Immunotherapy and Targeted Therapies in the Treatment of Non-small Cell Lung Cancer

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In the last decade, the emergence of targeted therapies has changed the treatment paradigm for non-small cell lung cancer (NSCLC). The growing availability of therapies targeting specific genetic alterations, such as epidermal growth factor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements, have led to changes in the guidelines to reflect the need for molecular profiling. More recently, immunotherapeutic approaches have been investigated in the treatment setting of NSCLC, and these may provide superior outcomes and have substantially better tolerability compared to chemotherapy. Immunotherapies currently available for NSCLC include the checkpoint inhibitors anti-PD-1 antibodies nivolumab and pembrolizumab. Several other anti-PD-L1 compounds such as atezolizumab, durvalumab and avelumab are also very advanced in clinical investigation, in monotherapy as well as in combination with immune priming phase activators anti-CTLA4 ipilimumab and tremelimumab, across all treatment lines. The challenge facing oncologists is identifying which therapy is best suited to the individual patient.

Keywords

Non-small cell lung cancer, targeted therapy, checkpoint inhibitors, immunotherapy

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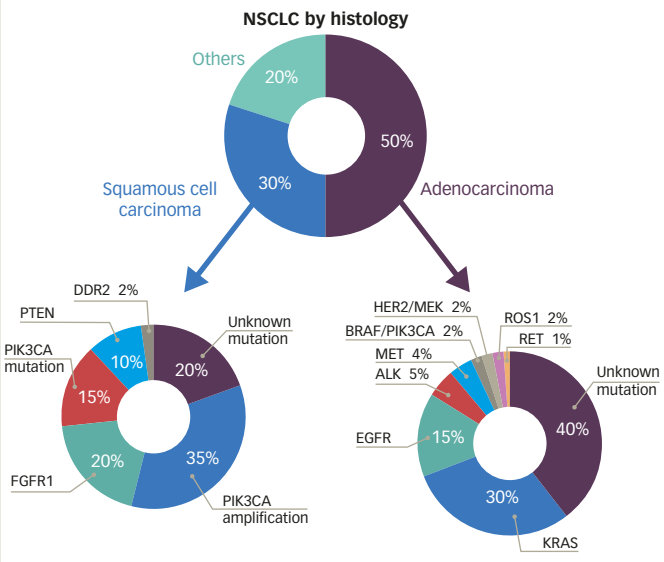
Lung cancer is the leading cause of cancer mortality worldwide[1] and remains one of the major therapeutic challenges in oncology. Traditionally, lung cancer is subdivided based on histology: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) have completely different molecular and therapeutic profiles. The most common class is NSCLC, accounting for 85% of all cases.[2] The prognosis of NSCLC dramatically changed following the discovery of genetic alterations affecting oncogenes, called drivers, including epidermal growth factor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangement, ROS1 or RET rearrangements, MET mutations or amplification, as well as BRAF or HER2 mutations (see *Figure 1*). The ability to target tumours at the molecular level has led to a paradigm shift in the management of patients with these mutations.

The availability of new therapies with differing modes of action is potentially confusing, not only for primary care physicians but also for medical oncologists. Furthermore, unmet needs remain in the treatment of NSCLC, including the development of resistance to targeted therapies and the fact that not all molecular subtypes are actionable to date. Furthermore, a large group of patients does not suffer from tumours characterised by oncogenic alterations, with the vast majority deprived of any actionable genetic change. These patients are currently treated by chemotherapy. There is a need for new treatments for these patients, and immunotherapy represents a promising approach, but also confers a challenge: identifying patients who will benefit optimally from these treatments. This article aims to discuss the use of targeted therapies and immunotherapy in the setting of NSCLC.

Targeted therapies for non-small cell lung cancer

Standard-of-care molecular characterisation of advanced NSCLC is performed by analysis of activating mutations of EGFR (in exons 19 and 21) and detection of an ALK rearrangement.[3] Such screening of NSCLC patients for driver mutations have been standardised and validated.[4] However, mutations on the EGFR gene are seen in fewer than 10% of NSCLC patients in Western populations,[5,6] although this is higher (up to 50%) in Asian populations.[5,7] The mutation has been reported with a higher frequency in non-smokers, women, and presence of adenocarcinoma.[6] Clinical trials of approved targeted therapies for NSCLC are summarised in *Table 1*. The use of EGFR tyrosine kinase inhibitors (TKIs) is recommended as first-line therapy

Figure 1: Diagrammatic representation of subdivision of non-small cell lung cancer according to mutations



ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer. Reproduced from Chan and Hughes, 2015[128] under an open access license.

for patients with an EGFR driver mutation, following an accumulation of evidence of superiority compared with chemotherapy. The first EGFR TKI was gefitinib[8–11] followed by erlotinib[12–14] and the second-generation TKI afatinib.[15,16] In addition, dacomitinib is being evaluated as first-line therapy.[17] However, despite high response rates, resistance to EGFR inhibitors invariably ensues in the majority of patients. One of the most common mechanisms of EGFR TKI resistance has been attributed to a single recurrent missense mutation: T790M within the EGFR kinase domain, which occurs in around half of resistant cases.[18,19] Other mutations exist, including EGFR point mutations, EGFR amplification, bypass tracks and 15–20% unknown mechanisms.[20] Several other agents are in clinical development.

Second-generation irreversible pan-HER EGFR TKIs, such as afatinib,[21] dacomitinib[22] and neratinib,[23] do not seem to be highly effective after progression on first-generation TKI. As a result, third-generation EFGR inhibitors have been developed that selectively target EGFR-activating mutations (del19 and L858R), preserving their affinity in the presence of the T790M resistance mutation, but relatively sparing of EGFR wild type (WT) kinase. The most advanced of these are osimertinib (AZD9291)[24] and rociletinib (CO-1686).[25] In a phase I study, osimertinib showed a response rate of 61% and a progression-free survival (PFS) of 9.6 months among 127 T790M-positive patients previously treated with EGFR TKIs.[26] The latest data from the two phase II studies (AURA extension and AURA2) showed a consistent efficacy and tolerability profile.[27] Osimertinib received approval from the US Food and Drug Administration (FDA) in November 2015 and the European Medicines Agency (EMA) in December 2015 for EGFR T790M-positive NSCLC progressing after prior therapy with an EGFR TKI. Results of the confirmatory AURA3 phase III study are pending.

Rociletinib has also shown high efficacy (objective response rate [ORR] 59%, PFS 13.1 months) in T790M-mutated patients in a phase I/II study.[28] However, due to a high proportion of unconfirmed responses, rociletinib has not received FDA approval yet and development has been halted. Interestingly, osimertinib and rociletinib also seem active in T790M-negative NSCLC with lower response rates than in T790M-positive NSCLC.

Unfortunately, resistance to third-generation EGFR TKIs occurs and new mechanisms of resistance have been found,[29,30] which may differ for osimertinib, rociletinib and other agents in development. Of note, a few cases of NSCLC progressing after rociletinib have been shown to respond to osimertinib.[31] Osimertinib and rociletinib are currently being tested in the first-line setting against first-generation TKIs. The results of these trials are eagerly awaited, as osimertinib have shown promising high efficacy (ORR 75%, 72% of PFS at 12 months) in preliminary data of first-line cohorts.[32,33] The right sequence of EGFR TKIs is thus a big challenge. The choice may be guided by response to brain metastases: osimertinib and rociletinib appear to have almost as high efficacy in patients with brain metastases than without.[34,35] Other agents in clinical development include HM61713[36] and EGF816.[37]

The ALK fusion gene is present in about 5% of NSCLC cases. The ALK inhibitor crizotinib received FDA approval in 2013, and has demonstrated ORR of over 70% in phase III studies in both first- and second-line settings.[38,39] However, again, resistance inevitably develops after less than a year.[20] Increased understanding of the mechanism of resistance has led to the development of second-generation ALK inhibitors. Ceritinib[40–43] and alectinib[44–47] are effective in more than 50% of patients who progressed on or were intolerant to crizotinib, and have received FDA approval in this second-line treatment setting.

In addition, ceritinib and alectinib have demonstrated remarkable activity in patients with brain metastases.[40,48–55] By contrast, studies of crizotinib showed low brain response rates.[56] In recent phase I/II clinical trials, the dual ALK/EGFR inhibitor brigatinib (AP26113), showed significant antitumour activity in ALK-positive NSCLC patients with brain metastasis following crizotinib.[57] Subsequently, the large (n=222) phase II ALTA trial recruited advanced ALK+ NSCLC patients whose disease progressed on crizotinib and who had received no other ALK TKI. Recently presented data showed that brigatinib gave substantial responses.[58] A phase III study is planned, and brigatinib and has received breakthrough therapy designation by the FDA.[59] Other second-generation ALK inhibitors in clinical development include the dual ALK/ROS 1 inhibitor lorlatinib (PF-06463922), which has demonstrated durable clinical responses in a phase I/II study of ALK+ and ROS1+ NSCLC patients, most of whom had CNS metastases and had received at least one prior TKI;[60] X-396;[61] ASP3026;[62] TSR-011;[63] CEP28122/CEP-37440; and entreclinib.

Second-generation ALK inhibitors are also promising as first-line treatment options. The phase III J-ALEX study randomised patients without prior ALK inhibitor treatment to alectinib or crizotinib. Recently released data from this study shows that alectinib demonstrated significantly prolonged PFS compared with crizotinib and was well tolerated.[64] This study was specific for Japanese patients only, and was selecting patients based on stringent ALK positivity criteria (ALK centralised testing, immunohistochemistry [IHC] and fluorescence *in situ* hybridisation [FISH] or reverse transcription polymerase chain reaction [RT-PCR]). Around half of the patients had received one prior line of chemotherapy. Of note, slightly more patients in the crizotinib group had brain metastases at baseline. Ceritinib[40,65] and brigatinib[66] are also further currently being investigated as frontline therapy in ALK-positive NSCLC. Current available data on ALK inhibitors are summarised in *Table 1*.

Although ALK inhibitors are generally well tolerated, they target multiple pathways, and have the potential for a wide range of treatment-emergent adverse events (AEs), including gastrointestinal AEs and hepatotoxicity.[67] In addition, individual drugs present with very different toxicity profiles, such as the report of interstitial lung disease (ILD) on brigatinib; increase

Table 1: Key clinical studies in targeted approaches in non-small cell lung cancer

