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Immune checkpoint inhibitor treatment in patients with oncogene-addicted non-small cell lung cancer (NSCLC): summary of a multidisciplinary round-table discussion

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ABSTRACT

The introduction of targeted treatments and more recently immune checkpoint inhibitors (ICI) to the treatment of metastatic non-small cell lung cancer (NSCLC) has dramatically changed the prognosis of selected patients. For patients with oncogene-addicted metastatic NSCLC harbouring an epidermal growth factor receptor (*EGFR*) or v-Raf murine sarcoma viral oncogene homologue B1 (*BRAF*) mutation or an anaplastic lymphoma kinase (*ALK*) or ROS proto-oncogene 1, receptor tyrosine kinase (*ROS1*) gene alteration (translocation, fusion, amplification) mutation-specific tyrosine kinase inhibitors (TKI) are already first-line standard treatment, while targeted treatment for other driver mutations affecting *MET, RET,* human epidermal growth factor receptor (*HER)* 2, tropomyosin receptor kinases (*TRK*) 1–3 and others are currently under investigation. The role of ICI in these patient subgroups is currently under debate. This article summarises a round-table discussion organised by ESMO Open in Vienna in July 2018. It reviews current clinical data on ICI treatment in patients with metastatic oncogene-addicted NSCLC and discusses molecular diagnostic assessment, potential biomarkers and radiological methods for response evaluation of ICI treatment. The round-table panel concluded ICI should only be considered in patients with oncogene-addicted NSCLC after exhaustion of effective targeted therapies and in some cases possibly after all other therapies including chemotherapies. More clinical trials on combination therapies and biomarkers for ICI therapy based on the specific differing characteristics of oncogene-addicted NSCLC need to be conducted.

INTRODUCTION

The management of patients with metastatic non-small cell lung cancer (NSCLC) underwent significant transformation in the last 10–15 years by the development of precision medicine based on molecular characterisation. Molecular analysis revealed distinct targetable driver mutations in about 10%–20% of patients with metastatic NSCLC.[1] The most frequently observed targetable mutations are aberrations in the epidermal growth factor receptor (*EGFR*) gene (about 10%–15% in Caucasians), followed by gene rearrangements/gene fusions in the anaplastic lymphoma kinase (*ALK*) gene (about 5%) and ROS proto-oncogene 1, receptor tyrosine kinase (*ROS1*) (about 1%–3%). In addition, mutations in v-Raf murine sarcoma viral oncogene homologue B1 (*BRAF*) (about 4%) can be observed and targeted therapeutically with mutation-specific tyrosine kinase inhibitors (TKI).[1] Besides these targetable genetic alterations, also the expression of programmed death-ligand 1 (PD-L1), an immune suppressive molecule, needs to be considered for therapeutic decision-making. The programmed cell death protein 1 (PD-1) immune checkpoint inhibitor (ICI) pembrolizumab was shown to have higher efficacy as first-line treatment compared with platin-based chemotherapy in patients without the presence of a driver oncogene alteration but PD-L1 expression in more than 50% of tumour cells[2] and to increase efficacy of platin-based chemotherapy in patients with a lower PD-L1 expression level.[3]

Therefore, NSCLC is a molecularly heterogenous disease and initial molecular diagnosis forms the basis for systemic treatment decisions, given the clinical superiority of TKI over chemotherapy in patients harbouring a predictive molecular alteration. However, resistance to targeted therapies and progression occurs in almost all patients and especially brain metastases can be observed frequently as an area of progression.[4] Treatment options on exhaustion of targeted therapies and chemotherapy are few, underscoring the need to explore the new and

promising treatment category of ICI, also in patients with oncogene-addicted metastatic NSCLC.

ICI target the inhibitory T cell co-receptors and thereby increase the capacity of the tumour-specific immune response. This new category of immune-modulating therapies has revolutionised oncology as in comparison to targeted therapies and chemotherapy long lasting and durable responses can be achieved in a subfraction of patients.[5] Here, PD-L1 inhibitors, PD-1 inhibitors and cytotoxic T-lymphocyte-associated protein 4 inhibitors have been investigated in patients with metastatic NSCLC.[6]

In the context of NSCLC, patients with oncogene addiction were frequently excluded from registration trials, resulting in so far limited clinical knowledge on the efficacy of ICI in the subcohort of molecularly altered NSCLC.[7–14] This article aims to review the available clinical data on ICI treatment in patients with metastatic oncogene-addicted NSCLC and discusses molecular diagnostic assessment, potential biomarkers and radiological methods for response evaluation of ICI treatment.

