapy plus placebo group (HR = 0.87, p = 0.23) [78]. Grade 3/4 AEs occurred in 37% of patients in the chemotherapy arm, 41% in the concurrent ipilimumab arm, and 39% in the phased ipilimumab arm. Although the study was not powered to detect differences in irPFS between squamous cell and non-squamous cell subgroups, subgroup analysis revealed that patients with squamous cell carcinoma had a greater improvement in irPFS if they received phased ipilimumab plus chemotherapy as opposed to the chemotherapy only regimen (HR = 0.55; 95% confidence intervals [CI]: 0.27–1.12) (Fig. 4) [74]. To further characterise the benefit of this regimen, a phase III trial is underway to determine whether the phased combination of ipilimumab with carboplatin and paclitaxel increases OS in patients with stage IV or recurrent squamous cell NSCLC (NCT01285609).

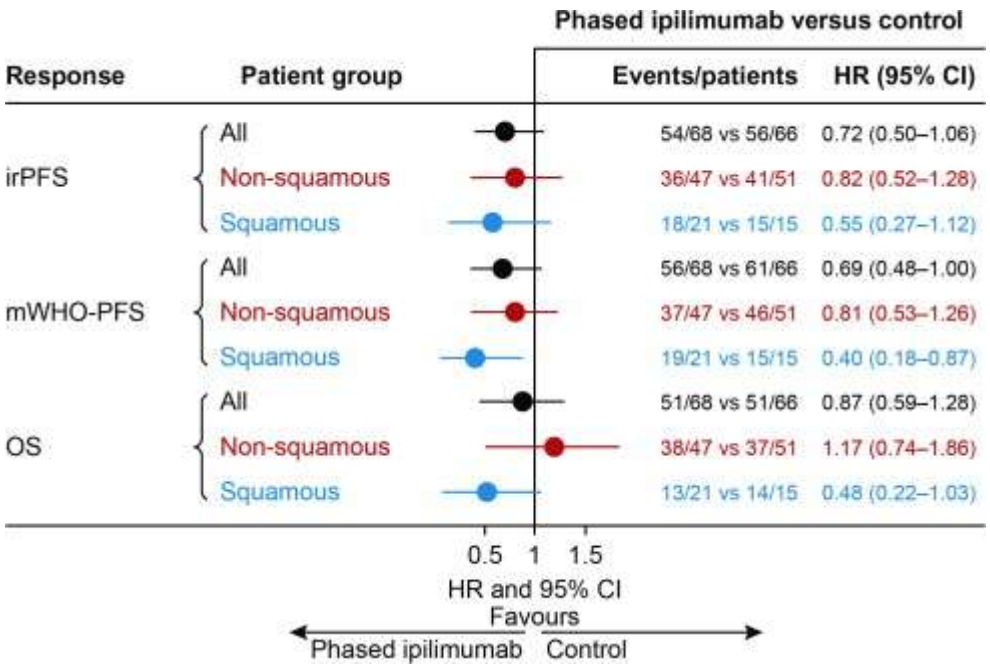

Fig. 4.

Immune-related responses in the phase II study of chemotherapy (carboplatin and paclitaxel) plus concurrent and phased ipilimumab as first-line treatment in advanced (stage IIIB or IV) NSCLC. *Abbreviations:* CI, confidence interval; HR, hazard ratio; irPFS, immune-related progression-free survival; mWHO-PFS, modified World Health Organization progression-free survival; OS, overall survival [Zielinski C et al, Rationale for targeting the immune system through checkpoint molecule blockade in the treatment of non-small-cell lung cancer, Annals of Oncology, 2013, 24(5), 1170–1179, by permission of the European Society for Medical Oncology [73]].

Figure options

Tremelimumab, a fully human anti-CTLA-4 immunoglobulin G2 monoclonal antibody, failed to improve PFS versus BSC in a phase II maintenance setting in 87 patients with stable or responding advanced NSCLC after first-line platinum-based chemotherapy [79]. Nine (20.9%; 90% CI: 11.4–33.7) patients receiving tremelimumab and 6 (14.3%; 90% CI: 6.4–26.3) patients receiving BSC were progression-free at 3 months. However, 5% of patients had objective radiological responses.

Tremelimumab is being evaluated in combination with the TKI gefitinib in NSCLC (NCT02040064) [95] and the anti-programmed death-1 ligand (anti-PD-L1) antibody MEDI-4736 in advanced solid tumours and NSCLC (NCT01975831 and NCT02000947). Tremelimumab is also currently under investigation in a phase IIb trial for the second-line and third-line treatment of unresectable pleural or peritoneal mesothelioma (NCT01843374) [96].

PD-1 pathway inhibition in NSCLC

Another important immune checkpoint pathway interaction that is being assessed as a therapeutic target in NSCLC is that between the PD-1 receptor expressed on activated T cells and its ligands, PD-L1 and programmed death-2 ligand (PD-L2), produced by stromal and tumour cells [97].

PD-1 is an inhibitory checkpoint receptor on T cells and the pathway is an important modulator of peripheral tolerance, protecting tissues from autoimmune damage and maintaining a balance between T-cell activation and tolerance [98]. PD-1 overexpression on CD8+ T cells has been observed in patients with NSCLC, with PD-1+ CD8+ T cells having reduced capacity to produce cytokines and proliferate [99]. Furthermore, upregulation of PD-L1 on tumour cells is associated with poor prognosis and is highly expressed in many cancers, including NSCLC [100], [101] and [102]. Thus, inhibiting the PD-1 pathway may facilitate restoration of tumour-specific T-cell function and diminish tumour-induced immune suppression [103].

Immuno-oncology agents targeting PD-1

The safety and clinical efficacy of nivolumab, a fully human monoclonal antibody directed against the PD-1 receptor, were evaluated in a phase I study in previously treated (up to 5 prior lines of therapy; >50% received >3 lines) patients with a range of solid tumours, including patients with advanced squamous and non-squamous NSCLC [80]. ORR was 17% and median duration of response was 17.1 months in patients with NSCLC, with similar ORRs recorded in PD-L1+ and PD-L1− patients (15% and 14%, respectively) [80]. Follow-up indicated median OS of 9.9 months, with median 1-, 2- and 3-year OS rates of 42%, 24% and 18%, respectively, for all patients. Median OS was 14.9 months for patients receiving 3 mg/kg nivolumab, with 1-, 2- and 3-year OS rates of 56%, 42% and 27%, respectively. Nivolumab had an acceptable safety profile; AEs were generally manageable using systemic glucocorticoids and/or other immunosuppressive agents. Similar median OS rates were reported for squamous and non-squamous subtypes (9.2 and 10.1 months, respectively) and PD-L1+ and PD-L1− patients (7.8 and 10.5 months, respectively). Clinical activity (ORR) was also observed across all patient subgroups, including those who had received <3 (12%) and $\geqslant$3 (21%) prior therapies and those with or without EGFR (17% and 20%, respectively) or Kirsten rat sarcoma viral oncogene homologue (14% and 25%, respectively) mutations. Subgroup analysis suggested that a history of smoking was associated with significantly improved response; ORR was 0% in patients with a smoking exposure $\leqslant$5 pack-years versus 30% in those with an exposure >5 pack-years [104]. A single-arm phase II study of nivolumab (CheckMate 063; NCT01721759) in patients with advanced or metastatic squamous NSCLC who have received at least two prior systemic regimens reported an ORR of 17%, with 76% of responses ongoing at the