Trial name	Description	Treatment	Efficacy outcomes	Safety outcomes
EGFR mutations				
Gefitinib				
IPASS, phase III[8]	Advanced stage IIIB/IV pulmonary adenocarcinoma, non-smokers or former light smokers, chemotherapy naive, ECOG 0–2, East Asian pts, n=1217. Subgroup of EGFR positive pts, n=261	Gefitinib vs carboplatin-paclitaxel, first-line	12-month PFS=24.9% with gefitinib vs 6.7% with carboplatin-paclitaxel (HR 0.74, 95% CI 0.65–0.85, p<0.001). In the EGFR positive subgroup PFS was significantly longer in gefitinib group (HR 0.48, 95% CI 0.360.64, p<0.001)	Rash or acne (all grade AEs: 66.2%, grade ≥3: 3.1%) and diarrhoea (all grade: 46.6%, grade ≥3: 3.8%) in the gefitinib group vs neurotoxic effects (all grade: 69.9%, grade ≥3: 4.9%), neutropenia (67.1%, grade ≥3: 67.1%) and alopecia (all grade 58.4%) in the carboplatin-paclitaxel group
WJTOG3405, phase III[10]	Advanced or recurrent stage IIIB/IV NSCLC with activating EGFR mutations (exon 19 deletion or exon 21 L858R point mutation), ECOG 0-1, Japanese pts, n=177	Gefitinib vs cisplatin-docetaxel, first-line	Median PFS=9.2 mo with gefitinib vs 6.3 mo with chemotherapy (HR 0.49, 95% CI 0.34–0.71, p<0.0001)	Skin toxicity (all grade: 85.1%, grade ≥3: 2.3%), liver dysfunction (all grade 85.1%, grade ≥3 16.1–27.6%) and diarrhoea (all grade: 54.0%, grade ≥3: 1.1%) were more frequent in the gefitinib group. Two patients (2.3%) in the gefitinib group developed interstitial lung disease, one of whom died
NEJ002, phase III[9,11]	Advanced NSCLC with EGFR mutation, no T790M mutation, chemotherapy naïve, ECOG 0–2, Japanese pts, n=230	Gefitinib vs carboplatin-paclitaxel, first-line	Gefitinib group had a longer median PFS (10.8 mo vs 5.4 mo in the chemotherapy group; HR 0.30, 95% CI 0.22–0.41, p<0.001), as well as a higher ORR (73.7% vs 30.7%, p<0.001). Median OS was 30.5 mo in the gefitinib group vs 23.6 mo in the chemotherapy group (p=0.31)	Most common AEs in the gefitinib group were rash (all grade: 71.1%, grade ≥3: 5.3%) and elevated aminotransferase levels (all grade: 55.3%, grade ≥3: 26.3%), and in the chemotherapy group, neutropenia (all grade: 77.0%, grade ≥3: 65.5%), anaemia (all grade: 64.6%, grade ≥3: 5.3%), appetite loss (all grade: 56.6%, grade ≥3: 6.2%) and sensory neuropathy (all grade: 54.9%, grade ≥3: 6.2%). One patient receiving gefitinib died from interstitial lung disease
Erlotinib				
OPTIMAL, phase III[12]	Advanced or recurrent stage IIIB/IV NSCLC with activating EGFR mutation (exon 19 deletion or exon 21 L858R mutation), ECOG 0–2, Chinese pts, n=165	Erlotinib vs carboplatin-gemcitabine, first-line	Median PFS=13.1 mo (95% CI 10.6–16.5 mo) with erlotinib vs 4.6 mo (95% CI 4.2–5.4 mo) with chemotherapy (HR 0.16, 95% CI 0.10–0.26, p<0.0001)	Most common AEs with erlotinib were skin rash (all grade: 73%, grade ≥3: 2%), increased alanine aminotransferase (all grade: 37%, grade ≥3: 4%) and diarrhoea (all grade: 25%, grade ≥3: 1%). Serious erlotinib-related AEs in two pts (2%), both with hepatic dysfunction. More grade ≥3 AEs in chemotherapy group (65% vs 17% in erlotinib group), including neutropenia (42%), thrombocytopenia (40%) and anaemia (13%)
ENSURE, phase III[14]	Stage IIIB/IV NSCLC with activating EGFR mutation (exon 19 deletion or exon 21 L858R mutation), ECOG 0–2, chemotherapy naive, East Asian pts, n=217	Erlotinib vs cisplatin-gemcitabine, first-line	Median PFS=11.0 mo with erlotinib vs 5.6 mo with chemotherapy (HR 0.42, 95% CI 0.27–0.66, p=0.0001). Median OS=26.3 with erlotinib vs 25.5 mo with chemotherapy (HR 0.91, 95% CI 0.63–1.31, p=0.607). ORR was 62.7% with erlotinib and 33.6% with chemotherapy	Most common AEs in the erlotinib group were rash (all grade: 70.9%, grade ≥3: 6.4%) and diarrhoea (all grade: 45.5%, grade ≥3: 1.8%).Treatment-related serious AEs in 2.7% with erlotinib vs 10.6% with chemotherapy. One fatal AE with erlotinib due to pulmonary embolism
EURTAC, phase III[13]	Advanced or recurrent stage IIIB/IV NSCLC with activating EGFR mutation (exon 19 deletion or exon 21 L858R mutation), ECOG 0–2, European pts, n=174	Erlotinib vs standard chemotherapy (cisplatin-docetaxel or cisplatin-gemcitabine), first-line	Median PFS=9.7 mo (95% CI 8.4–12.3) with erlotinib vs 5.2 mo (95% CI 4.5–5.8) with chemotherapy (HR 0.37, 95% CI 0.25–0.54, p<0.0001	Most common AEs in the erlotinib group were rash (all grade: 79.8%, grade ≥3: 13.1%), diarrhoea (all grade: 57.1%, grade ≥3: 4.8%) and fatigue (all grade: 57.1%, grade ≥3: 6.0%). Treatment-related severe AEs in 6.0% with erlotinib vs 19.5% with chemotherapy. Erlotinib-related death in one patient (1.2%) due to hepatotoxicity

Table 1: Cont.

Trial name	Description	Treatment	Efficacy outcomes	Safety outcomes
Afatinib				
LUX-Lung 3, phase III[15]	Advanced stage IIIB/IV NSCLC with EGFR mutation, treatment naive, ECOG 0–1, pts from Asia, Europe, North America, South America and Australia, n=345	Afatinib vs cisplatin-pemetrexed, first-line	Median PFS=11.1 mo with afatinib vs 6.9 mo with chemotherapy (HR 0.58, 95% CI 0.43–0.78, p=0.001). Median PFS among those with exon 19 deletions and L858R EGFR mutations (n=308) was 13.6 mo with afatinib and 6.9 mo with chemotherapy (HR 0.47, 95% CI 0.34–0.65, p=0.001)	Most common treatment-related AEs for afatinib were diarrhoea (all grade: 95.2%, grade ≥3: 14.4%), rash/acne (all grade: 89.1%, grade ≥3: 16.2%), stomatitis/mucositis (all grade: 72.1%, grade ≥3: 8.7%) and paronychia (all grade: 56.8%, grade ≥3: 11.4%). Three cases (1%) of potentially related interstitial lung disease, and four potential afatinib-related deaths (two respiratory decompensations, one sepsis, and one unknown)
LUX-Lung 6, phase III[16]	Advanced stage IIIB/IV adenocarcinoma with EGFR mutation, treatment-naive, ECOG 0–1, Asian pts, n=364	Afatinib vs cisplatin-gemcitabine, first-line	Median PFS=11.1 mo for afatinib vs 5.6 mo for chemotherapy (HR 0.28, 95% CI 0.20-0.39, p<0.0001). Median PFS among those with exon 19 deletions and L858R EGFR mutations (n=324) was 11.0 mo with afatinib and 5.6 mo with chemotherapy (HR 0.25, 95% CI 0.18–0.35, p<0.0001)	Most common treatment-related AEs were diarrhoea (all grade: 88.3%, grade ≥3: 5.4%), rash/acne (all grade: 80.8%, grade ≥3: 14.6%), stomatitis/mucositis (all grade: 51.9%, grade ≥3: 5.4%) and paronychia (all grade: 32.6%, grade ≥3: 0%) with afatinib. One case of potentially afatinib-related sudden death. One patient with grade 4 afatinib-related interstitial pneumonitis
Osimertinib				
AURA, phase I/II dose-escalation and dose-expansion cohorts[26,27]	Advanced or metastatic NSCLC with activating EGFR mutation or with prior clinical benefit from EGFR TKI, who had disease progression under such EGFR TKI, ECOG 0–1, pts from Asia, Europe, North America and Australia, n=253	Osimertinib, ≥2nd line	Across all doses (n=239), ORR was 51% (95% CI 45-58); among pts with EGFR T790M (n=127), ORR was 61% (95% CI 52–70); among pts without EGFR T790M (n=61), ORR was 21% (95% CI 12–34). Median PFS was 9.6 mo (95% CI 8.3–NR; 30% maturity) in EGFR T790M-positive pts and 2.8 mo (95% CI 2.1–4.3;71% maturity) in EGFR T790M-negative pts. At 80 mg cohort (n=61), ORR was 71% (95% CI 57–82), median PFS 9.7 mo (95% CI 8.3–13.6), 12 mo PFS 41%, 18 mo PFS 29% and 24 mo PFS 17%	Across all doses, most common AEs were diarrhoea (all grade: 47%, grade ≥3: 2%), rash/acne (all grade: 40%, grade ≥3: 1%) and nausea (all grade: 22%, grade ≥3: 1%). Diarrhoea and rash/acne increased in frequency in a dose-dependent manner. At 80 mg (n=92), most common AEs were diarrhoea (all grade: 33%, grade ≥3: 1%), rash/acne (all grade: 32%, grade ≥3: 0%) and nausea (all grade: 18%, grade ≥3: 0%). Six cases (2.4%) of potential pneumonitis. Seven fatal AEs (2.8%), one of which possibly drug-related (pneumonia)
Pooled phase II: AURA phase II extension and AURA2[27]	For AURA, see characteristics above, n=201. For AURA2: advanced or metastatic NSCLC with activating EGFR mutation and T790M mutation, who had disease progression after previous EGFR TKI, pts from Asia, Europe and North America, n=210	For AURA, osimertinib, second- or further-line. For AURA2: osimertinib, 2nd EGFR TKI (second-line or further-line with chemotherapy)	At 80 mg, ORR was 66% (95% CI 61–71), median PFS=11.0 mo (95% CI 9.6–12.4), 12 mo PFS 48% (95% CI 42–53)	Most common AEs were rash (all grade: 41%, grade ≥3: 1%), diarrhoea (all grade: 38%, grade ≥3: 1%), dry skin (all grade: 30%, grade ≥3: 0%) and paronychia (all grade: 29%, grade ≥3: 0%). Twelve cases (3%) of interstitial lung disease, four of which died due to this AE (1%). Fourteen cases (3%) of QT prolongation
ALK rearrangements				
Crizotinib				
PROFILE 1005, phase II[154]	Advanced or metastatic NSCLC with ALK rearrangement who had received one prior chemotherapy regimen, n=439	Crizotinib, second-line	Median ORR=53% (95% CI 47–60). Median DOR=43 weeks (96% CI 36–50). Median PFS=8.5 months (95% CI 6.2–9.9)	Most common AEs were visual effects (50%), nausea (46%), vomiting (39%) and diarrhoea (35%), mostly grade 1–2. 6.6% had treatment-related SAEs, including dyspnoea and pneumonitis (four patients each; 0.9%), and febrile neutropenia and renal cyst (two patients each; 0.5%)
PROFILE 1007, phase III[38]	Advanced or metastatic non-squamous NSCLC with ALK rearrangement who had received one prior platinum-based regimen, ECOG 0–2, pts from Asia, Europe, North America, and Australia, n=347	Crizotinib vs pemetrexed or docetaxel, second-line	Median PFS=7.7 mo for crizotinib vs 3.0 mo for chemotherapy (HR 0.49, 95% CI 0.37–0.64, p<0.001). ORR=65% (95% CI 58–72) with crizotinib, vs 20% (95% CI 14–26, p<0.001). No benefit in OS with crizotinib in the interim analysis (HR 1.02, 95% CI 0.68–1,54, p=0.54)	Most common AEs associated with crizotinib were visual disorder (all grade: 60%, grade ≥3: 0%), diarrhoea (all grade: 60%, grade ≥3: 0%), nausea/vomiting (all grade: 47–55%, grade ≥3: 1%), constipation (all grade: 42%, grade ≥3: 2%) and elevated liver aminotransferase (all grade: 38%, grade ≥3: 16%). Four crizotinib-related deaths (2%) due to ventricular arrhythmia, interstitial lung disease or pneumonitis and hepatic failure

Table 1: Cont.

