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

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

La versione definitiva è disponibile alla URL:

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](image)

**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]].

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].

![CTLA-4 pathway and PD-1 pathway](image)

**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.

<table>
<thead>
<tr>
<th>Refs.</th>
<th>Regimen¹</th>
<th>Phase/settling (N)</th>
<th>OR R (%)</th>
<th>Median PFS</th>
<th>Median OS</th>
<th>1-/2-year OS (%)</th>
<th>Summary</th>
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<tbody>
<tr>
<td>Lynch [78]</td>
<td>Ipilimumab + carboplatin /paclitaxel (phased)</td>
<td>II/first line (N = 68)</td>
<td>32</td>
<td>5.1 months</td>
<td>12.2 months</td>
<td>42/16</td>
<td>Significant improved irPFS (primary)</td>
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<td>Refs.</td>
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<td>Phase/setting (N)</td>
<td>OR (R) (%)</td>
<td>Median PFS</td>
<td>Median OS</td>
<td>1-/2-year OS (%)</td>
<td>Summary</td>
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<td>Ipilimumab + carboplatin/paclitaxel (concurrent)</td>
<td>II/first line (N = 70)</td>
<td>21</td>
<td>4.1 months irPFS</td>
<td>5.5 months</td>
<td>9.7 months</td>
<td>50/18</td>
<td>Most irAEs were grade 1–2 and manageable. No impact of ipilimumab on toxicities seen with paclitaxel and carboplatin.</td>
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<td>Zatloukal [79]</td>
<td>Tremelimumab after ≥4 cycles first-line platinum-based chemotherapy</td>
<td>II/maintenance (N = 44)</td>
<td>4.8</td>
<td>NR (21% progression-free at 3 months)</td>
<td>NR</td>
<td>NR</td>
<td>No significant improvement in irPFS. Similar safety profile to phased regimen.</td>
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<td>Gettinger [80]</td>
<td>Nivolumab</td>
<td>I/pretreated (N = 129)</td>
<td>17</td>
<td>2.3 months</td>
<td>9.9 months</td>
<td>42/24</td>
<td>Encouraging survival profile and clinical activity. Manageable safety.</td>
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<td>Refs.</td>
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<td>Phase/setting (N)</td>
<td>OR (%)</td>
<td>Median PFS</td>
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<td>Rizvi [81]</td>
<td>Nivolumab</td>
<td>I/first line (N = 52)</td>
<td>21</td>
<td>15.6 weeks</td>
<td>98.3 weeks</td>
<td>NR</td>
<td>Durable responses observed regardless of tumour histology</td>
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<td>Tolerable safety profile</td>
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<td>Ramalingham [82]</td>
<td>Nivolumab</td>
<td>II/pretreated (N = 117)</td>
<td>15</td>
<td>2 months</td>
<td>8.2 months</td>
<td>41/NR</td>
<td>Durable responses observed regardless of tumour histology</td>
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<td>Garon [83]</td>
<td>Pembrolizumab</td>
<td>I/naive (N = 38)</td>
<td>26</td>
<td>27 weeks</td>
<td>NR</td>
<td>NR</td>
<td>Durable objective responses</td>
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<td>Well tolerated</td>
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<td></td>
<td>Pembrolizumab</td>
<td>I/pretreated (N = 217)</td>
<td>20</td>
<td>10 weeks</td>
<td>8.2 months</td>
<td>NR</td>
<td>Durable objective responses</td>
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<td>Well tolerated</td>
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<tr>
<td>Soria [84]</td>
<td>MPDL3280A</td>
<td>I/pretreated³ (N = 37)</td>
<td>24</td>
<td>NR (24-week PFS 45%)</td>
<td>NR</td>
<td>NR</td>
<td>Rapid and durable responses</td>
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<td>PD-L1 tumour status correlated with response</td>
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<td>Refs.</td>
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<td>ORR (%)</td>
<td>Median PFS</td>
<td>Median OS</td>
<td>1-/2-year OS (%)</td>
<td>Summary</td>
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<tr>
<td>Brahmer [85]</td>
<td>MEDI-4736</td>
<td>I/first line and pretreated (N = 13)</td>
<td>23</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Durable remissions were achieved</td>
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<td>Antonia [86]</td>
<td>Nivolumab (1 mg/kg) + ipilimumab (3 mg/kg)</td>
<td>I/first line (N = 24)</td>
<td>13</td>
<td>NR (44% at 24 weeks)</td>
<td>NR</td>
<td>65/NR</td>
<td>Combination is feasible with antitumour activity in PD-L1+ and PD-L1− patients</td>
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<td>Antonia [87]</td>
<td>Nivolumab (3 mg/kg) + ipilimumab (1 mg/kg)</td>
<td>I/first line (N = 25)</td>
<td>20</td>
<td>NR (33% at 24 weeks)</td>
<td>NR</td>
<td>44/NR</td>
<td>Combination is feasible with antitumour activity in PD-L1+ and PD-L1− patients</td>
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<td>Antonia [87]</td>
<td>Nivolumab + platinum doublet chemotherapy</td>
<td>I/first line (N = 25)</td>
<td>33–47</td>
<td>NR</td>
<td>51–83 weeks</td>
<td>NR (18-month OS = 33–86%)</td>
<td>Manageable safety profile</td>
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<td>Rizvi [88]</td>
<td>Nivolumab + bevacizumab</td>
<td>I/second line (N = 12)</td>
<td>8</td>
<td>37.1</td>
<td>NR</td>
<td>75/NR</td>
<td>PFS similar to other agents approved for</td>
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\(^a\) ORR calculated in 