time of analysis [82]. Median OS was 8.2 months and 1-year OS was 42% after a median follow-up of 8 months. Clinical activity was observed in PD-L1+ and PD-L1− patients and the safety profile was consistent with previous nivolumab trials. A randomised phase III study that compared nivolumab with docetaxel in patients with squamous NSCLC (regardless of PD-L1 status) in this setting was recently stopped early (CheckMate 017; NCT01642004). An independent Data Monitoring Committee concluded that the study met its endpoint, demonstrating superior median OS with nivolumab (9.2 months; 95% CI: 7.3–13.3) versus docetaxel (6.0 months; 95% CI: 5.1–7.3) with an HR of 0.59 (95% CI: 0.44–0.79; $p = 0.0002$) [105]. Nivolumab was subsequently approved for the treatment of metastatic squamous NSCLC with progression on or after platinum-based chemotherapy. A randomised phase III study of nivolumab in patients with non-squamous NSCLC is ongoing (CheckMate 057; NCT01673867).

An ongoing phase I trial is testing nivolumab monotherapy and nivolumab combinations with chemotherapy, targeted therapy and ipilimumab, as first-line treatments in chemotherapy-naïve NSCLC (CheckMate 012, NCT01454102). Preliminary data from the first 52 patients receiving nivolumab monotherapy in this study indicated a tolerable safety profile and an ORR of 21%; ORR was 31% in patients with PD-L1+ and 10% in PD-L1− patients [81]. Median PFS was 15.6 weeks and median OS was 98.3 weeks. Subgroup analysis suggested that response rates were higher in patients with a history of smoking. A phase III study of first-line therapy with nivolumab versus investigator's choice chemotherapy in patients with stage IIIB/IV or recurrent PD-L1+ NSCLC is currently recruiting patients (Table 2) [106].

Table 2.

Current stages of development of selected checkpoint inhibitors in NSCLC. www.clinicaltrials.gov.

Agent	Target	Phase of development in NSCLC	Clinicaltrials.gov identifier(s)	Pharmaceutical company
Ipilimumab	CTLA-4	Phase III	NCT01285609 NCT01450761	Bristol-Myers Squibb
Tremelimumab	CTLA-4	Phase II	NCT02179671	MedImmune
Nivolumab	PD-1	Phase III	NCT01642004 NCT02041533 NCT02066636 NCT01673867	Bristol-Myers Squibb
Pembrolizumab	PD-1	Phase III	NCT02220894 NCT02142738 NCT01905657	Merck
MPDL3280A	PD-L1	Phase III	NCT02008227	Genentech
MEDI-4736	PD-L1	Phase III	NCT02125461 NCT02154490	MedImmune
BMS-936559	PD-L1	Phase I	NCT00729664	Bristol-Myers Squibb
Ipilimumab + nivolumab	CTLA-4 + PD-1	Phase I	NCT01454102	Bristol-Myers Squibb

Agent	Target	Phase of development in NSCLC	Clinicaltrials.gov identifier(s)	Pharmaceutical company
Tremelimumab + MEDI-4736	CTLA-4 + PD-L1	Phase I	NCT02000947	MedImmune

Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen-4; NSCLC, non-small cell lung cancer; PD-1, programmed death-1 receptor; PD-L1, programmed death-1 ligand.

Table options

In a phase I study of 38 previously treated patients with advanced NSCLC receiving pembrolizumab, ORR was 21% using RECIST and 24% using immune-related response criteria (irRC). The median PFS reported for pembrolizumab-treated patients was 9.1 weeks, with a median OS of 51 weeks [83]. In an ongoing phase I study of first-line pembrolizumab in 45 patients with locally advanced or metastatic NSCLC (KEYNOTE-001), ORR was 36% by irRC and 52% of patients experienced a drug-related AE [107]. Pooled analysis of treatment-naïve and pretreated patients (*n* = 262) receiving pembrolizumab showed an ORR of 21% using RECIST and 23% using irRC; ORR was 23%/25% in patients with PD-L1+ tumours and 9%/13% in patients with PD-L1− tumours [83]. Grade 3–5 drug-related AEs were observed in 9% of patients. Pembrolizumab is currently being assessed versus docetaxel in patients with NSCLC whose disease has relapsed after platinum-based chemotherapy (NCT01905657).

Immuno-oncology agents targeting PD-L1

In a phase I expansion trial of MPDL3280A, a best ORR using RECIST was reported in 24% of patients with NSCLC, with a stable disease rate at 6 months of 17% [82], [84], [108] and [109]. The responses were durable, with 6-month PFS of 45%, and almost all responders were progression-free after 1 year. PD-L1 expression had a stronger correlation with ORR than other immune checkpoints [84]. One phase III and three phase II trials of MPDL3280A are currently ongoing in NSCLC; the phase II FIR and BIRCH trials are investigating the safety and efficacy of MPDL3280A in patients with PD-L1+ tumours (NCT01846416 and [110]), while the phase III OAK and phase II POPLAR trials are investigating MPDL3280A in comparison with docetaxel as second-line treatment (NCT01903993 and [110]).

Interim results are available from a phase I trial in which MEDI-4736 was given every 2 weeks in 6-week cycles to patients with solid tumours, including lung cancers. Several durable remissions were achieved in patients with NSCLC (*n* = 18) and MEDI-4736 had an acceptable safety profile [87]. Expansion cohorts are currently being enrolled for this trial to further test the safety and efficacy of MEDI-4736 in advanced solid tumours, including lung cancer (NCT01693562). MEDI-4736 will also be part of the multi-drug biomarker-driven phase II/III Lung-MAP trial that will assess several different drugs (MEDI-4736, rilotumumab, AZD4547, GDC-0032 or palbociclib) and combinations (anti-PD-L1 plus anti-CTLA-4) in NSCLC (NCT02154490). Furthermore, the phase II ATLANTIC study will assess the effects of MEDI-4736 as third-line therapy in patients with advanced or metastatic NSCLC (NCT02087423), while the phase III PACIFIC study will assess the effects of MEDI-4736 following concurrent chemoradiation in patients with stage III unresectable NSCLC (NCT02125461).

Other immuno-oncology agents targeting checkpoint inhibitors

Other agents currently in clinical development include an anti-LAG-3 (lymphocyte-activation protein 3) monoclonal antibody (BMS-986016), which is being evaluated both as a monotherapy and in combination with nivolumab in a phase I clinical trial in patients with solid tumours (NCT01968109). In addition, lirilumab (an anti-killer cell immunoglobulin-like receptor (KIR) antibody) is being assessed in combination with nivolumab or ipilimumab in patients with advanced solid tumours (NCT01714739, NCT01750580). Data are currently limited for these trials.