Trial name	Description	Treatment	Efficacy outcomes	Safety outcomes
PROFILE 1014, phase III[39]	Advanced, recurrent or metastatic non-squamous NSCLC with ALK rearrangement, no previous treatment for advanced disease, ECOG 0–2, pts from Asia, Europe, North America and Australia, n=343	Crizotinib vs pemetrexed plus cisplatin/carboplatin, first-line	Median PFS=10.9 mo for crizotinib vs 7.0 mo for chemotherapy (HR 0.45; 95% CI 0.35–0.60, p<0.001). ORR=74% and 45%, respectively (p<0.001). Median OS not reached in either group (HR 0.82; 95% CI 0.54–1.26, p=0.36)	Most common AEs with crizotinib were vision disorders (all grade: 71%, grade ≥3: 1%), diarrhoea (all grade: 61%, grade ≥3: 2%), oedema (all grade: 49%, grade ≥3: 1%), vomiting (all grade: 46%, grade ≥3: 2%), constipation (all grade: 43%, grade ≥3: 2%), elevated aminotransferases (all grade: 36%, grade ≥3: 14%) and upper respiratory infection (all grade: 32%, grade ≥3: 0%). One case of crizotinib-related death due to pneumonitis
Ceritinib				
ASCEND-1, phase I[41]	Advanced or metastatic NSCLC with ALK rearrangement, prior treatment including ALK TKIs allowed, ECOG 0–2, pts from Asia, Australia, Europe and North America, n=130	Ceritinib, ≥1st line	ORR was 58% (95% CI 48–67). Among 80 pts who had received crizotinib previously, ORR was 56% (95% CI 45–67)	Dose-limiting toxic events included diarrhoea, vomiting, dehydration, elevated aminotransferase levels and hypophosphatemia. Most common AEs were nausea (all grade: 82%, grade ≥3: 5%), diarrhoea (all grade: 75%, grade ≥3: 7%), vomiting (all grade: 65%, grade ≥3: 5%), fatigue (all grade: 47%, grade ≥3: 5%) and increased alanine aminotransferase (all grade: 35%, grade ≥3: 21%). Four cases of possibly ceritinib-related interstitial lung disease
ASCEND-1, phase I, updated results at the recommended dose of 750 mg/day in the dose-escalation and expansion cohorts[40]	Advanced or metastatic NSCLC with ALK rearrangement, prior treatment including ALK TKIs allowed, ECOG 0–2, pts from Asia, Australia, Europe and North America, n=255	Ceritinib, ≥1st line	ORR was 72% (95% CI 61–82) in 83 ALK inhibitor-naive pts and 56% (95% CI 49–64) in 163 ALK inhibitor-pretreated pts. Median DOR was 17.0 mo (95% CI 11.3–NE) in ALK inhibitor-naive pts and 8.3 mo (95% CI 6.8–9.7) in ALK inhibitor-pretreated pts. Median PFS was 18.4 mo (95% CI 11.1-NE) in ALK inhibitor-naive pts and 6.9 mo (95% CI 5.6–8.7) in ALK inhibitor-pretreated pts. Of 94 pts with brain metastases, intracranial disease control was 79% (95% CI 54–94) in 19 ALK inhibitor-naive pts and 65% (95% CI 54–76) in 75 ALK inhibitor-pretreated pts	Most common grade ≥3: AEs were increased alanine aminotransferase (30%) and increased aspartate aminotransferase (10%), diarrhoea (6%) and nausea (6%). Two ceritinib-related deaths, one due to interstitial lung disease and one due to multiorgan failure with infection and ischaemic hepatitis
ASCEND-2, phase II[43]	NSCLC with ALK rearrangement, prior chemotherapy who progressed ≤30 days from last treatment with crizotinib, n=140	Ceritinib, second-line	ORR=38.6% (95% CI 30.5–47.2). Median DOR=9.7 mo (95% CI 7.1–11.1). Median PFS 5.7 mo (95% CI 5.4–7.6). In pts with active baseline brain metastases (n=20), intracranial ORR was 45.0% (95% CI 23.1–68.5)	Most common AEs (mostly grade 1/2) were nausea (81.4%), diarrhoea (80.0%) and vomiting (62.9%). Eleven (7.9%) pts discontinued due to AEs, with no one AE predominating
ASCEND-3, phase II[54]	Advanced or metastatic NSCLC with ALK rearrangement, prior chemotherapy allowed, ALK inhibitor-naïve, ECOG 0–2, pts from Asia, Australia, Europe and North America, n=124	Ceritinib, first ALK TKI line (first- or further-line with chemotherapy)	ORR=63.7% (95% CI 54.6–72.2). Median DOR=23.9 mo (95% CI 16.6–NE). Median PFS=18.4 mo (95% CI 10.9–26.3). 12-mo OS was 85.1% and 24-mo OS 67.5%. In pts with brain metastases (n=49), whole-body ORR was 63.3% (95% CI 48.3–76.6), intracranial ORR 61.5% (95% CI 31.6–86.1), intracranial DCR 76.9% 895% CI 46.2–95.0), median DOR 14.7 mo (95% CI 7.5–20.3) and median PFS 11.0 mo (95% CI 7.4–19.4). Brain responses were observed even in pts with no prior brain radiation treatment	Most common AEs (mostly grade 1/2) were gastrointestinal: diarrhoea (all grade: 85.5%, grade ≥3: 3.2%), nausea (all grade: 77.4%, grade ≥3: 6.5%), vomiting (all grade: 71.8%, grade ≥3: 6.5%), decrease appetite (all grade: 53.2%, grade ≥3: 3.2%), increased ALT (all grade 50%, grade ≥3: 21.0%). Dose interruptions or adjustments due to AEs were observed in 80.6% pts, mainly due to ALT increase, AST increase, vomiting, diarrhoea and nausea. 7.3% pts discontinued due to AEs

Table 1: Cont.

Trial name	Description	Treatment	Efficacy outcomes	Safety outcomes
ASCEND-5, phase III[55]	Advanced or metastatic NSCLC with ALK rearrangement, progressing after crizotinib and 1–2 prior chemotherapy, ECOG 0–2, pts from Asia, Australia, Europe and North America, n=231	Ceritinib vs chemotherapy (pemetrexed or docetaxel), second ALK TKI line (third- or further-line with chemotherapy)	Median PFS was 5.4 mo (95% CI 4.1–6.9) with ceritinib vs 1.6 mo (95% CI 1.4–2.8 mo) for chemotherapy (HR 0.49, 95% CI 0.36–0.67, p<0.001); ORR was 39.1% (95% CI 30.2–48.7) vs 6.9% (95% CI 3.0–13.1), DCR 76.5% (95% CI 67.7–83.9) vs 36.2% (95% CI 27.5–45.6), respectively	Most common AEs were gastrointestinal and occurred more frequently with ceritinib than chemotherapy. Serious AEs occurred in 42.6% with ceritinib vs 31.9% with chemotherapy. Grade 3–4 AEs occurred in 77.4% with ceritinib (most common ALT increased (20.9%), GGT increased (20.9%), AST increased (13.9%), nausea (7.8%) and vomiting (7.8%) vs 63.7% with chemotherapy
Alectinib				
AF-001JP, phase I/II[47]	Advanced NSCLC with ALK rearrangement, n=345	Alectinib, first ALK TKI line	ORR=93.5% (95% CI 82.1–98.6%) with 4.2% CR and 89.1% PR	Treatment-related grade 3 AEs were recorded in 26%, including two patients each experiencing decreased neutrophil count and increased blood creatine phosphokinase. Serious AEs occurred in 11%
AF-002JG, phase I/II[49]	Advanced or metastatic NSCLC with ALK rearrangement, who progressed on or were intolerant to crizotinib, prior chemotherapy allowed, ECOG 0–2, pts from US, n=47	Alectinib, second ALK TKI line	ORR=55%, with a 2% CR, 32% confirmed PR and 20% unconfirmed PR. Of 21 pts with CNS metastases at baseline, ORR was 52%; with 29% CR and 24% PR	Most common AEs were fatigue (all grade: 30%, grade ≥3: 0%), myalgia (all grade: 17%, grade ≥3: 0%), peripheral oedema (all grade: 17%, grade ≥3: 2%), increased creatine kinase (all grade: 15 %, grade ≥3: 0%) and nausea (all grade: 15 %, grade ≥3: 0%). Most common grade ≥3 AEs were increased levels of gamma-glutamyl transpeptidase (4%), reduced number of neutrophils (4%) and hypophosphatemia (4%)
NP28673, phase II[44]	Advanced or metastatic NSCLC with ALK rearrangement, who progressed on or were intolerant to crizotinib, prior chemotherapy allowed, ECOG 0–2, pts from Asia, Australia, Europe, and North America, n=138	Alectinib, second ALK TKI line	ORR was 50% (95% CI 41–59%) for all pts, 45% (95% CI 35–55%) for 96 pts (79%) previously treated with chemotherapy, and 69% (95% CI 48–68) for 26 (21%) chemotherapy-naïve pts. Among 61 pts with PR, median DOR was 11.2 mo (95% CI 9.6–NR). Median PFS was 8.9 mo (95% CI 5.6–11.3) for all pts, and 13.0 mo (95% CI 5.5–NR) for 28 chemotherapy-naïve pts. CNS disease control rate was 83% (95% CI 74–91%) in 84 pts with baseline CNS metastases. Of 35 pts with baseline measurable CNS lesions, CNS ORR was 57% (95% CI 39–74%), with seven (20%) CNS CR. Of 23 patients with baseline CNS metastases and no prior brain radiation, 43% had a complete CNS response. At 12 months, the cumulative CNS progression rate (24.8%) was lower than the cumulative non-CNS progression rate (33.2%) for all patients	Most common AEs were constipation (all grade: 33%, grade ≥3: 0%), fatigue (all grade: 26%, grade ≥3: 1%), peripheral oedema (all grade: 25%, grade ≥3: 1%), myalgia (all grade: 23%, grade ≥3: 1%), asthenia (all grade: 18%, grade ≥3: 1%). The incidence of grade ≥3 AEs was low. Four cases (3%) of AEs leading to death, due to intestinal perforation, dyspnoea, pulmonary embolism and haemorrhage; only the intestinal perforation was possibly alectinib-related
NP28761, phase I/II[46]	Advanced or metastatic NSCLC with ALK rearrangement, who progressed on or were intolerant to crizotinib, prior chemotherapy allowed, ECOG 0–2, pts from North America, n=87	Alectinib, second ALK TKI line	ORR=47.8% (95% CI 35.6–60.2). In 16 pts with baseline measurable CNS disease, CNS ORR was 68.8% (95% CI 41.3–89.0), including two CRs, and CNS DCR was 100%	Most common AEs were constipation (36%), fatigue (33%), myalgia (24%) and peripheral oedema (23%), Most common grade ≥3 AEs were seen in 31% of pts, including increased blood CPK (8%), increased ALT (6%) and increased AST (5%). One possibly alectinib-related death due to haemorrhage

Table 1: Cont.