Molecular diagnostic assessment in NSCLC

Personalised cancer therapy comes with increased and complex diagnostic testing. In clinical practice and as recommended by clinical guidelines,[15] selection of targeted therapies for NSCLC requires testing for *EGFR* and *BRAF* mutations, rearrangements or fusion protein expression involving the *ALK* and *ROS1* genes and the expression of PD-L1. Therefore, molecular testing should be carried out in all patients who have a definite, probable or possible diagnosis of adenocarcinoma, for whom this diagnosis cannot be reasonably excluded, and for patients with non-small cell carcinoma or for patients with squamous cell carcinoma who have a high risk of a target mutation or rearrangement (never or light smokers, very long-term ex-smokers or young women).[2 16]

Given the high amount of analysis to be made on often sparse tumour material, strong recommendations on tissue preservation for biomarker studies have been outlined by several guidelines.[2] It is critical that pathology laboratories develop policies for integrating biomarker testing into their routine tissue-processing workflows to minimise the number of ancillary stains performed for the diagnosis and classification. The time point of molecular testing, right after pathology diagnosis as indicated by the pathologist (reflex testing) or only after additional claim by the treating clinician (bespoke testing), is currently a topic of debate and organised differently throughout centres.[17] Molecular testing initiated by the pathologist immediately after diagnosis of cancer (reflex testing) provides results in 5–10 working days, in contrast to bespoke testing requested by the oncologist or the multidisciplinary team only when the test is needed. Reflex testing has the advantages of a quicker molecular profiling for clinical decisions and a higher efficiency in the diagnostic process in the laboratory. However, it increases needed resources and potentially results in costly testing in patients without therapeutic consequence[18 19] (figure 1).

Testing of driver mutations can be performed by targeted sequencing, a combined sequencing and immunohistochemistry/immunofluorescence approach or next generation sequencing (NGS). *EGFR* and *BRAF* testing are conducted by DNA sequencing, while in several laboratories due to cost-effectiveness, *ALK* and *ROS1* testing are mostly performed by immunohistochemistry (IHC) and/or fluorescence in situ hybridisation (FISH). Currently, the approved method for PD-L1 testing is IHC.[20] NGS is rapidly emerging as an option for the delivery of multiplexed genomic testing in lung cancer, especially in academic centres. NGS testing potentially provides more data on genetic alterations than the treating clinicians would usually include in their decision-making. Alterations for which no treatment is available or for which treatment is available only through a clinical trial could therefore also be detected. Moreover, NGS approaches are becoming available for the identification of uncommon fusion genes involving *ALK* and *ROS1*, but experience of the clinical significance of these aberrations is still limited in the absence of IHC or FISH alterations.[17] NGS is still relatively costly and its use will depend on whether it is considered cost-effective compared with doing several single-gene tests (figure 2).

Liquid biopsies

Liquid biopsy is a broad term that refers to the analysis of biomarkers that can be isolated from body fluid of patients with cancer. However, the analysis of cell-free DNA (cfDNA) isolated from the plasma fraction of peripheral blood is the only approach that entered clinical practice so far.[21] In patients with advanced NSCLC, cfDNA testing can provide information on the presence of driver alterations at the time of therapy decision or on the mechanisms of acquired resistance to TKI in those with driver genetic alterations. Indeed, liquid biopsy is the preferred approach for the assessment of the p.T790M *EGFR* variant in *EGFR*-mutant patients who progress after treatment with first-generation or second-generation TKI.[22] Additional tissue rebiopsy is usually reserved to patients whose results are negative at liquid biopsy testing. Evidence from trials with third-generation TKI in *EGFR* T790M-mutant patients suggests that tissue and liquid biopsy might provide complementary information.[23 24] A negative liquid biopsy T790M test in patients with tumour positive for T790M is associated with a better prognosis compared with the prognosis of patients with both tissue and tumour positive. This finding most likely reflects the correlation between cfDNA levels and tumour burden and/or aggressiveness of the disease—the higher the tumour load, the higher is the amount of cfDNA. On the other hand, patients with a positive blood T790M test and negative tissue have an intermediate outcome as these patients are likely to carry a heterogeneous expression of the T790M leading to a mixed response to third-generation TKI.[22 24]