Immuno-oncology based combination therapy

There is a strong rationale to add a further treatment modality to immuno-oncology based therapies. This approach includes combining two immuno-oncology agents that target different signalling pathways, as well as combining an immuno-oncology agent with chemotherapy, radiotherapy or a targeted agent. For example, there are several early phase trials in patients with solid tumours investigating the potential of combining a CTLA-4 inhibitor with a PD-1 targeting agent. Early data in patients with advanced melanoma suggest that the concurrent combination of nivolumab and ipilimumab induces encouraging antitumour activity including rapid, deep and durable tumour responses, which appeared to be higher than published monotherapy data [111] and [112]. Preliminary results from an ongoing phase I trial of first-line ipilimumab and nivolumab in patients with advanced NSCLC (*n* = 49) also highlight the promise of this approach [86]. ORR was 13% in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg arm and 20% in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg arm; PFS at 24 weeks was 44% and 33% and 1-year OS was 65% and 44%, respectively. Combination therapy was associated with a safety profile that was manageable using well-established safety guidelines, and activity was observed in PD-L1+ and PD-L1− patients. The recommended combination dose for phase II/III trials has yet to be determined. A trial combining tremelimumab with MEDI-4736 in advanced solid tumours is ongoing (NCT01975831). Interim data from 12 patients indicate promising response rates and a manageable safety profile [113].

Early evidence from a phase II study demonstrated that ipilimumab plus chemotherapy significantly improved irPFS (versus chemotherapy alone) in patients with NSCLC or extensive-disease SCLC [78]. A large phase I trial (CheckMate 012, NCT01454102) is evaluating nivolumab as monotherapy and in a range of combinations in patients with NSCLC. Preliminary data from the cohort receiving nivolumab in combination with platinum-based doublet chemotherapy (gemcitabine/cisplatin or pemetrexed/cisplatin or paclitaxel/carboplatin) showed acceptable ORRs ranging from 33% to 47% across treatment arms, with a manageable safety profile reflective of additive toxicities [87]. An encouraging 18-month OS rate of 86% was shown with nivolumab (5 mg/kg) in combination with paclitaxel/carboplatin. In a second cohort of patients who did not progress on first-line platinum-based chemotherapy, switching to nivolumab, either as monotherapy or in combination with bevacizumab, demonstrated median PFS (21.4 and 37.1 weeks, respectively) similar to agents already approved for maintenance therapy in advanced NSCLC and an acceptable safety profile [88]. A phase I trial of nivolumab in combination with chemotherapy in Japanese patients has also shown encouraging antitumour activity and a manageable safety profile [114]. A study with pembrolizumab in combination with cisplatin/pemetrexed or carboplatin/paclitaxel in advanced solid tumours is ongoing (NCT01840579).

Data from preclinical studies suggest that combination of PD-1 blockade with EGFR TKIs may be a promising therapeutic strategy, particularly in maintenance therapy, to extend the duration of treatment response and delay development of resistance in NSCLC [115]. Several early-phase trials combining targeted agents with immuno-oncology agents are therefore underway. Preliminary data from the cohort of CheckMate 012 with EGFR mutated advanced NSCLC receiving nivolumab

and erlotinib suggest that this combination may provide durable clinical benefit coupled with an acceptable safety profile [89]. OS at 18 months was 64% in patients receiving nivolumab and erlotinib, while ORR was 19%, median PFS was 29.4 weeks and the median duration of response was not reached.

Safety of immuno-oncology agents

Although immuno-oncology agents are in relatively early clinical development in NSCLC, they appear to be comparatively well tolerated. Despite being associated with immune-related AEs (irAEs) that are inflammatory in nature, many events are minor and/or reversible. The most notable irAEs are diarrhoea/colitis and pneumonitis. Pneumonitis, although rare, is of particular relevance in patients with NSCLC as compromised respiratory function is common. Although appropriate management with steroids and dose interruption can minimise complications, development of guidelines to ensure the early diagnosis and appropriate treatment of irAEs are vital. Such guidelines are currently being used in clinical trials.

The spectrum and frequency of AEs also differ somewhat between anti-PD-L1 and anti-CTLA-4 agents, emphasising the distinct biological features of the two pathways [116]. Agents targeting the PD-1 pathway appear to have lower toxicity than those targeting CTLA-4, potentially because the CTLA-4 interaction takes place centrally, whereas the PD-1/PD-L1 interaction occurs in the peripheral tissues.

Assessing response to immuno-oncology agents

The methods employed to assess treatment efficacy may need to evolve to reflect the unique properties of immuno-oncology agents. For instance, immune-specific criteria, as opposed to traditional methods for assessing treatment responses such as RECIST, may be required due to the different kinetics of response. Furthermore, long-term survival rather than conventional outcome measures such as ORR and PFS might be more suitable to fully capture the clinical benefit of immuno-oncology agents.

Biomarkers for immuno-oncology agents

Moving forward, the identification of predictive factors and biomarkers will be vital to establish patient populations in which immuno-oncology agents are effective. Several putative candidates have been investigated, including immune cell populations, smoking status, and gene signatures [117], [118] and [119]. However, perhaps the most studied biomarker to date is PD-L1 expression, which has shown some utility for predicting response to agents targeting the PD-1 pathway in several but not all studies [80], [81], [82], [83], [84] and [87]. The use of PD-L1 as a biomarker is complicated by a number of factors including the heterogeneity and dynamism of PD-L1 expression within tumours, variability in tissue collection timing, the antibody used for staining, definition of positivity, non-standardised test design, and the role of PD-L1 expression on tumour infiltrating lymphocytes and other immune cells versus tumour cells [120], [121], [122], [123] and [124]. Moreover, for immune-based therapies, ORR may not be the optimal endpoint to assess the predictive role of biomarkers [123]. Consequently, findings from ongoing phase III trials should provide further information on PD-L1 and other biomarkers of response with immuno-oncology agents and lead to harmonisation of the assessment techniques used.

Summary

Recognition of the limits of chemotherapy and targeted therapy for NSCLC has served to underscore the urgent need for new treatment approaches for this intractable disease. While

advances in our understanding of NSCLC have led to the development of new targeted therapies, there is still a demand for alternative approaches that offer meaningful improvements in symptom relief, QoL and survival.

Improved awareness of the immune profile of NSCLC has led to a variety of immuno-oncology strategies, including the development of checkpoint inhibitory molecules responsible for ameliorating the antitumour immune response. Preliminary evidence of clinical efficacy with these agents is promising across several cancer types, including NSCLC. Unlike other systemic therapies that target the tumour directly or act to inhibit angiogenesis, immuno-oncology agents target the immune system. Initial evidence suggests that immuno-oncology agents can achieve efficacy across a broad patient profile as they do not require the presence of specific mutations or other tumour molecular characteristics. The safety profile of immuno-oncology agents is also different to that of traditional chemotherapies and targeted agents. However, immune-related effects within healthy tissue are usually manageable with early intervention and adherence to well established management guidelines, which might offer an advantage over the unpleasant toxicity profiles associated with chemotherapies in particular.