Trial name	Description	Treatment	Efficacy outcomes	Safety outcomes
ROS1 rearrangements				
Crizotinib				
J-ALEX, phase III[64]	Advanced, recurrent or metastatic NSCLC with ALK rearrangement, crizotinib, ALK inhibitor-naïve, one prior line of chemotherapy allowed, ECOG 0–2, pts from Japan, n=207	Alectinib vs crizotinib, 1st ALK TKI line (first- or second-line with chemotherapy)	Median PFS was not reached (95% CI 20.3–NE) with alectinib vs 10.2 mo (95% CI 8.2–12.0) with crizotinib (HR 0.34, 99.68% CI 0.17–0.7, p<0.0001)	Most common AEs were constipation (36%) with alectinib vs nausea (74%), diarrhoea (73%), vomiting (59%), visual disturbance (55%), dysgeusia (52%), constipation (46%), ALT elevation (32%) and AST elevation (31%) with crizotinib. Grade ≥3 AEs were more frequent with crizotinib (51% vs 27% with alectinib)
BRAF mutations				
Dabrafenib				
PROFILE 1001, phase I[70]	Advanced NSCLC with ROS1 rearrangement, prior treatment allowed, ECOG 0–2, pts from US, Korea, Australia and Stockholm, n=50	Crizotinib, ≥1st line	ORR=72% (95% CI 58–84), with 6% CR and 66% PR. Median DOR was 17.6 mo (95% CI 14.5–NR). Median PFS was 19.2 mo (95% CI 14.4–NR)	Similar to safety profile in ALK-rearranged pts. Most common AEs were visual impairment (all grade: 82%, grade ≥3: 0%), diarrhoea (all grade: 44%, grade ≥3: 0%), nausea (all grade: 40%, grade ≥3: 0%), peripheral oedema (all grade: 40%, grade ≥3: 0%), constipation (all grade: 34%, grade ≥3: 0%), vomiting (all grade: 34%, grade ≥3: 2%) and elevated AST (all grade: 22%, grade ≥3: 2%)
Phase II[72]	Stage IV NSCLC with BRAF V600E mutation, previously treated or untreated, BRAF and MEK inhibitor naïve, ECOG 0–2, pts from Europe, North America and Asia, n=84	Dabrafenib, ≥1st line	ORR=33% (95% CI 23–45), DCR=53% (95% CI 40-66), DOR=9.9 mo (95% CI 4.2–NR), PFS=5.5 mo (95% CI 2.8–6.9)	Most common grade ≥3 AEs were cutaneous squamous-cell carcinoma (12%), asthenia (5%) and basal-cell carcinoma (5%). One possibly dabrafenib-related death due to intracranial haemorrhage
Phase II[73]	Stage IV NSCLC with BRAF V600E mutation, who progressed after ≥1 prior platinum-based chemotherapy and ≤3 previous systemic treatments, BRAF and MEK inhibitor naïve, ECOG 0–2, pts from Europe, North America and Asia, n=57	Dabrafenib plus trametinib, ≥2nd line	ORR=63.2% (95% CI 49.3–75.6), DCR=75.4% (95% CI 62.2-85.9), DOR=9.0 mo (95% CI 5.8–17.6), PFS=8.6 mo (95% CI 5.2-19.1)	Most common serious AEs were in 56% pts, including pyrexia (16%), anaemia (5%), confusion (4%), decreased appetite (4%), haemoptysis (4%), hypercalcaemia (4%), nausea (4%) and cutaneous squamous cell carcinoma (4%). Most common grade ≥3 AEs were neutropenia (9%), hyponatraemia (7%) and anaemia (5%). Four fatal treatment-unrelated AEs (retroperitoneal haemorrhage, subarachnoid haemorrhage, respiratory distress, severe disease progression)
Vemurafenib				
VE-BASKET, phase II basket trial[74]	Advanced or metastatic non-melanoma solid tumours or multiple myeloma with BRAF V600 mutation, BRAF and MEK inhibitor naïve (beside sorafenib), ECOG 0–2, pts from Europe and North America, n=122 for total patients, n=20 for NSCLC cohort	Vemurafenib, ≥2nd line	In the cohort with NSCLC (n=20), ORR was 42% (95% CI 20–67) and median PFS 7.3 mo (95% CI 3.5–10.8)	Safety was similar to that in prior studies of vemurafenib for melanoma

AE = adverse event; ALK = anaplastic lymphoma kinase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CNS = central nervous system; CR = complete response; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor gene; GGT = gamma-glutamyl transferase; HR = hazard ratio; mo = months; NA = not assessed; NE = non-estimable; NR = not reached; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; pts = patients; PFS = progression-free survival; PR = partial response; SAEs = serious adverse events; TKIs = tyrosine kinase inhibitors.

in creatine phosphokinase (CPK) and muscular AEs on alectinib; QT increase on crizotinib and ceritinib, and more gastrointestinal AEs on ceritinib than on other ALK inhibitors. However, the majority of toxicities are reversible, manageable with proactive monitoring and treatment, and not severe if treated promptly.[67]

It must be noted that resistance to second-generation ALK inhibitors also occurs and novel ALK mutations have been detected.[68] In addition, new mutations may confer sensitivity to other ALK inhibitors.[69] Ideally, subsequent biopsies should be performed in order to determine the optimum sequencing of ALK inhibitors. However, very few centres perform repeat biopsies at relapse. Determining optimal sequencing of ALK inhibitors in the clinic is an important emerging question that warrants further study.

Among other gene mutations in NSCLC, the most important include ROS1 fusions, for which crizotinib was approved after demonstrating an ORR of 72% in patients with advanced ROS1-rearranged NSCLC.[70]

Mutations of the BRAF gene have been identified in up to 3% of patients with NSCLC.[71] Monotherapy with dabrafenib demonstrated a disease control rate of 53% at 12 weeks and a median duration of response of

9.9 months in previously treated patients.[72] This agent has been shown to be even more effective when combined with trametinib.[73] In addition, in a phase II study, 42% of a cohort with NSCLC showed a response to vemurafenib.[74] Resistance mechanisms to this MAPK pathway multilevel inhibition are under investigation.

Other oncogenic alterations are currently being investigated; these include RET fusions, neurotrophic tyrosine kinase receptor type 1 (NTFK1) fusions, MET mutations or amplification, fibroblast growth factor receptor 1 (FGFR1) amplification, as well as human EGFR 2 (HER2) mutations.[75]

In summary, targeted therapies offer the opportunity to target specific genetic driver alterations, but they have limitations. Known mutations are not present in many cases: genetic changes have been identified in patients with non-squamous NSCLC, while EGFR and ALK mutations are rarely seen in squamous NSCLC.[76] To date, no targeted interventions are available for patients with squamous NSCLC. In addition, a relatively small proportion of Caucasian patients with non-squamous NSCLC harbour EGFR mutations. Although 65% of patients present with a tumour characterised by an oncogenic alteration, many are still not treatable. More importantly, targeted therapies are not curative in patients with metastatic NSCLC and disease inevitably progresses after a median of 8–12 months, highlighting the urgent need for additional, more effective strategies. Current therapeutic approaches are therefore developing in another direction, utilising the immune response in solid tumours.

Immunotherapy in non-small cell lung cancer

Although NSCLC was not believed to be an immunogenic malignancy due to lack of efficacy of immunomodulatory cytokines such as interleukin 2 (IL-2) and interferon (IFN), and of early vaccines,[77–79] recent data demonstrating the efficacy of immune checkpoint inhibitors have established the importance of the immune response in NSCLC (see *Table 2*). In addition, neoantigen-reactive tumour-infiltrating T cell lymphocytes (TILs), which can potentially induce tumour regression, were identified in NSCLC.[80,81]

Inhibitory immune checkpoints are inhibitory signalling pathways that down-modulate the immune system responses of T cells, blocking the inappropriate recognition of normal tissue by activated immune cells and preventing autoimmunity.[82] Various checkpoint molecules have been identified, including cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), T cell immunoglobulin domain and mucin domain-3 (TIM-3), and lymphocyte-activation gene-3 (LAG-3), among others.[82]

The use of CTLA-4 inhibitors is widespread in immunotherapy, and while the efficacy of ipilimumab (Yervoy®, Bristol-Myers Squibb, New York, US) in melanoma is well established,[83] its potential in NSCLC has not yet been fully explored. In a phase II trial, ipilimumab, in combination with first-line chemotherapy, improved PFS in patients with metastatic NSCLC.[84] In a phase II study, tremelimumab did not demonstrate superiority over best supportive care in NSCLC patients but a partial response rate was seen in 4.8% versus 0% with best supportive care, suggesting that combined therapeutic approaches with tremelimumab warrant further investigation.[85]

Many cells, including T cells, B cells, natural killer (NK) cells, NKT cells, dendritic cells (DCs), and macrophages, express the transmembrane protein PD-1. Cancer cells can affect the binding of the PD-1 receptor to one of two ligands, programmed death-ligand 1 (PD-L1) and PD-L2, on activated T cells, rendering the cell unable to exert its immunologic actions and thus enabling tumour cells to evade immunological surveillance.[86,87] Therapeutic PD-1 blockade using the anti-PD-1 monoclonal antibody (mAb) nivolumab (Opdivo®, Bristol-Myers Squibb, New York, US) has demonstrated efficacy in patients with refractory NSCLC. In March 2015, nivolumab became the first immunotherapy to be approved for NSCLC, when it received FDA approval for squamous cell NSCLC; in October, this approval was expanded to include non-squamous NSCLC. Nivolumab has also received approval from the EMA for squamous and non-squamous NSCLC, regardless of PD-L1 expression.

Regulatory approval was based on data from the phase III CheckMate 017 trial in previously treated patients with squamous cell NSCLC, showing that nivolumab significantly improved overall survival compared with docetaxel, regardless of PD-L1 expression level.[88,89] The CheckMate 057 study found that nivolumab also improved survival over docetaxel in the second-line treatment of non-squamous cell NSCLC, with striking survival and response benefit in patients with PD-L1 expression greater than 1%, but equivalent overall survival to docetaxel in the patients who were PD-L1 negative.[89,90]

A phase II study of nivolumab in refractory patients with squamous cell NSCLC, CheckMate 063, included patients who had received two or more previous treatments; two-thirds of patients had progressed following three systemic regimens. Although the response rate was only 14.5%, almost all responders had ongoing responses (median duration of response not reached).[91] Nivolumab was associated with two treatment-associated deaths caused by pneumonia and ischaemic stroke that occurred in patients with multiple comorbidities in the setting of progressive disease.[91] However, other AEs associated with nivolumab are manageable.[92]

Data are also emerging for other anti–PD-1 agents. In October 2015, pembrolizumab (Keytruda®, Merck & Co., Inc., New Jersey, US) received accelerated FDA approval for the treatment of NSCLC after failure of first-line therapy that includes platinum-based chemotherapy or after anti-EGFR or anti-ALK therapy in oncogene-addicted NSCLC patients with appropriate mutations, and with 50% PDL-1 expression or more. In a phase I study (KEYNOTE-001) in patients with advanced NSCLC, pembrolizumab showed a response rate of 19.4%, a duration of response of 12.5 months, as well as a tolerable toxicity profile.[93] Recent long-term data (median follow-up duration 23.1 months) showed that the overall survival was 22.1 months for treatment-naive patients and 10.6 months for previously treated patients. The survival benefit seems to raise with increasing PD-L1 positivity (that is, patients with PD-L1 ≥1%).[94] In an open-label, phase II/III study KEYNOTE-010, patients with PD-L1 positive (PD-L1 ≥1%) NSCLC were randomised to pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel. Overall survival was significantly longer for pembrolizumab 2 mg/kg versus docetaxel and for pembrolizumab 10 mg/kg versus docetaxel (in patients with PD-L1 >1% only),[95] leading to EMA registration this year.