NR: Not reported
### Table

<table>
<thead>
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<th>Regimen</th>
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<th>ORR (%)</th>
<th>Median PFS</th>
<th>Median OS</th>
<th>1-/2-year OS (%)</th>
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<td>Nivolumab + erlotinib</td>
<td>I/first line (N = 21)</td>
<td>19</td>
<td>29.4</td>
<td>NR</td>
<td>NR (18-month OS = 33–64%)</td>
<td>Encouraging safety profile</td>
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</tbody>
</table>

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.

### 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]].]
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 Ib 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 ≥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 ≤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-naive 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.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Phase of development in NSCLC</th>
<th>Clinicaltrials.gov identifier(s)</th>
<th>Pharmaceutical company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>Phase III</td>
<td>NCT01285609, NCT01450761</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Tremelimumab</td>
<td>CTLA-4</td>
<td>Phase II</td>
<td>NCT02179671</td>
<td>MedImmune</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Phase III</td>
<td>NCT01642004, NCT02041533, NCT02066636, NCT01673867</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Phase III</td>
<td>NCT02220894, NCT02142738, NCT01905657</td>
<td>Merck</td>
</tr>
<tr>
<td>MPDL3280A</td>
<td>PD-L1</td>
<td>Phase III</td>
<td>NCT02008227</td>
<td>Genentech</td>
</tr>
<tr>
<td>MEDI-4736</td>
<td>PD-L1</td>
<td>Phase III</td>
<td>NCT02125461, NCT02154490</td>
<td>MedImmune</td>
</tr>
<tr>
<td>BMS-936559</td>
<td>PD-L1</td>
<td>Phase I</td>
<td>NCT00729664</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Ipilimumab + nivolumab</td>
<td>CTLA-4 + PD-1</td>
<td>Phase I</td>
<td>NCT01454102</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Agent</td>
<td>Target</td>
<td>Phase of development in NSCLC</td>
<td>Clinicaltrials.gov identifier(s)</td>
<td>Pharmaceutical company</td>
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</tr>
<tr>
<td>Tremelimumab + MEDI-4736</td>
<td>CTLA-4 + PD-L1</td>
<td>Phase I</td>
<td>NCT02000947</td>
<td>MedImmune</td>
</tr>
</tbody>
</table>

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.

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-naive 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, ritolumumab, 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


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.

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