Future research will help determine when and how immuno-oncology agents can be used synergistically alongside or sequentially with other treatment modalities to improve patient outcomes and maximise their clinical benefit. Regimens combining two immune checkpoint inhibitors (e.g. anti-PD-1, anti-CTLA-4, anti-KIR, anti-LAG) are a particularly promising approach currently under investigation. The hope is that such combinations will form the foundation of a new treatment paradigm in NSCLC that may one day negate the requirement for chemotherapy. Alternative therapeutic avenues that are worthy of investigation are the maintenance setting, either in metastatic or locally advanced disease, and the inclusion of immune checkpoint inhibitors as part of adjuvant treatment in the setting of completely resected NSCLC. Small pivotal neo-adjuvant studies of immune checkpoint inhibitors as single agents or in combination with other immunological agents are another potential area of research.

Conflicts of interest

J.F. Vansteenkiste: Research funding at University Hospitals KU Leuven: AstraZeneca, Amgen. Advisory functions: GlaxoSmithKline, Merck Serono, Novartis, Bristol-Myers Squibb. Speaker bureau: Eli Lilly. G.V. Scagliotti: Honoraria: Eli Lilly, Roche, Pfizer, AstraZeneca, Clovis Oncology. P. Bironzo: No conflicts of interest.

Acknowledgements

The authors take full responsibility for the content of this publication, and confirm that it reflects their viewpoint and medical expertise. StemScientific, funded by Bristol-Myers Squibb, provided writing and editing support. Bristol-Myers Squibb did not influence the content of the manuscript, nor did the authors receive financial compensation for authoring the manuscript.

References

[1]
S.G. Spiro, M.K. Gould, G.L. Colice, American College of Chest Physicians
Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes: ACCP Evidenced-based Clinical Practice Guidelines (2nd edition)
Chest, 132 (Suppl. 3) (2007) 149–60S
[2]
D.S. Ettinger, W. Akerley, H. Borghaei, A.C. Chang, R.T. Cheney, L.R. Chirieac, *et al.*

Non-small cell lung cancer
J Natl Compr Canc Netw, 10 (1) (2012), pp. 1236–1271
[3]
National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: non-small cell lung cancer. Version V4.2014. <www.nccn.org> [accessed 10.09. [4]
A. Thomas, R. Hassan
Immunotherapies for non-small-cell lung cancer and mesothelioma
Lancet Oncol, 13 (7) (2012), pp. e301–e310
[5]
R.N. Younes, J.R. Pereira, A.L. Fares, J.L. Gross
Chemotherapy beyond first-line in stage IV metastatic non-small cell lung cancer
Rev Assoc Med Bras, 57 (6) (2011), pp. 686–691
[6]
M. Reck, S. Popat, N. Reinmuth, D. De Ruysscher, K.M. Kerr, S. Peters, *et al.*
Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
Ann Oncol, 25 (Suppl. 3) (2014), pp. iii27–iii39
[7]
J. Ferlay, E. Steliarova-Foucher, J. Lortet-Tieulent, S. Rosso, J.W. Coebergh, H. Comber, *et al.*
Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012
Eur J Cancer, 49 (6) (2013), pp. 1374–1403
[8]
Anon [no author listed]. The threat of lung cancer in European women. Lancet 2013;381(9867):600.
[9]
C.J. Langer, J. Manola, P. Bernardo, J.W. Kugler, P. Bonomi, D. Cella, *et al.*
Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial
J Natl Cancer Inst, 94 (3) (2002), pp. 173–181
[10]
P. Maione, A. Rossi, P.C. Sacco, M.A. Bareschino, C. Schettino, M.L. Ferrara, *et al.*
Treating advanced non-small cell lung cancer in the elderly
Ther Adv Med Oncol, 2 (4) (2010), pp. 251–260
[11]
G. Meoni, F.L. Cecere, E. Lucherini, F. Di Costanzo
Medical treatment of advanced non-small cell lung cancer in elderly patients: a review of the role of chemotherapy and targeted agents
J Geriatr Oncol, 4 (3) (2013), pp. 282–290
[12]
B. Besse, A. Adjei, P. Baas, P. Meldgaard, M. Nicolson, L. Paz-Ares, *et al.*
2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease
Ann Oncol, 25 (8) (2014), pp. 1475–1484
[13]
R. Lilenbaum, V.M. Villaflor, C. Langer, K. O'Byrne, M. O'Brien, H.J. Ross, *et al.*
Single-agent versus combination chemotherapy in patients with advanced non-small cell lung cancer and a performance status of 2: prognostic factors and treatment selection based on two large randomized clinical trials
J Thorac Oncol, 4 (7) (2009), pp. 869–874
[14]
P. Perez-Moreno, E. Brambilla, R. Thomas, J.C. Soria

Squamous cell carcinoma of the lung: molecular subtypes and therapeutic opportunities
Clin Cancer Res, 18 (9) (2012), pp. 2443–2451
[15]
M.S. Ginsberg, R.K. Grewal, R.T. Heelan
Lung cancer
Radiol Clin North Am, 45 (1) (2007), pp. 21–43
[16]
L. Righi, P. Graziano, A. Fornari, G. Rossi, M. Barbareschi, A. Cavazza, *et al.*
Immunohistochemical subtyping of non-small cell lung cancer not otherwise specified in fine-needle aspiration cytology: a retrospective study of 103 cases with surgical correlation
Cancer, 117 (15) (2011), pp. 3416–3423
[17]
C. Fumarola, M.A. Bonelli, P.G. Petronini, R.R. Alfieri
Targeting PI3K/AKT/mTOR pathway in non small cell lung cancer
Biochem Pharmacol, 90 (3) (2014), pp. 197–207
[18]
C.M. Blakely, T.G. Bivona
Resiliency of lung cancers to EGFR inhibitor treatment unveiled, offering opportunities to divide and conquer EGFR inhibitor resistance
Cancer Discov, 2 (10) (2012), pp. 872–875
[19]
L. Crinò, G. Metro
Therapeutic options targeting angiogenesis in nonsmall cell lung cancer
Eur Respir Rev, 23 (131) (2014), pp. 79–91
[20]
Smith DL, Acquaviva J, Sequeira M, Jimenez JP, Zhang C, Sang J, et al. The HSP90 inhibitor ganetespib potentiates the antitumor activity of EGFR tyrosine kinase inhibition in mutant and wild-type non-small cell lung cancer. Target Oncol 2014 Aug 1 [Epub ahead of print].
[21]
T. Takano, T. Fukui, Y. Ohe, K. Tsuta, S. Yamamoto, H. Nokihara, *et al.*
EGFR mutations predict survival benefit from gefitinib in patients with advanced lung adenocarcinoma: a historical comparison of patients treated before and after gefitinib approval in Japan
J Clin Oncol, 26 (34) (2008), pp. 5589–5595
[22]
Shaw AT, Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 2014;27;370(13):1189–97.
[23]
T. Seto, K. Kiura, M. Nishio, K. Nakagawa, M. Maemondo, A. Inoue, *et al.*
CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1-2 study
Lancet Oncol, 14 (7) (2013), pp. 590–598
[24]
R. Rosell, E. Carcereny, R. Gervais, A. Vergnenegre, B. Massuti, E. Felip, *et al.*
Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial
Lancet Oncol, 13 (3) (2012), pp. 239–246
[25]
F. Cappuzzo, T. Ciuleanu, L. Stelmakh, S. Cicenas, A. Szczésna, E. Juhász, *et al.*

Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study
Lancet Oncol, 11 (6) (2010), pp. 521–529
[26]
T.S. Mok, Y.L. Wu, S. Thongprasert, C.H. Yang, D.T. Chu, N. Saijo, *et al.*
Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma
N Engl J Med, 361 (10) (2009), pp. 947–957
[27]
L.V. Sequist, J.C. Yang, N. Yamamoto, K. O'Byrne, V. Hirsh, T. Mok, *et al.*
Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations
J Clin Oncol, 31 (27) (2013), pp. 3327–3334
[28]
A.T. Shaw, D.W. Kim, K. Nakagawa, T. Seto, L. Crinó, M.J. Ahn, *et al.*
Crizotinib versus chemotherapy in advanced ALK-positive lung cancer
N Engl J Med, 368 (25) (2013), pp. 2385–2394
[29]
M. Fukuoka, Y.L. Wu, S. Thongprasert, P. Sunpaweravong, S.S. Leong, V. Sriuranpong, *et al.*
Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS)
J Clin Oncol, 29 (21) (2011), pp. 2866–2874
[30]
M. Maemondo, A. Inoue, K. Kobayashi, S. Sugawara, S. Oizumi, H. Isobe, *et al.*
Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR
N Engl J Med, 362 (25) (2010), pp. 2380–2388
[31]
C. Zhou, Y.L. Wu, G. Chen, J. Feng, X.Q. Liu, C. Wang, *et al.*
Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study
Lancet Oncol, 12 (8) (2011), pp. 735–742
[32]
G. Chen, J. Feng, C. Zhou, Y.L. Wu, X.Q. Liu, C. Wang, *et al.*
Quality of life (QoL) analyses from OPTIMAL (CTONG-0802), a phase III, randomised, open-label study of first-line erlotinib versus chemotherapy in patients with advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC)
Ann Oncol, 24 (6) (2013), pp. 1615–1622
[33]
Y.L. Wu, D.T. Chu, B. Han, X. Liu, L. Zhang, C. Zhou, *et al.*
Phase III, randomized, open-label, first-line study in Asia of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer: evaluation of patients recruited from mainland China
Asia Pac J Clin Oncol, 8 (3) (2012), pp. 232–243
[34]
B.J. Solomon, T. Mok, D.W. Kim, Y.L. Wu, K. Nakagawa, T. Mekhail, *et al.*
First-line crizotinib versus chemotherapy in ALK-positive lung cancer
N Engl J Med, 371 (23) (2014), pp. 2166–2177
[35]
Z. Kan, B.S. Jaiswal, J. Stinson, V. Janakiraman, D. Bhatt, H.M. Stern, *et al.*
Diverse somatic mutation patterns and pathway alterations in human cancers

Nature, 466 (7308) (2010), pp. 869–873
[36]
M. D'Arcangelo, A. D'Incecco, F. Cappuzzo
Rare mutations in non-small-cell lung cancer
Future Oncol, 9 (5) (2013), pp. 699–711
[37]
US Food and Drug Administration. Ceritinib. Available at:
<http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm395386.htm> [accessed September 2014].
[38]
F. Hoffmann-La Roche Ltd. Media release 4 July 2014. Available at:
<http://www.roche.com/media/media_releases/med-cor-2014-07-04.htm> [accessed December 2014]
[39]
G.V. Scagliotti, P. Parikh, J. Von Pawel, B. Biesma, J. Vansteenkiste, C. Manegold, *et al.*
Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer
J Clin Oncol, 26 (21) (2008), pp. 3543–3551
[40]
K.N. Syrigos, J. Vansteenkiste, P. Parikh, J. von Pawel, C. Manegold, R.G. Martins, *et al.*
Prognostic and predictive factors in a randomized phase III trial comparing cisplatin-pemetrexed versus cisplatin-gemcitabine in advanced non-small-cell lung cancer
Ann Oncol, 21 (3) (2010), pp. 556–561
[41]
P. Ceppi, M. Volante, S. Saviozzi, I. Rapa, S. Novello, A. Cambieri, *et al.*
Squamous cell carcinoma of the lung compared with other histotypes shows higher messenger RNA and protein levels for thymidylate synthase
Cancer, 107 (7) (2006), pp. 1589–1596
[42]
M.A. Ahn, J. Sun, J.S. Ahn, S. Jung, K. Park
Cisplatin plus pemetrexed (CP) versus cisplatin plus gemcitabine (CG) according to thymidylate synthase expression in non-squamous NSCLC: a biomarker-stratified randomized phase II trial
Ann Oncol, 25 (4) (2014), pp. v1–v41 [abstract LBA42PR]
[43]
A. Sandler, R. Gray, M.C. Perry, J. Brahmer, J.H. Schiller, A. Dowlati, *et al.*
Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer
N Engl J Med, 355 (24) (2006), pp. 2542–2550
[44]
M. Reck, J. von Pawel, P. Zatloukal, *et al.*
Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil
J Clin Oncol, 27 (8) (2009), pp. 1227–1234
[45]
M. Reck, J. von Pawel, P. Zatloukal, R. Ramlau, V. Gorbounova, V. Hirsh, *et al.*
Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL)
[46]
D.H. Johnson, L. Fehrenbacher, W.F. Novotny, R.S. Herbst, J.J. Nemunaitis, D.M. Jablons, *et al.*
Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer

J Clin Oncol, 22 (11) (2004), pp. 2184–2191
[47]
T. Ciuleanu, T. Brodowicz, C. Zielinski, J.H. Kim, M. Krzakowski, E. Laack, *et al.*
Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study
Lancet, 374 (9699) (2009), pp. 1432–1440
[48]
L.G. Paz-Ares, F. de Marinis, M. Dediu, M. Thomas, J.L. Pujol, P. Bidoli, *et al.*
PARAMOUNT: final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer
J Clin Oncol, 31 (23) (2013), pp. 2895–2902