It is worth noting that histology is not useful for selecting patients for immunotherapy: clinical trial data have indicated that these agents have similar efficacy for both squamous and non-squamous NSCLC.[96,97]

PD-L1 is one of two ligands that interact with PD-1 (another one is PD-L2) to render T cells ineffective, and is expressed on tumour cells and tumour-infiltrating immune cells. To date, no significant difference in activity or toxicity profile has been observed between anti-PD-1 and anti-PD-L1 compounds. Differential activity attributable to the mechanism of action might be observed in the combination setting in the future

Table 2: Key clinical studies in immune-oncological approaches in non-small cell lung cancer

Trial name	Description	Treatment	Efficacy outcomes	Safety outcomes
Anti-PD-1				
Nivolumab				
CheckMate 063, phase II[91]	Advanced or metastatic squamous NSCLC, who progressed after ≥2 prior systemic treatment including a platinum-based chemotherapy, ECOG 0–1, pts from North America and Europe, n=117	Nivolumab vs docetaxel, ≥3rd line	ORR was 14.5% (95% CI 8.7–22.2). Median TTR was 3.3 mo (IQR 2.2–4.8), median DOR not reached (95% CI 8.31–NA). 77% of responses were ongoing at time of analysis, with 26% SD (median duration 6.0 mo, 95% CI 4.7–10.9). Median PFS was 1.9 mo (95% CI 1.8–3.2), with PFS of 25.9% at 6 mo and 20.0% at 12 mo. Median OS was 8.2 mo and OS at 1 year was 40.8%	Most common nivolumab-related AEs were fatigue (all grade: 33%, grade ≥3: 4%), decreased appetite (all grade: 19%, grade ≥3: 0%), nausea (all grade: 15%, grade ≥3: 0%), asthenia (all grade: 12%, grade ≥3: 0%), rash (all grade: 11%, grade ≥3: 1%) and diarrhoea (all grade: 10%, grade ≥3: 3%).Two possibly treatment-related deaths due to pneumonia and ischaemic stroke
CheckMate 017, phase III[88]	Advanced or metastatic squamous NSCLC, who progressed after one prior platinum-based chemotherapy, ECOG 0–1, pts from North America and Europe, n=272	Nivolumab vs docetaxel, 2nd line	Median OS was 9.2 mo (95% CI 7.3–13.3) with nivolumab vs 6.0 mo (95% CI 5.1–7.3) with docetaxel. Risk of death was 41% lower with nivolumab (HR 0.59, 95% CI 0.44–0.79, p<0.001). At 1 year, OS was 42% (95% CI 34–50) with nivolumab vs 24% (95% CI 17–31) with docetaxel. ORR was 20% with nivolumab versus 9% with docetaxel (p=0.008). Median PFS was 3.5 mo with nivolumab vs 2.8 mo with docetaxel (HR 0.62; 95% CI 0.47–0.81, p<0.001)	Treatment-related AEs occurred less frequently with nivolumab (all grade: 58%, grade ≥3: 7%) vs docetaxel (all grade: 86%, grade ≥3: 57%). Most common nivolumab-related AEs were fatigue (all grade: 16%, grade ≥3: 1%), decreased appetite (all grade: 11%, grade ≥3: 1%), asthenia (all grade: 10%, grade ≥3: 0%), nausea (all grade: 9%, grade ≥3: 0%) and diarrhoea (all grade: 8%, grade ≥3: 0%). Three possible immune-related grade 3 AEs with tubulointerstitial nephritis, colitis and pneumonitis
CheckMate 057, phase III[90]	Advanced, metastatic or recurrent non-squamous NSCLC, who progressed after one prior platinum-doublet chemotherapy, ECOG 0–1, pts from North America and Europe, n=582	Nivolumab vs docetaxel, 2nd line	Median OS was 12.2 mo (95% CI 9.7–15.0) with nivolumab vs 9.4 mo (95% CI 8.1–10.7). Risk of death was 27% lower with nivolumab (HR 0.73, 96% CI 0.59–0.89, p=0.002). At 1 year, OS was 51% (95% CI 45–56) with nivolumab vs 39% (95% CI 33–45) with docetaxel. At 18 mo, OS was 39% (95% CI 34–45) with nivolumab vs 23% (95% CI 19–28) with docetaxel. ORR was 19% with nivolumab vs 12% with docetaxel (p=0.02). PFS did not favour nivolumab over docetaxel (median, 2.3 mo and 4.2 mo, respectively), but PFS at 1 year was higher with nivolumab (19% and 8%, respectively)	Treatment-related AEs occurred less frequently with nivolumab (all grade: 69%, grade ≥3: 10%) vs docetaxel (all grade: 88%, grade ≥3: 54%). Most common nivolumab-related AEs were fatigue (all grade: 16%, grade ≥3: 1%), nausea (all grade: 16%, grade ≥3: 1%), decreased appetite (all grade: 10%, grade ≥3: 0%), asthenia (all grade: 10%, grade ≥3: 0.3%) and diarrhoea (all grade: 8%, grade ≥3: 1%). One possibly nivolumab-related death due to encephalitis
CheckMate 026, phase III[156]	Stage IV or recurrent NSCLC with PD-L1 expression (≥1%), no prior systemic treatment for advanced disease, ECOG 0–1, pts from North America, Europe, Asia and Australia, n=541	Nivolumab vs investigator's choice of platinum-based chemotherapy (cisplatin-pemetrexed or carboplatin-pemetrexed for non-squamous NSCLC; cisplatin-gemcitabine, carboplatin-gemcitabine or carboplatin-paclitaxel for squamous NSCLC), 1st line	In pts expressing PD-L1 ≥ 5% (n=423), median PFS was 4.2 mo (95% CI 3.0–5.6) with nivolumab vs 5.9 mo (95% CI 54–6.9 mo) with chemotherapy (HR 1.15, 95% CI 0.91–1.45, p=0.2511); median OS was 14.4 mo (95% CI 11.7–17.4) vs 13.2 mo (95% CI 10.7–17.1), respectively (HR 1.02, 95% CI 0.80–1.30); ORR was 25.1 % (95% CI 20.3–32.5) vs 33.5% (95% CI 27.2–40.3), respectively; median DOR was 12.1 mo (95% CI 8.8–NE) vs 5.7 mo (95% CI 4.2–8.5), respectively	Treatment-related AEs occurred less frequently with nivolumab (all grade: 71%, grade ≥3: 18%) vs chemotherapy (all grade: 92%, grade ≥3: 51%). Most common nivolumab-related AEs were fatigue (all grade: 21%, grade ≥3: 1%), diarrhoea (all grade: 14%, grade ≥3: 1%), decreased appetite (all grade: 12%, grade ≥3: 0.4%) and nausea (all grade: 12%, grade ≥3: 0.4%). Two possibly nivolumab-related death due to multi-organ failure and pneumonitis
CheckMate 012, phase I[120]	Stage IIIB/IV NSCLC, cohorts with no prior chemotherapy, ECOG 0–1, pts from North America, n=49	Nivolumab + ipilimumab, 1st line	Interim data: ORR and median PFS were respectively 13% and 10.6 mo 4 cycles of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg q3w followed by nivolumab q2w (n=31), 25% and 4.9 mo for nivolumab 1 mg/kg q2w plus ipilimumab 1 mg/kg q6w (n=40), 39% and 8.0 mo for nivolumab 3 mg/kg q2w plus ipi 1 mg/kg q12w (n=38), and 31% and 8.3 mo for nivolumab 3 mg/kg q2w plus ipilimumab 1 mg/kg q6w (n=39). ORR was higher in PD-L1 positive vs PD-L1 negative cohorts	Treatment-related grade 3 or 4 AEs in 58% and 44% (28% to 35% in lower doses), and 37% of AEs led to study discontinuation. Treatment-related deaths (n=3) were due to respiratory failure, bronchopulmonary haemorrhage and toxic epidermal necrosis

Table 2: Cont.

Trial name	Description	Treatment	Efficacy outcomes	Safety outcomes
CheckMate 227, phase III[121]	Stage IV or recurrent NSCLC, no prior systemic anticancer therapy for advanced disease, ECOG 0–1, pts from North America, South America, Australia, Asia, Europe and Africa, estimated n=1,980	Nivolumab with ipilimumab vs nivolumab monotherapy vs nivolumab with platinum-doublet chemotherapy vs standard platinum-doublet chemotherapy, 1st line	Ongoing, no data yet	Ongoing
Pembrolizumab				
KEYNOTE-001, phase I[93]	Advanced or metastatic NSCLC, previously treated or untreated, ECOG 0–1, pts from North America, Europe, Asia and Australia, n=495	Pembrolizumab, ≥1st line	ORR was 19.4% (95% CI 16.0–23.2) for all pts, 18.0% (95% CI 14.4–22.2) in 394 previously treated pts, and 24.8% (95% CI 16.7–34.3) in 101 previously untreated pts. Median DOR was 12.5 mo for all pts, 10.4 mo for previously treated pts, and 23.3 mo in previously untreated pts. Median PFS was 3.7 mo (95% CI 2.9–4.1) for all pts, 3.0 mo (95% CI 2.2–4.0) for previously treated pts, and 6.0 mo (95% CI 4.1–8.6) for previously untreated pts. Median OS was 12.0 mo (95% CI 9.3–14.7) for all pts, 9.3 mo (95% CI 8.4–12.4) for previously treated pts, and 16.2 mo (95% CI 16.2–NR) for untreated pts. Among 73 patients with ≥50% PD-L1 expression, ORR was 45.2% (95% CI 33.5–57.3) for all pts, 43.9% (95% CI 30.7–57.6) for previously treated pts, and 50.0 (95% CI 24.7–75.5) for previously untreated pts; median PFS was 6.3 mo (95% CI 2.9–12.4) for all pts, 6.1 mo for previously treated pts, and 12.5 mo (95% CI 2.4–12.5) for previously untreated pts; median OS was not reached for all pts (95% CI 13.7–NR), previously treated (95% CI 9.3–NR) and untreated pts (95% CI NR–NR)	Most common pembrolizumab-related AEs were fatigue (all grade: 19.4%, grade ≥3: 0.8%), pruritus (all grade: 10.7%, grade ≥3: 0%), decreased appetite (all grade: 10.5%, grade ≥3: 1.0%), rash (all grade: 9.7%, grade ≥3: 0.2%), arthralgia (all grade: 9.1%, grade ≥3: 0.4%) and diarrhoea (all grade: 8.1%, grade ≥3: 0.6%). Treatment-related grade ≥3 AEs occurred in 9.5%. Possible immune-mediated AEs occurred in 2% pts, including infusion-related reaction (all grade: 3%, grade ≥3: 0.2%), hypothyroidism (all grade: 6.9%, grade ≥3: 0.2%) and pneumonitis (all grade: 3.6%, grade ≥3: 1.8%). One treatment-associated deaths due to pneumonitis
KEYNOTE-010, phase II/III[95]	Advanced NSCLC with ≥1% PD-L1 expression, who progressed after ≥2 cycles of platinum doublet chemotherapy (as well as TKI inhibitor for those with EGFR mutation or ALK rearrangement), ECOG 0–1, pts from North America, South America, Europe, Asia, Africa and Australia, n=1,034	Pembrolizumab 2 mg/kg vs 10 mg/kg vs docetaxel, ≥2nd line	Median OS was 10.4 mo (95% CI 9.4–11.9) with pembrolizumab 2 mg/kg, 12.7 mo (95% CI 10.0–17.3) with pembrolizumab 10 mg/kg, and 8.5 mo (95% CI 7.9–9.8) with docetaxel. One year OS was 43.2%, 52.3% and 34.6%, respectively. OS was longer for pembrolizumab 2 mg/kg vs docetaxel (HR 0.71, 95% CI 0.58–0.88, p=0.0008) and for pembrolizumab 10 mg/kg vs docetaxel (HR 0.61, 95% CI 0.49–0.75, p<0.0001). Median PFS was 3.9 mo with pembrolizumab 2 mg/kg, 4.0 mo with pembrolizumab 10 mg/kg, 4.0 mo with docetaxel. Among patients with ≥50% PD-L1 expression, OS was longer with pembrolizumab 2 mg/kg vs docetaxel (14.9 mo vs 8.2 mo; HR 0.54, 95% CI 0.38–0.77, p=0.0002) and with pembrolizumab 10 mg/kg vs docetaxel (17.3 mo vs 8.2 mo; HR 0.50, 95% CI 0.36–0.70, p<0.0001); PFS was longer with pembrolizumab 2 mg/kg vs docetaxel (5.0 mo vs 4.1 mo; HR 0.59, 95% CI 0.44–0.78, p=0.0001) and with pembrolizumab 10 mg/kg vs docetaxel (5.2 mo vs 4.1 mo; HR 0.59, 95% CI 0.45–0.78, p<0.0001)	Treatment-related grade ≥3 AEs occurred in 13% with 2 mg/kg pembrolizumab, 16% with 10 mg/kg, and 35% with docetaxel. Possibly immune-related AEs occurred in 20% pts with pembrolizumab 2 mg/kg and 19% with 10 mg/kg. The most common immune-related AEs were hypothyroidism (all grade: 8%, grade ≥3: 0%), hyperthyroidism (all grade: 4–6%, grade ≥3: 0–1%) and pneumonitis (all grade: 4–5%, grade ≥3: 2%). Pembrolizumab-related deaths occurred in three pts with 2 mg/kg (two pneumonitis and one pneumonia) and in 3 pts with 10 mg/kg (one myocardial infarction, one pneumonia, one pneumonitis)

Table 2: Cont.

Trial name	Description	Treatment	Efficacy outcomes	Safety outcomes
KEYNOTE-024, phase III[157]	Stage IV NSCLC with high PD-L1 expression (≥50%), no prior systemic treatment for advanced disease, ECOG 0–1, pts from Asia, Australia, Europe and North America, n=305	Pembrolizumab vs platinum-based chemotherapy (carboplatin-paclitaxel, cisplatin-pemetrexed, carboplatin-pemetrexed, cisplatin-gemcitabine or carboplatin-gemcitabine), 1st line	Median PFS was 10.3 mo with pembrolizumab vs 6.0 mo with chemotherapy (HR 0.50, 95% CI 0.37–0.68, p<0.001). Median OS was not reached, but clearly favoured pembrolizumab (HR 0.60 95% CI 0.41–0.89). ORR was 45% with pembrolizumab vs 28% with chemotherapy (p=0.001), and median DOR was NR (1.9–14.5 mo) vs 6.3 mo (2.1–12.6), respectively	Treatment-related AEs occurred less frequently with pembrolizumab (all grade: 73%, grade ≥3: 26%) vs docetaxel (all grade: 90%, grade ≥3: 51%). Most common pembrolizumab-related AEs were diarrhoea (all grade: 14%, grade ≥3: 4%), fatigue (all grade: 10%, grade ≥3: 1%), pyrexia (all grade: 10%, grade ≥3: 0%) and nausea (all grade: 10%, grade ≥3: 0%). Most common immune-mediated AEs were hypothyroidism (all grade: 9%, grade ≥3: 0%), hyperthyroidism (all grade: 8%, grade ≥3: 0%) and pneumonitis (all grade: 6%, grade ≥3: 3%) One possibly pembrolizumab-related sudden death of unknow cause
KEYNOTE-042, phase III[109]	Advanced or metastatic NSCLC with PD-L1 expression, no prior systemic treatment for advanced disease, ECOG 0–1, pts from Asia, Europe, North America and South America, expected n=1,240	Pembrolizumab vs investigator's choice of platinum-based chemotherapy (carboplatin-paclitaxel or carboplatin-pemetrexed), 1st line	Ongoing, no data yet	Ongoing
KEYNOTE-021 cohort G, phase II[112]	Stage IIIB/IV non-squamous NSCLC, no prior systemic treatment, ECOG 0–1, pts from US and Taiwan, n=123	Pembrolizumab + carboplatin-pemetrexed vs carboplatin-pemetrexed, 1st line	ORR was 55% (95% CI 42–68) for pembrolizumab + chemotherapy vs 29% (95% CI 18–41) for chemotherapy alone (p=0.0016). A higher ORR with the combination treatment was observed in pts with ≥50% PD-L1 expression (80%, n=20), whereas pts with <50% PD-L1 expression had lower ORR (26%, n=19). Median PFS was 13.0 mo (95% CI 8.3–NR) for the combination vs 8.9 mo (95% CI 4.4–10.3) for chemotherapy alone (HR 0.53, 95% CI 0.31–0.91, p=0.010). Median OS was not reached for both arms, but seemed similar (HR 0.90, 95% CI 0.42–1.91, p=0.39), with 6-mo OS 92% for both arms, and 12-mo OS 75% for the combination vs 72% for chemotherapy alone	Grade ≥3 treatment-related AEs occurred 39% with pembrolizumab + chemotherapy vs 26% with chemotherapy alone. Most common grade ≥3 treatment-related AEs in the combination group were anaemia (12%), decreased neutrophil count (5%), thrombocytopenia (3%), decreased lymphocyte count (3%), neutropenia (3%) and sepsis (3%); Possible immune-related AEs occurred in 22% pts with the combination, the most common being hypothyroidism (15%), hyperthyroidism (8%) and pneumonitis (5%), with three events (6%) of grade ≥3 (infusion reaction, skin reaction and pneumonitis) and one (2%) treatment-related death due to sepsis
KEYNOTE-021 cohort D, phase I[158]	Advanced solid tumours including stage IIIB/IV NSCLC, who progressed after ≤2 prior regimens, ECOG 0–1, n=17	Pembrolizumab + ipilimumab, ≥2nd line	Interim data: ORR was 33% for pembrolizumab 10 mg/kg + ipilimumab 3 mg/kg (n=3), 67% for pembrolizumab 10 mg/kg + ipilimumab 1 mg/kg (n=3) and 60% for pembrolizumab 2 mg/kg + ipilimumab 1 mg/kg (n=5)	Ten pts (59%) experienced treatment-related AEs; none led to discontinuation or death. Two (20%) grade 3 treatment-related AEs, both rash
KEYNOTE-021 cohort D and H, phase I/II[119]	Advanced NSCLC, who progressed after ≥ 1 prior regimen, ECOG 0–1, n=4	Pembrolizumab + ipilimumab, ≥2nd line	ORR was 24%, median DOR 14 mo, median PFS 6 mo, and median OS 17 mo. There was no link between PD-L1 status and outcome	Sixty-seven percent of pts experienced treatment-related AEs, with 24% grade ≥ 3, most commonly diarrhea (0.4%). Four (9%) pts discontinued treatment because of treatment-related AEs. One treatment-related death was due to pancreatitis
Anti-PD-L1				
Atezolizumab				
FIR, phase II[102]	Advanced, metastatic or recurrent NCSLC with PD-L1 expression, ECOG 0–1, pts from North America and Europe, n=137	Atezolizumab (MPDL3280A), cohort 1: 1st line; cohort 2: ≥2nd line without brain metastases; and cohort 3: ≥2nd line with treated asymptomatic brain metastases	Interim data: ORR was 29% (95% CI 13–45) for cohort 1 (n=31), 17% (95% CI 8–26) for cohort 2 (n=71) and 17% (95% CI 0–38) for cohort 3 (n=12). For pts with high PD-L1 expression (TC3 or IC3), ORR was 29% (95% CI 0–62) for cohort 1 (n=7), 17% (95% CI 10–44) for cohort 2 (n=26), and 25% (95% CI 0–55) for cohort 3 (n=8). 24-wk PFS was 39% (95% CI 22–56) for cohort 1 and 35% (95% CI 23–46) for cohort 2. For pts with high PD-L1 expression, 24-wk PFS was 43% (95% CI 6–80) for cohort 1 and 49% (95% CI 30–69) for cohort 2	Treatment-related AEs occurred in 67% pts, most often fatigue (26%), nausea (15%) and decreased appetite (14%). Treatment-related grade 3 or 4 AEs occurred in in 15% pts. Treatment-associated death in one patient (constrictive pericarditis)

Table 2: Cont.

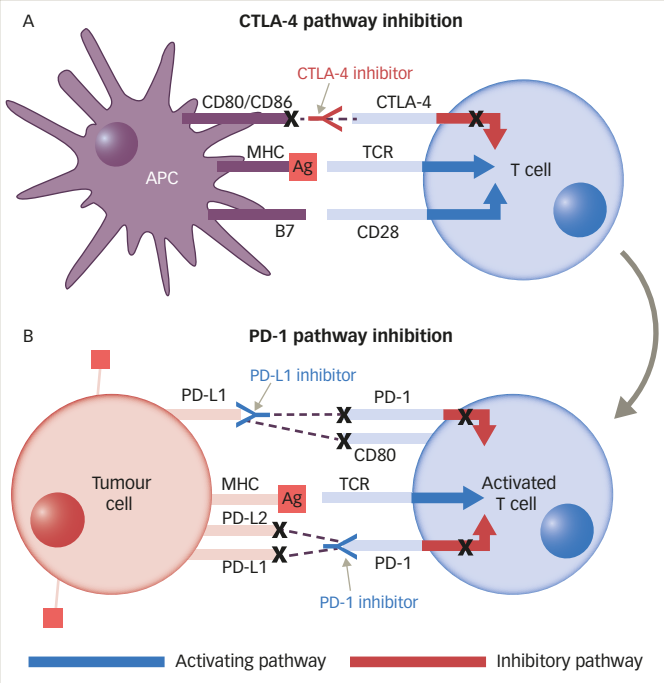
Trial name	Description	Treatment	Efficacy outcomes	Safety outcomes
POPLAR, phase II[103]	Advanced or metastatic NSCLC, who progressed after prior platinum-based chemotherapy, ECOG 0–1, pts from Europe and North America, n=287	Atezolizumab vs docetaxel, ≥2nd line	Median OS was 12.6 mo (95% CI 9.7–16.4) with atezolizumab vs 9.7 mo (95% CI 8.6–12.0) with docetaxel (HR 0.73, 95% CI 0.53–0.99, p=0.04). Increasing improvement in OS was associated with increasing PD-L1 expression: TC3/IC3 (HR 0.49) > TC2–3/IC2–3 (HR 0.54) > TC1–3/IC1–3 (HR 0.59) > TC0/IC0 (HR 1.04). In pts with highest PD-L1 expression (TC3/IC3), median PFS was 7.8 mo for atezolizumab vs 3.9 mo for docetaxel (HR 0.60), whereas PFS was similar in pts unselected for PD-L1 expression (2.7 mo vs 3.0 mo; HR 0.94) and in pts without PD-L1 expression (TC0/IC0)	Most common AEs with atezolizumab were decreased appetite (all grade: 34%, grade ≥3: 1%), dyspnoea (all grade: 27%, grade ≥3: 7%), nausea (all grade: 22%, grade ≥3: 1%), pyrexia (all grade: 17%, grade ≥3: 0%), diarrhoea (all grade: 17%, grade ≥3: 1%), arthralgia (all grade: 15%, grade ≥3: 2%). Treatment-related grade 3– 4 AEs occurred in 11% with atezolizumab vs 39% with docetaxel. Most common atezolizumab-related grade 3 AEs were pneumonia (2%) and increased AST (2%). Immune-mediated AEs were increased AST (all grade: 4%, grade ≥3: 2%), increased ALT (all grade: 4%, grade ≥3: 2%), pneumonitis (all grade: 3%, grade ≥3: 1%), colitis (all grade: 1%, grade ≥3: 1%) and hepatitis (all grade: 3%, grade ≥3: 1%). Five fatal AEs with atezolizumab due to cardiac failure (treatment-related), pneumonia, ulcer haemorrhage, pneumothorax, pulmonary embolism and embolism
BIRCH, phase II[105]	Advanced, metastatic or recurrent NSCLC with strong PD-L1 expression (TC2/3 or IC2/3), either treatment naïve (cohort 1) or who progressed after 1 prior platinum-based therapy (cohort 2) or after ≥2 prior chemotherapy regimens (cohort 3), ECOG 0–1, pts from North America, Europe and Asia, n=667	Atezolizumab vs docetaxel, cohorts with 1st, 2nd or 3rd line	Interim data: ORR in cohort 1 was 19% and 17% in cohorts 2 and 3 in patients with TC2/3 or IC2/3 PD-L1 expression. Stronger ORR was seen in patients with higher expression (TC3 or IC3): 26%, 24%, and 27% in cohorts 1, 2, and 3, respectively. Median OS was 14 mo, NR and NR in cohorts 1, 2 and 3. 6-month OS was achieved by 82%, 76%, 71% of pts with TC2/3 or IC2/3 expression in cohorts 1, 2 and 3, respectively, and by 79 %, 80% and 75 % by pts with TC3/IC3 expression. 6-month PFS were 46%, 29% and 31% for intermediate PD-L1 expression, and 48%, 34% and 39% for higher expression, in cohort 1, 2 and 3, respectively	Most common related AEs were fatigue (18%) and nausea (10%). 11% pts had grade 3/4 treatment-related AEs and 6% AEs leading to study discontinuation. One fatal treatment-related AEs due to pneumonia
OAK, phase III[106]	Advanced or metastatic NSCLC, who progressed after 1–2 prior chemotherapies including at least 1 platinum-based therapy, ECOG 0–1, pts from North America, Europe and Asia, n=850	Atezolizumab vs docetaxel, 2nd or 3rd line	Median OS was 13.8 mo (95% CI 11.8–15.7) with atezolizumab vs 9.6 mo (95% CI 8.6–11.2) with docetaxel (HR 0.73, 95% CI 0.62–0.87, p=0.0003). Increasing improvement in OS was associated with increasing PD-L1 expression: TC3/IC3 (HR 0.41) > TC2-3/IC2-3 (HR 0.67) > TC1-3/IC1-3 (HR 0.74), but OS was improved also in PD-L1 negative (TC0/IC0, HR 0.75). OS benefit was similar in pts with squamous or nonsquamous histology. In pts with highest PD-L1 expression (TC3/IC3), median PFS was 4.2 mo for atezolizumab vs 3.3 mo for docetaxel (HR 0.63), whereas PFS was similar in pts unselected for PD-L1 expression (2.7 mo vs 4.0 mo; HR 0.95) and in pts without PD-L1 expression (TC0/IC0) (2.6 mo vs 4.0 mo, HR 1.0). ORR was 13.6% for atezolizumab vs 13.4% for docetaxel, and mDOR was 16.3 mo vs 6.2%	Treatment-related grade 3/4 AEs occurred in 15% with atezolizumab vs 43% with docetaxel. AEs leading to treatment discontinuation were 8% with atezolizumab vs 19% with docetaxel. Immune-mediated AEs were pneumonitis (all grade: 1.0%, grade ≥3: 0.7%), colitis (all grade: 0.3%, grade ≥3: 0%) and hepatitis (all grade: 0.3%, grade ≥3: 0.3%). There was no death with atezolizumab
Durvalumab				
Phase I/II[99]	Advanced solid tumours including NSCLC, ECOG 0–1, pts from US, n=198	Durvalumab, ≥2nd line	Interim data: at 24 weeks ORR was 14% (23% in PD-L1 positive pts) and DCR at 24 wks was 24%. ORR was higher in squamous (21%) than non-squamous pts (10%). Responses were durable with 76% ongoing	Treatment-related grade 3/4 AEs occurred in 6%, mostly fatigue (14%), decreased appetite (9%), and nausea (8%). Grade ≥3 treatment-related AEs were reported in 6% of pts. Treatment-related AEs led to study discontinuation in 2% of pts. Pneumonitis (grade 1–2) occurred in two (1%) pts