[49]
P.M. Fidias, S.R. Dakhil, A.P. Lyss, D.M. Loesch, D.M. Waterhouse, J.L. Bromund, *et al.*
Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer
J Clin Oncol, 27 (4) (2009), pp. 591–598
[50]
Y.Y. Soon, M.R. Stockler, L.M. Askie, M.J. Boyer
Duration of chemotherapy for advanced non-small-cell lung cancer: a systematic review and meta-analysis of randomized trials
J Clin Oncol, 27 (20) (2009), pp. 3277–3283
[51]
M. Behera, T.K. Owonikoko, Z. Chen, S.A. Kono, F.R. Khuri, C.P. Belani, *et al.*
Single agent maintenance therapy for advanced stage non-small cell lung cancer: a meta-analysis
Lung Cancer, 77 (2) (2012), pp. 331–338
[52]
D. Gerber, J. Schiller
Maintenance chemotherapy for advanced non-small-cell lung cancer: new life for an old idea
J Clin Oncol, 31 (8) (2013), pp. 1009–1020
[53]
M. Di Maio, P. Chiodini, V. Georgoulias, D. Hatzidaki, K. Takeda, F.M. Wachters, *et al.*
Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer
J Clin Oncol, 27 (11) (2009), pp. 1836–1843
[54]
F.A. Shepherd, J. Dancey, R. Ramlau, K. Mattson, R. Gralla, M. O'Rourke, *et al.*
Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell-lung cancer previously treated with platinum-based chemotherapy
J Clin Oncol, 18 (10) (2000), pp. 2095–2103
[55]
N. Hanna, F.A. Shepherd, F.V. Fossella, J.R. Pereira, F. De Marinis, J. von Pawel, *et al.*
Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy
J Clin Oncol, 22 (9) (2004), pp. 1589–1597
[56]
F.A. Shepherd, J. Rodrigues Pereira, T. Ciuleanu, E.H. Tan, V. Hirsh, S. Thongprasert, *et al.*
Erlotinib in previously treated non-small-cell lung cancer
N Engl J Med, 353 (2) (2005), pp. 123–132
[57]

J.K. Lee, S. Hahn, W. Kim, J.K. Suh, B. Keam, T. Kim, *et al.*
Epidermal growth factor receptor tyrosine kinase inhibitors vs conventional chemotherapy in non-small cell lung cancer harbouring wild-type epidermal growth factor receptor: a meta-analysis
JAMA, 311 (14) (2014), pp. 1430–1437
[58]
C. Rolfo, L.E. Raez, G. Bronte, E.S. Santos, K. Papadimitriou, L. Buffoni, *et al.*
BIBF 1120/nintedanib: a new triple angiokinase inhibitor-directed therapy in patients with non-small cell lung cancer
Expert Opin Investig Drugs, 22 (8) (2013), pp. 1081–1088
[59]
M. Reck, R. Kaiser, A. Mallemgaard, J.Y. Douillard, S. Orlov, M. Krzakowski, *et al.*
Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial
Lancet Oncol, 15 (2) (2014), pp. 143–155
[60]
Boehringer Ingelheim GmbH. Press release 27 November 2014. Available at:
<http://www.boehringeringelheim.com/news/news_releases/press_releases/2014/27_november_2014_oncology.html> [accessed December 2014].

[61]
U.S. Food and Drug Administration News Release. FDA expands approved use of Opdivo to treat lung cancer. 4 March 2015. Available at:
<http://www.fda.gov.uk/NewsEvents/Newsroom/PressAnnouncements/ucm436534.htm>
[accessed March 2015].
[62]
M. Perol, T.-E. Ciuleanu, O. Arrieta, K. Prabhash, K.N. Syrigos, T. Göksel, *et al.*
REVEL: a randomized, double-blind, phase III study of docetaxel (DOC) and ramucirumab (RAM; IMC-1121B) versus DOC and placebo (PL) in the second-line treatment of stage IV non-small cell lung cancer (NSCLC) following disease progression after one prior platinum-based therapy
J Clin Oncol, 32 (Suppl. 5) (2014) [abstract LBA8006^]
[63]
N. Girard, P. Jacoulet, M. Gainet, R. Elleuch, D. Pernet, A. Depierre, *et al.*
Third-line chemotherapy in advanced non-small cell lung cancer: identifying the candidates for routine practice
J Thorac Oncol, 4 (12) (2009), pp. 1544–1549
[64]
M. Scartozzi, P. Mazzanti, R. Giampieri, R. Berardi, E. Galizia, S. Gasparini, *et al.*
Clinical predictive factors for advanced non-small cell lung cancer (NSCLC) patients receiving third-line therapy: selecting the unselectable?
Lung Cancer, 68 (3) (2010), pp. 433–437
[65]
E. Massarelli, F. Andre, D.D. Liu, J.J. Lee, M. Wolf, A. Fandi, *et al.*
A retrospective analysis of the outcome of patients who have received two prior chemotherapy regimens including platinum and docetaxel for recurrent non-small-cell lung cancer
Lung Cancer, 39 (1) (2003), pp. 55–61
[66]
L.V. Sequist, B.A. Waltman, D. Dias-Santagata, S. Digumarthy, A.B. Turke, P. Fidias, *et al.*
Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors
Sci Transl Med, 3 (75) (2011), p. 75ra26
[67]
J.F. Gainor, A.T. Shaw

Emerging paradigms in the development of resistance to tyrosine kinase inhibitors in lung cancer
J Clin Oncol, 31 (31) (2013), pp. 3987–3996
[68]
M.D. Vesely, M.H. Kershaw, R.D. Schreiber, M.J. Smyth
Natural innate and adaptive immunity to cancer
Annu Rev Immunol, 29 (2011), pp. 235–271
[69]
I. Mellman, G. Coukos, G. Dranoff
Cancer immunotherapy comes of age
Nature, 480 (7378) (2011), pp. 480–489
[70]
E. Tartour, L. Zitvogel
Lung cancer: potential targets for immunotherapy
Lancet Respir Med, 1 (7) (2013), pp. 551–563
[71]
D.M. Pardoll
The blockade of immune checkpoints in cancer immunotherapy
Nat Rev Cancer, 12 (4) (2012), pp. 252–264
[72]
M.R. Jadus, J. Natividad, A. Mai, Y. Ouyang, N. Lambrecht, S. Szabo, *et al.*
Lung cancer: a classic example of tumor escape and progression while providing opportunities for immunological intervention
Clin Dev Immunol, 2012 (2012), p. 160724

[73]
C. Zielinski, S. Knapp, C. Mascaux, F. Hirsch
Rationale for targeting the immune system through checkpoint molecule blockade in the treatment of non-small-cell lung cancer
Ann Oncol, 24 (5) (2013), pp. 1170–1179
[74]
B.T. Fife, J.A. Bluestone
Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways
Immunol Rev, 224 (2008), pp. 166–182
[75]
J.R. Brahmer
Harnessing the immune system for the treatment of non-small-cell lung cancer
J Clin Oncol, 31 (8) (2013), pp. 1021–1028
[76]
G.E. Holt, E.R. Podack, L.E. Raez
Immunotherapy as a strategy for the treatment of non-small-cell lung cancer
Therapy, 8 (1) (2011), pp. 43–54
[77]
F.A. Shepherd, J.Y. Douillard, G.R. Blumenschein Jr.
Immunotherapy for non-small-cell lung cancer: novel approaches to improve patient outcomes
J Thorac Oncol, 6 (10) (2011), pp. 1763–1773
[78]
T.J. Lynch, I. Bondarenko, A. Luft, P. Serwatowski, F. Barlesi, R. Chacko, *et al.*
Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study
J Clin Oncol, 30 (17) (2012), pp. 2046–2054

[79]
P. Zatloukal, D.S. Heo, K. Park, J. Kang, C. Butts, D. Bradford, *et al.*
Randomized phase II clinical trial comparing tremelimumab (CP-675,206) with best supportive care (BSC) following first-line platinum-based therapy in patients (pts) with advanced non-small cell lung cancer (NSCLC)
J Clin Oncol, 27 (Suppl. 15) (2009) [abstract 8071]
[80]
S.N. Gettinger, L. Horn, L. Gandhi, D.R. Spigel, S.J. Antonia, N.A. Rizvi, *et al.*
Long-term survival, clinical activity, and safety of nivolumab (anti-PD-1; BMS-936558, ONO-4538) in patients (pts) with advanced non-small cell lung cancer (NSCLC)
Int J Radiat Oncol, 90 (5) (2014), p. S34
[81]
N.A. Rizvi, F.A. Shepherd, S.J. Antonia, J.R. Brahmer, L.Q. Chow, J. Goldman, *et al.*
First-line monotherapy with nivolumab (anti-PD-1; BMS-936558, ONO-4538) in advanced non-small cell lung cancer (NSCLC): safety, efficacy, and correlation of outcomes with PD-L1 status
Int J Radiat Oncol, 90 (5) (2014), p. S31
[82]
S.S. Ramalingam, J. Mazières, D. Planchard, T.E. Stinchcombe, G.K. Dy, S.J. Antonia, *et al.*
Phase II study of nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients with advanced, refractory squamous non-small cell lung cancer
Int J Radiat Oncol, 90 (5) (2014), pp. 1266–1267
[83]
E.B. Garon, L. Gandhi, N. Rizvi, R. Hui, A.S. Balmanoukian, A. Patnaik, *et al.*
Antitumor activity of pembrolizumab (Pembro; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients (pts) with advanced non-small cell lung carcinoma (NSCLC)
Ann Oncol, 25 (Suppl. 5) (2014), pp. v1–v41
[84]
J.-C. Soria, S. Gettinger, M. Gordon, R.S. Heist, L. Horn, D.R. Spigel, *et al.*
Biomarkers associated with clinical activity of PD-L1 blockade in non-small cell lung cancer (NSCLC) patients (pts) in a phase I study of MPDL3280A
Ann Oncol, 25 (Suppl. 4) (2014), pp. iv426–iv470
[85]
J.R. Brahmer, L. Horn, L. Gandhi, D.R. Spigel, S.J. Antonia, N.A. Rizvi, *et al.*
Nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients (pts) with advanced non-small-cell lung cancer (NSCLC): survival and clinical activity by subgroup analysis
J Clin Oncol, 32 (Suppl. 5) (2014) [abstract 8112^]
[86]
S.J. Antonia, S. Gettinger, J. Goldman, L.Q. Chow, R. Juergens, H. Borghaei, *et al.*
Safety and efficacy of first-line nivolumab (anti-PD-1; BMS-936558, ONO-4538) and ipilimumab in non-small cell lung cancer (NSCLC)
Int J Radiat Oncol, 90 (5) (2014), p. S32
[87]
S.J. Antonia, J.R. Brahmer, S. Gettinger, L.Q. Chow, R. Juergens, F.A. Shepherd, *et al.*
Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with platinum-based doublet chemotherapy (PT-DC) in advanced non-small cell lung cancer (NSCLC)
Int J Radiat Oncol, 90 (5) (2014), p. S2
[88]
N.A. Rizvi, S.J. Antonia, F.A. Shepherd, L.Q. Chow, J. Goldman, Y. Shen, *et al.*

Nivolumab (anti-PD-1; BMS-936558, ONO-4538) maintenance as monotherapy or in combination with bevacizumab (BEV) for non-small cell lung cancer (NSCLC) previously treated with chemotherapy
Int J Radiat Oncol, 90 (5) (2014), p. S31
[89]
S. Gettinger, L.Q. Chow, H. Borghaei, Y. Shen, C. Harbison, A.C. Chen, *et al.*
Safety and response with nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus erlotinib in patients (pts) with epidermal growth factor receptor mutant (EGFR MT) advanced non-small cell lung cancer (NSCLC)
Int J Radiat Oncol, 90 (5) (2014), p. S34
[90]
G.Q. Phan, J.C. Yang, R.M. Sherry, P. Hwu, S.L. Topalian, D.J. Schwartzentruber, *et al.*
Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma
Proc Natl Acad Sci USA, 100 (14) (2003), pp. 8372–8377
[91]
F.S. Hodi, S.J. O'Day, D.F. McDermott, R.W. Weber, J.A. Sosman, J.B. Haanen, *et al.*
Improved survival with ipilimumab in patients with metastatic melanoma
N Engl J Med, 363 (8) (2010), pp. 711–723
[92]
C. Robert, L. Thomas, I. Bondarenko, S. O'Day, J. Weber, C. Garbe, *et al.*
Ipilimumab plus dacarbazine for previously untreated metastatic melanoma
N Engl J Med, 364 (26) (2011), pp. 2517–2526
[93]
J.D. Wolchok, A. Hoos, S. O'Day, J.S. Weber, O. Hamid, C. Lebbé, *et al.*
Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria
Clin Cancer Res, 15 (23) (2009), pp. 7412–7420
[94]
A.B. Miller, B. Hoogstraten, M. Staquet, A. Winkler
Reporting results of cancer treatment
Cancer, 47 (1) (1981), pp. 207–214
[95]
D. Planchard, N. Chaput-Gras, F. Barlesi, J. Mazieres, N. Byrne, D. Vuillier, *et al.*
Phase I study of tremelimumab (Trem) in combination with gefitinib (Gef) in epidermal growth factor receptor mutant (EGFR-mut) non-small cell lung cancer (NSCLC)
Ann Oncol, 25 (Suppl. 4) (2014), pp. iv426–iv470
[96]
A. Scherpereel, R. Cornelissen, A. Di Pietro, H.L. Kindler, K. Nackaerts, S.J. Antonia, *et al.*
Randomized, double-blind, placebo-controlled study of tremelimumab for second-line and third-line treatment of unresectable pleural or peritoneal mesothelioma
Ann Oncol, 25 (Suppl. 4) (2014), pp. iv361–iv372
[97]
S.L. Topalian, C.G. Drake, D.M. Pardoll
Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity
Curr Opin Immunol, 24 (2) (2012), pp. 207–212
[98]
H.T. Jin, R. Ahmed, T. Okazaki
Role of PD-1 in regulating T-cell immunity
Curr Top Microbiol Immunol, 350 (2011), pp. 17–37
[99]