Table 2: Cont.

Trial name	Description	Treatment	Efficacy outcomes	Safety outcomes
Phase Ib[122]	Locally advanced or metastatic NSCLC, immunotherapy-naïve, ECOG 0–1, pts from US, n=102	Durvalumab + tremelimumab, ≥1st line	At median follow-up 18.8 weeks (IQR 11–33), the ORR was 23% (95% CI 9–44) in the combined tremelimumab 1 mg/kg cohort (n=26), comprising 22% (95% CI 3–60) of pts with PD-L1+ tumours (n=9) and 29% (95% CI 8–58) of pts with PD-L1- tumours (n=14)	80% pts had ≥1 treatment-related AEs, mostly diarrhoea (32%), fatigue (24%), and pruritus (21%). Most common treatment-related grade ≥3 AEs were diarrhoea (11%], colitis (9%), and increased lipase (8%). Discontinuations due to treatment-related AEs occurred in 28% of pts. Treatment-related serious AEs occurred in 36%. Three treatment-related deaths due to myasthenia gravis, pericardial effusion, and neuromuscular disorder
MYSTIC, phase III[123]	Stage IV NSCLC, EGFR and ALK wild-type, no prior systemic therapy for recurrent/metastatic NSCLC, ECOG 0–1, pts from North America, Europe, Asia, and Australia, estimated n=1,092	Durvalumab + tremelimumab vs durvalumab monotherapy vs standard of care, 1st line	Ongoing, no data yet	Ongoing
Avelumab				
JAVELIN Solid Tumors, phase Ib expansion trial[100]	Advanced or metastatic solid tumours including NSCLC, who progressed after 1 prior platinum-doublet chemotherapy, ECOG 0–1, pts from US, n=184	Avelumab, 2nd line	Interim data: ORR was 12% (95% CI 7.6–17.5). Median PFS was 11.6 weeks (95% CI 8.4–12.1) and 24–week PFS 25.4% (95% CI 18.3–33.2). Tumours were PD-L1 positive (≥1% cut-off) in 86% pts. ORR was 14.4% in PD-L1(+) pts and 10.0% in PD-L1(-) pts (n=20). Median PFS was 11.7 wks in PD-L1(+) pts vs 5.9 wks in PD-L1(-) pts	Treatment-related AEs occurred in 75.5% pts, most often fatigue, nausea, infusion-related reactions (IRRs), chills, decreased appetite and diarrhoea. Grade 3/4 treatment-related AEs occurred in 12% pts, including four IRRs. Three treatment-related deaths due to radiation pneumonitis, acute respiratory failure and disease progression
JAVELIN Solid Tumors, phase Ib expansion trial[101]	Advanced or metastatic solid tumours including NSCLC, no prior systemic treatment for advanced disease, ECOG 0–1, pts from North America and Europe, n=145	Avelumab, 1st line	Interim data: Among 75 pts with ≥3 mo follow-up, unconfirmed ORR was 18.7% (95% CI 10.6–29.3) and DCR was 64.0%. PD-L1 expression (≥1% cut-off) was evaluable in 45 pts (60.0%): 77.8% were PD-L1(+) and ORR was 20.0% (95% CI 8.4–36.9) in PD-L1(+) pts vs 0.0% (95% CI 0.0–30.8) in PD-L1(-) pts. Median PFS was 11.6 wks (95% CI 6.7–17.9) for all treated pts	Treatment-related AEs occurred in 56.6% pts, most often infusion-related reaction (16.6%) and fatigue (14.5%). Grade ≥3 treatment-related AEs were reported in 9.0% pts, most often IRR (2.1%) and fatigue (2.1%)
Anti CTLA-4				
Ipilimumab				
Phase II[84]	Stage IIIB/IV or recurrent NSCLC, no previous systemic therapy, ECOG 0–1, pts from Europe and North America, n=204	Concurrent ipilimumab plus carboplatin-paclitaxel vs phased ipilimumab plus carboplatin-paclitaxel vs carboplatin-paclitaxel, 1st line	Median irPFS was 5.68 mo (95% CI 4.76–7.79) for phased ipilimumab vs 4.63 mo (95% CI 4.14–5.52) for control (HR 0.72; 95% CI 0.50–1.06, p=0.05), and 5.52 mo (95% CI 4.17–6.74) for concurrent ipilimumab vs 4.63 mo (95% CI 4.14–5.52) for control (HR 0.81, 95% CI 0.55–1.17, p= 0.13). Median OS was 12.22 mo (95% CI 9.26–14.39) for phased ipilimumab vs 8.28 mo (95% CI 6.80–12.39) for control (HR 0.87; 95% CI 0.59–1.28, p=0.23), and 9.69 mo (95% CI 7.59–12.48) for concurrent ipilimumab vs 8.28 mo (95% CI 6.80–12.39) for control (HR 0.99, 95% CI 0.67–1.46, p=0.48)	Treatment-related adverse AEs occurred in 43% for control, 35% for concurrent ipilimumab and 43% for phased ipilimumab, most often alopecia (46%, 34% and 45%, respectively), nausea (31%, 25%, 31%) and fatigue (22%, 20%, 19%). Grade 3/4 treatment-related AEs occurred in 29% for control, 24% for concurrent ipilimumab and 31% for phased ipilimumab. Drug-related AEs caused treatment discontinuation in 5% control, 10% concurrent ipilimumab and 6% phased ipilimumab. One treatment-related death with concurrent ipilimumab due to septic shock secondary to epidermal necrolysis
CA 184-104, phase III[110]	Stage IV or recurrent squamous NSCLC, no previous systemic therapy, ECOG 0–1, pts from Europe, North America, South America, Asia and Australia, n=1,289	Phased ipilimumab plus carboplatin-paclitaxel vs carboplatin-paclitaxel, 1st line	Results pending	Results pending

AE = adverse event; ALK = anaplastic lymphoma kinase; CI = confidence interval; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; HR = hazard ratio; IC= tumour-infiltrating immune cells; IQR = interquartile range; mo = months; NE = non-estimable; NSCLC = non-small cell lung cancer; NR = not reached; ORR = overall response rate; OS = overall survival; PD-1 = programmed cell death; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; pts = patients; SD = stable disease; TC = tumour cells; TTR = time to response.

Figure 2: Mechanism of action of immune checkpoint inhibitors



APC = antigen-presenting cells; CTLA-4 = cytotoxic T-lymphocyte antigen-4; MHC = major histocompatibility complex; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; TCR = T cell receptor.

though. Anti-PD-L1 agents are also in active clinical development. These include atezolizumab (MPDL3280A),[98] durvalumab (MEDI4736)[99] and avelumab (MSB0010718C).[100,101] Atezolizumab (MPDL3280A) has shown clinical efficacy in both chemotherapy-naïve and previously treated NSCLC.[102] In the phase II POPLAR trial, atezolizumab significantly improved overall survival and overall response rates versus docetaxel in patients with non-squamous and squamous NSCLC with strong PD-L1 expression.[103] Extended follow-up revealed further separation later in the OS curves and increased benefit with atezolizumab versus docetaxel.[104] In the phase II BIRCH trial, atezolizumab also met its primary endpoint in patients with strong PD-L1 expression.[105] In the recently presented phase III OAK trial, atezolizumab showed an improved OS versus docetaxel in patients with advanced NSCLC who progressed after one or two prior chemotherapy. Interestingly, the OS benefit was seen regardless of PD-L1 expression, histology, sex or smoking status.[106] In October 2016, atezolizumab received FDA approval for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy.

In the first-line setting, two phase III clinical trials testing anti-PD-1 monotherapy have been recently presented at the European Society for Medical Oncology (ESMO) 2016: CheckMate 026 and KEYNOTE-024. CheckMate 026 investigated the efficacy of nivolumab compared to platinum-based chemotherapy in untreated advanced NSCLC with PD-L1 expression (defined as present in ≥5% tumour cells). The trial did not meet its primary endpoint, which was defined as PFS assessed by an independent radiology review committee in patients with ≥5% PD-L1 expression, while all patients with ≥1% PD-L1 could be enrolled: the median PFS was 4.2 months with nivolumab compared with 5.9 months with chemotherapy (hazard ratio [HR] 1.15).[107] The median OS was similar in both arms (14.4 months versus 13.2 months, HR 1.02), possibly reflecting the high rate of crossover to immunotherapy on the chemotherapy arm (60.4%). KEYNOTE-024 investigated the efficacy of pembrolizumab compared to platinum-based chemotherapy in untreated advanced NSCLC with high PD-L1 expression (defined as present in ≥ 50% of tumour cells, which represented about 30% of patients).[108] The trial met its primary endpoint, showing an improved PFS with pembrolizumab compared to chemotherapy (10.3 months versus 6.0 months, HR 0.50). A significant benefit in response rates, duration of response and overall survival (not reached in both arms, HR 0.60) was observed, even though the crossover rate was high (44% from chemotherapy to pembrolizumab). This is a landmark result in highly selected PD-L1 positive patients that will change clinical practice in the first-line setting. More studies are required to confirm these findings in patients with high PD-L1 expression, as well as in those with lower PD-L1 expression. The result of the phase III KEYNOTE-042 (first-line pembrolizumab versus platinum-based chemotherapy)[109] are awaited. Moreover, more research is needed to assess the difference with CheckMate 026 results and whether more stringent selection of patients may also confer a benefit of nivolumab compared to chemotherapy.

Combined immunotherapeutic approaches

Combined therapeutic strategies involving immunotherapy is an area of considerable interest. At present, there is no approved biomarker for response to anti-PD-1/anti-PD-L1 agents. The majority of PD-L1 positive patients do not respond to checkpoint inhibitors. Furthermore, more than half of patients with NSCLC have tumours that are PD-L1 negative, some of which have responded to checkpoint inhibitors. Therefore, PD-L1 expression is not the only factor determining response. Immunotherapy combinations may be employed in PD-L1 negative or undetermined tumours and may involve chemotherapy and other approaches, for example, antiangiogenic compounds or radiotherapy. Tumour-specific antigen released during chemotherapy-induced tumour necrosis may increase tumour-specific immunity and therefore enhance the efficacy of ipilimumab or other immunotherapeutics.

Several clinical studies are investigating combined approaches. As discussed earlier, ipilimumab has shown efficacy in treating patients with metastatic NSCLC in combination with first-line chemotherapy[84] and is currently being investigated in squamous NSCLC in a phase III trial.[110] A phase III study is investigating the combination of atezolizumab and chemotherapy in chemotherapy-naïve patients with advanced NSCLC.[111] The phase II KEYNOTE-021 cohort G study was recently presented at ESMO 2016, assessing the efficacy of adding pembrolizumab to carboplatin-pemetrexed compared to carboplatin-pemetrexed in first-line untreated advanced non-squamous NSCLC. The pembrolizumab combination showed a significant increase in ORR (55% versus 29%, p=0.0016) compared to chemotherapy alone. A higher response rate (80%) was observed in a few patients with ≥50% PD-L1 expression treated with the combination. The pembrolizumab combination also improved PFS (13.0 months versus 8.9 months, HR 0.53) compared to chemotherapy alone, while OS seemed similar (HR 0.90). Grade ≥3 treatment-AEs occurred more frequently with the combination, but this did not seem to impact on treatment discontinuation nor treatment-related deaths.[112] Results of phase III trials are awaited to confirm the efficacy of adding pembrolizumab to chemotherapy in the first-line setting, such as the ongoing phase III KEYNOTE-189 trial (platinum-pemetrexed chemotherapy plus or minus pembrolizumab in first-line advanced non-squamous NSCLC)[113] and KEYNOTE-407 (carboplatin with paclitaxel or nab-paclitaxel plus or minus pembrolizumab in first-line metastatic squamous NSCLC).[114]

Another promising combination is that of immunotherapy and radiotherapy: ionising radiation generates inflammatory signals that

may enable activation of tumour-specific T cells.[115] A case study has found that radiotherapy can elicit an immune-mediated abscopal (that is, away from the target) effect in NSCLC, when combined with ipilimumab.[116]

Preclinical data have suggested that targeting both PD-L1 and CTLA-4 may have additive or synergistic effects,[117] leading to a number of clinical studies. The phase I/II KEYNOTE-021 study is evaluating pembrolizumab in combination with standard therapies (including cohorts with pembrozilumab plus ipilimumab) compared to standard chemotherapy. In the phase I KEYNOTE-021 cohort D, this combination regime was feasible and has demonstrated clinical efficacy regardless of pembrozilumab dose or PD-L1 status in treatment-naive advanced NSCLC.[118] However, in the follow-up phase I/II KEYNOTE-021 cohort D plus H, this combination has shown a similar response rate (24%) than pembrolizumab alone, with more treatment-related grade ≥3 AEs (24%).[119] The CheckMate 012 trial is investigating the combination of ipilimumab and nivolumab as first-line treatment in advanced NSCLC. In a recent presentation, response rates of 13 to 39% were reported, with median duration of response not reached yet (median follow-up 16.6 months).[120] CheckMate 227 is investigating nivolumab with or without ipilimumab, compared with standard platinum-doublet chemotherapy with or without nivolumab depending on the PD-L1 status in the first-line treatment of advanced or metastatic NSCLC.[121] In a phase I study, the combination of durvalumab and tremelimumab showed a manageable tolerability profile, with antitumour activity in patients with locally advanced or metastatic NSCLC, irrespective of PD-L1 status.[122] This combination is now being investigated in a phase III study, MYSTIC, comparing to durvalumab monotherapy or standard chemotherapy in first-line advanced NSCLC.[123]

Lymphocyte-activation gene 3 (LAG3; CD223) is a co-inhibitory receptor expressed in activated T cells, Tregs, DCs and NK cells.[52] Further work is needed to characterise LAG3 in NSCLC; an ongoing phase I study is investigating the role of BMS-986016, a LAG3 mAb with or without nivolumab in advanced solid tumours.[124] OX40 is a co-stimulatory receptor that is transiently expressed by T cells upon antigen recognition. A phase Ib study is investigating the combination of atezolizumab and MOXR0916, a mAb that targets OX40, in patients with advanced solid tumours, including NSCLC. Preliminary data show that the combination is well tolerated.[125]

Rationale for selecting targeted and immunotherapies in non-small cell lung cancer

Targeted and immune-oncological approaches should not be regarded as competitive options for NSCLC; both should be considered as an option for treatment in any patient based on the patient's disease characteristics. Targeted therapies are associated with higher response rates than immunotherapy – response rates typically exceed 50%, while up to 25% is more typical for immunotherapy. This reflects the different principles and mechanisms of actions of the two approaches. As of yet, immunotherapy should not be considered as first-line therapy in patients with oncogene driver/target mutations. The labels for nivolumab and pembrolizumab state that EGFR and ALK patients should be treated with targeted drugs first and fail before immunotherapy is considered.[126,127]

Since immune checkpoint inhibitors are highly active in a select group of patients, there is a need for predictive biomarkers. Certain gene mutations, including EGFR or ALK, are more prevalent in non-smokers, whereas the majority of patients with NSCLC are smokers.[128] Anti-PD-1/anti-PD-L1 agents appear to be most effective in smokers, in whom somatic gene mutations are more abundant.[129] Patients with no smoking history might present with a lower response rate to PD-1 pathway blockade, despite the facts that only a few patients have been reported to date, and that some long-lasting benefit has also been observed in some of these patients.[130] It has thus been hypothesised that immunotherapeutic approaches are less effective in never-smokers with NSCLC as well as in patients with EGFR and ALK aberrations. Smoking history, as an indirect reflection of the patient mutation load, may therefore be useful in clinical decision-making.

In general, NSCLC is associated with a high mutation burden, especially in smokers,[131–135] but there is a large variability within both tumour types and patients. Interestingly, the high mutation burden of NSCLC may correlate with higher neoantigen quantities,[80,136] and with improved outcome under anti-PD-1 therapy.[80] Moreover, neoantigen-specific T cell reactivity was correlated with tumour regression after anti-PD-1 therapy, suggesting that anti-PD-1 therapy might enhance neoantigen-reactive T cells in NSCLC.[80]

Expression of PD-L1 has been associated with a higher response rate and overall survival in anti-PD-1 and anti-PD-L1 mAb treatment in some cases of non-squamous NSCLC.[90,98,137–139] However, the use of PD-L1 as biomarker is limited by the fact that PD-L1-negative tumours have responded to anti-PD-L1 treatment, and heterogeneity in tumour expression of PD-L1 exists.[140,141] Further studies are required to determine the value of this marker in prediction of response to treatments targeting this pathway. Measurement of TILs subpopulations is also a potentially useful strategy under investigation for predicting response to checkpoint inhibitors.[142]

There is a lack of clear knowledge of the activity of immunotherapy in oncogene addiction, that is, dependence of cancer cells on a single oncogenic protein for sustaining growth and proliferation. A recent study found that median PD-1 expression was highest in males, in current smokers, in individuals with adenocarcinoma histology, in EGFR wild type ALK negative patients, and in patients harbouring KRAS mutations. By contrast, PD-L1 expression was highest in females, in never/former smokers, in adenocarcinoma histology, in patients harbouring EGFR mutations, and in patients with ALK translocations.[143]

Combined targeted and immune-oncological approaches

Targeted therapy and immunotherapy may have complementary roles in cancer treatment. It has been postulated that tumour cell death resulting from targeted therapies causes antigen release. These antigens are taken up by antigen-presenting cells that activate T cells, leading to the upregulation of CTLA-4 and PD-1. Immune checkpoint therapy prevents attenuation of T cell responses, allowing T cells to kill tumour cells.[144] Combined targeted and immune-oncologic approaches therefore offer the potential to extend the duration of treatment response and delay development of resistance. The association between PD-L1 and the presence of EGFR mutations suggests that combination of PD-1 blockade and EGFR TKIs may be a promising therapeutic strategy.[143,145]

It is essential to evaluate doses and dosing schedules in the evaluation of combined therapeutic regimes. Although toxicities may be non-overlapping, it is impossible to predict whether activity and risks might be attenuated in combined approaches. In two clinical trials of BRAF inhibitors in melanoma, liver toxicity due to the combination of vemurafenib and ipilimumab led to discontinuation of the trial,[146]

while the combination of dabrafenib and ipilimumab appears to be well-tolerated.[147] Recently, two clinical trials of the combination of osimertinib and durvalumab were halted following reports of ILD.[148] A recent analysis of these data found that the combined ILD rate of 38% with five cases of grades 3/4 reported for the combination was much greater than either sole agent.[149] However, there was no apparent increase in the severity of ILD, and tumour response rate suggests encouraging clinical activity of osimertinib plus durvalumab in EGFR-mutant NSCLC. According to the authors, the tolerability and safety of combining these agents warrants further investigation.[149]

The combination of immunotherapy and targeted therapies is also potentially useful for patients with oncogenic alterations who are refractory to targeted treatment and do not present a treatable oncogenic resistance mediating alteration (such as T790M for EGFR TKI). However, it is important to establish the correct sequence of treatments; it is not known whether combined regimens should be employed as first-line therapy or in treatment-refractory patients.

Future perspectives

Among future strategies, the combination of vaccines and checkpoint inhibitors may be promising: cancer vaccine-based immunotherapy may overcome the resistance of certain cancers to immune checkpoint inhibitors, while immune checkpoint inhibitors may enhance the efficacy of the cancer-vaccine therapies. As an example, a recently initiated phase Ib/II study will investigate vaccination with viagenpumatucel-L (HS-110) in combination with multiple treatment regimens including nivolumab.[150] In addition, molecular approaches to NSCLC are an area of active clinical development. These include targeting cancer stem cells,[151] adoptive cell therapy with gene-modification of peripheral T cell with engineered T cell receptors or chimeric antigen receptors.[152,153]

Summary and concluding remarks

The one-size-fits all approach to cancer therapeutics is no longer applicable to NSCLC. We are moving into an era of personalised treatment of NSCLC. In addition to histological subtyping, NSCLC should now be further sub-classified by driver mutation if present. Optimal management of NSCLC in the future will require screening for a range of biomarkers that help to predict sensitivity to targeted therapy; point mutations and rearrangements in specific genes including *HER2*, *BRAF*, *NUT*, *MET*, *ROS1*, *DDR2*, *FGFR1* and *KRAS*, might potentially provide useful information for clinical decision making.[154]

The subset of patients with treatable oncogenic alterations should receive appropriate targeted therapies. Within this group, specific resistance mechanisms have been identified; however, these can be treated specifically. The majority of patients with NSCLC are still not defined by treatable oncogenic alterations. Such patients may be treated using chemotherapy but are ideal candidates for immune-oncologic treatment. The PD-1 inhibitors, nivolumab and pembrolizumab, have shown a survival benefit in NSCLC. However, not all patients respond to immunotherapy and at present, the reliability and availability of predictive biomarkers is poor. There is an urgent need to identify high precision biomarkers to select patients for immune-oncologic treatment. Expression of PD-L1 has been associated with higher response rate and overall survival in several clinical trials evaluating anti-PD-1 and anti-PD-L1 mAbs, but further studies are needed to establish its potential role as a predictive biomarker.

Finally, the combination of immunotherapy and targeted therapies is currently an area of active clinical research. These two distinct approaches – one that targets the cancer and the other that targets the patient – may ultimately merge to provide an individualised approach to NSCLC therapy. ❑

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