Y. Zhang, S. Huang, D. Gong, Y. Qin, Q. Shen
Programmed death-1 upregulation is correlated with dysfunction of tumor-infiltrating CD8+ T lymphocytes in human non-small cell lung cancer
Cell Mol Immunol, 7 (5) (2010), pp. 389–395
[100]
A.J. Korman, K.S. Peggs, J.P. Allison
Checkpoint blockade in cancer immunotherapy
Adv Immunol, 90 (2006), pp. 297–339
[101]
M.J. Butte, M.E. Keir, T.B. Phamduy, A.H. Sharpe, G.J. Freeman
Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses
Immunity, 27 (1) (2007), pp. 111–122
[102]
W. Zou, L. Chen
Inhibitory B7-family molecules in the tumour microenvironment
Nat Rev Immunol, 8 (6) (2008), pp. 467–477
[103]
J. Weber
Immune checkpoint proteins: a new therapeutic paradigm for cancer–preclinical background: CTLA-4 and PD-1 blockade
Semin Oncol, 37 (5) (2010), pp. 430–439
[104]
M.D. Hellmann, B.C. Creelan, K. Woo, C.S. Sima, W.T. Iams, S.J. Antonia, *et al.*
Smoking history and response to nivolumab in patients with advanced NSCLCs
Ann Oncol, 25 (Suppl. 4) (2014), pp. iv426–iv470
[105]
OPDIVO (nivolumab) US Prescribing Information. Available at: <http://www.accessdata.fda.gov.uk/drugsatfda_docs/label/2015/125527s000lbl.pdf> [accessed March 2015].
[106]
D.P. Carbone, M.A. Socinski, A.C. Chen, P. Bhagavatheeswaran, M. Reck, L. Paz-Ares
A phase III, randomized, open-label trial of nivolumab (anti-PD-1; BMS-936558, ONO-4538) versus investigator's choice chemotherapy (ICC) as first-line therapy for stage IV or recurrent PD-L1+ non-small cell lung cancer (NSCLC)
J Clin Oncol, 32 (Suppl. 5) (2014) [abstract TPS8128]
[107]
A.S. Balmanoukian, N.A. Rizvi, E.B. Garon, A. Patnaik, L. Gandhi, N.B. Leighl, *et al.*
Safety and clinical activity of MK-3475 as initial therapy in patients with advanced non-small cell lung cancer (NSCLC)
Int J Radiat Biol, 90 (5) (2014), pp. S1–S2
[108]
L. Horn, R. Herbst, D. Spiegel
An analysis of the relationship of clinical activity to baseline EGFR status, PD-L1 expression and prior treatment history in patients with non-small cell lung caners (NSCLC) following PD-L1 blockade with MPD-L3280A (anti-PDL1)
J Thorac Oncol, 8 (Suppl. 2) (2013) [abstract MO18.01]
[109]
R.S. Herbst, M.S. Gordon, G.D. Fine, J.A. Sosman, J.-C. Soria, O. Hamid, *et al.*
A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors

J Clin Oncol, 31 (Suppl.) (2013) [abstract 3000]
[110]
N.A. Rizvi, L.Q.M. Chow, L.Y. Dirix, S.N. Gettinger, M.S. Gordon, F.F. Kabbinavar, *et al.*
Clinical trials of MPDL3280A (anti-PDL1) in patients (pts) with non-small cell lung cancer (NSCLC)
J Clin Oncol, 32 (Suppl. 5) (2014) [abstract TPS8123]
[111]
J.D. Wolchok, H.M. Kluger, M.K. Callahan, M.A. Postow, R.A. Gordon, N.H. Segal, *et al.*
Safety and clinical activity of nivolumab (anti-PD-1, BMS-936558, ONO-4538) in combination with ipilimumab in patients (pts) with advanced melanoma (MEL)
J Clin Oncol, 31 (Suppl.) (2013) [abstract 9012^]
[112]
J.D. Wolchok, H. Kluger, M.K. Callahan, M.A. Postow, N.A. Rizvi, A.M. Lesokhin, *et al.*
Nivolumab plus ipilimumab in advanced melanoma
N Engl J Med, 369 (2) (2013), pp. 122–133
[113]
S.J. Antonia, S. Goldberg, A. Balmanoukian, R. Narwal, P.B. Robbins, G. D'Angelo, *et al.*
A phase I open-label study to evaluate the safety and tolerability of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in combination with tremelimumab in patients with advanced non-small cell lung cancer (NSCLC)
Ann Oncol, 25 (Suppl. 4) (2014), pp. iv426–iv470
[114]
S. Kanda, K. Goto, H. Shiraishi, E. Kubo, A. Tanaka, H. Utsumi, *et al.*
Phase I study of anti-PD-1 antibody ONO-4538 (nivolumab) and chemotherapy in patients with advanced non-small-cell lung cancer
Ann Oncol, 25 (Suppl. 4) (2014), pp. iv426–iv470
[115]
E.A. Akbay, S. Koyama, J. Carretero, A. Altabef, J.H. Tchaicha, C.L. Christensen, *et al.*
Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors
Cancer Discov, 3 (12) (2013), pp. 1355–1363
[116]
A. Ribas, L.H. Camacho, G. Lopez-Berestein, D. Pavlov, C.A. Bulanhagui, R. Millham, *et al.*
Antitumor activity in melanoma and anti-self responses in a phase I trial with the anti-cytotoxic T lymphocyte-associated antigen 4 monoclonal antibody CP-675,206
J Clin Oncol, 23 (35) (2005), pp. 8968–8977
[117]
K. Shimizu, M. Nakata, Y. Hirami, T. Yukawa, A. Maeda, K. Tanemoto, *et al.*
Tumor-infiltrating Foxp3+ regulatory T cells are correlated with cyclooxygenase-2 expression and are associated with recurrence in resected non-small cell lung cancer
J Clin Oncol, 5 (5) (2010), pp. 585–590
[118]
F. Ulloa-Montoya, J. Louahed, B. Dizier, O. Gruselle, B. Spiessens, F. Lehmann, *et al.*
Predictive gene signature in MAGE-A3 antigen-specific cancer immunotherapy
J Clin Oncol, 31 (19) (2013), pp. 2388–2396
[119]
M.D. Hellman, B.C. Creelan, K. Woo, C.S. Sima, W.T. Iams, S.J. Antonia, *et al.*
Smoking history and response to Nivolumab in patients with advanced NSCLC
J Clin Oncol, 25 (4) (2014), pp. 426–470

[120]

McLaughlin J. OncoTherapy Network. Available at: <http://www.oncotherapynetwork.com/lung-cancer-targets/pd-I1-predictive-biomarker-anti-pd-1anti-pd-I1-therapies-non-small-cell-lung-cancer> [accessed March 2015].
[121]
K.M. Mahoney, M.B. Atkins
Prognostic and predictive markers for the new immunotherapies
Oncology, 28 (3) (2014), pp. 39–48
[122]
J. Naidoo, D.B. Page, J.D. Wolchok
Immune modulation for cancer therapy
Br J Cancer, 111 (2014), pp. 2214–2219
[123]
J.R. Brahmer, L. Horn, L. Gandhi, D.R. Spigel, S.J. Antonia, N.A. Rizvi, *et al.*
Nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients (pts) with advanced non-small-cell lung cancer (NSCLC): survival and clinical activity by subgroup analysis
J Clin Oncol, 32 (5s) (2014) [abstract 8112^]
[124]
N. Rizvi, L. Chow, H. Borghaei, Y. Shen, C. Harbison, S. Alaparthy, *et al.*
Safety and response with nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus erlotinib in patients (pts) with epidermal growth factor receptor mutant (EGFR MT) advanced NSCLC
J Clin Oncol, 32 (5s) (2014) [abstract 8022]