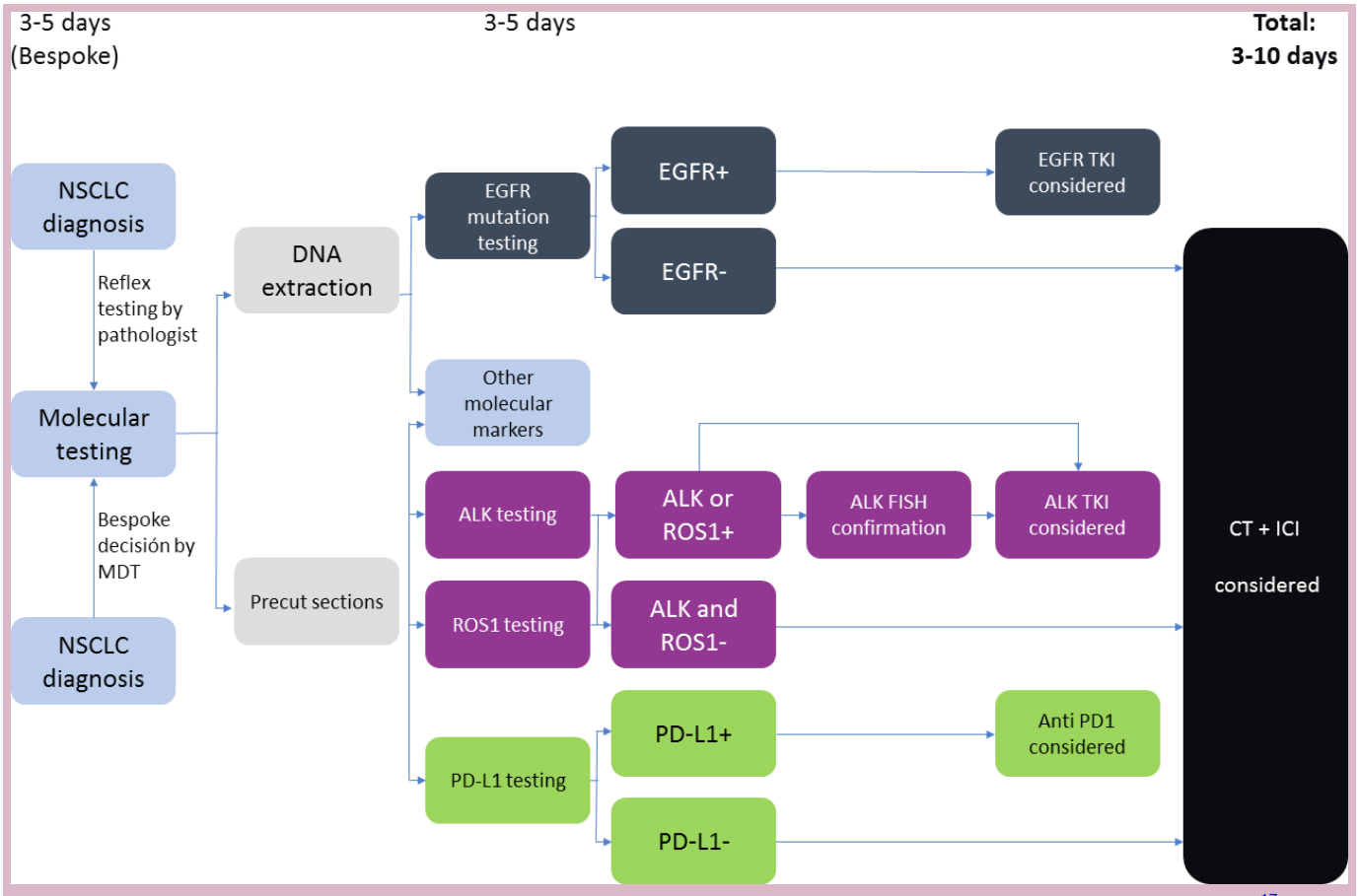

Figure 1 Molecular testing parallel algorithm without next generation sequencing (adapted from Kerr and López-Ríos[17]). ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridisation; ICI, immune checkpoint inhibitor; MDT, multidisciplinary team; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor

NGS-based analysis of liquid biopsy revealed that approximately 50% of T790M-positive resistant patients also carry additional genetic alterations.[25] The presence of multiple resistance mechanisms has been associated with resistance to treatment with third-generation TKI.[25–28] This highlights that the genetic background of *EGFR*-mutant lung cancer might significantly change over time. In fact, the molecular complexity of the disease is likely to increase after each line of treatment because of the emergence of multiple clones of resistant cells. In consequence, liquid biopsy testing with NGS-based techniques might better recapitulate the genetic landscape of the disease compared with tissue biopsy in resistant patients.[29]

The emergence of resistance against *EGFR* targeting TKI in precision treatment of NSCLC

Patients with NSCLC who harbour mutations in the *EGFR* gene are candidates to receive treatment with TKI. After a mean time of treatment of 10–14 months, patients usually stop responding to first-generation and second-generation TKI and in consequence show tumour progression which might be systemic, oligoprogression or restricted to the central nervous system (CNS).[4] Mechanisms involved in resistance development have been extensively studied not only for first-generation or second-generation inhibitors but also for third-generation *EGFR* TKI.[30]

Resistance against first-generation and second-generation TKI

Emergence of resistance to first-generation and second-generation TKI may be due to alterations in the target gene *EGFR* or to the acquisition of alterations in other genes. The most frequent resistance mechanism is the acquisition of the mutation affecting the amino acid threonine located at position 790 of the *EGFR* protein.[31 32] This mutation increases the binding of the ATP molecule, compared with the inhibitor and therefore compensates the inhibition of the *EGFR*. The mutation p.T790M is found in more than 50% of *EGFR*-mutated patients at the time of progression. It may be detected alone or simultaneously to the amplification of the *EGFR* gene, or to other resistance mechanisms. Other mutations affecting the *EGFR* gene have also been found in a limited number of patients, such as *EGFR* p.L747S, p.D761Y and p.T854A.[33–35] Mechanisms of resistance involving genes different from *EGFR* have been also detected, although to a lesser extent. Among these the most recurrently found are: *MET* and human epidermal growth factor

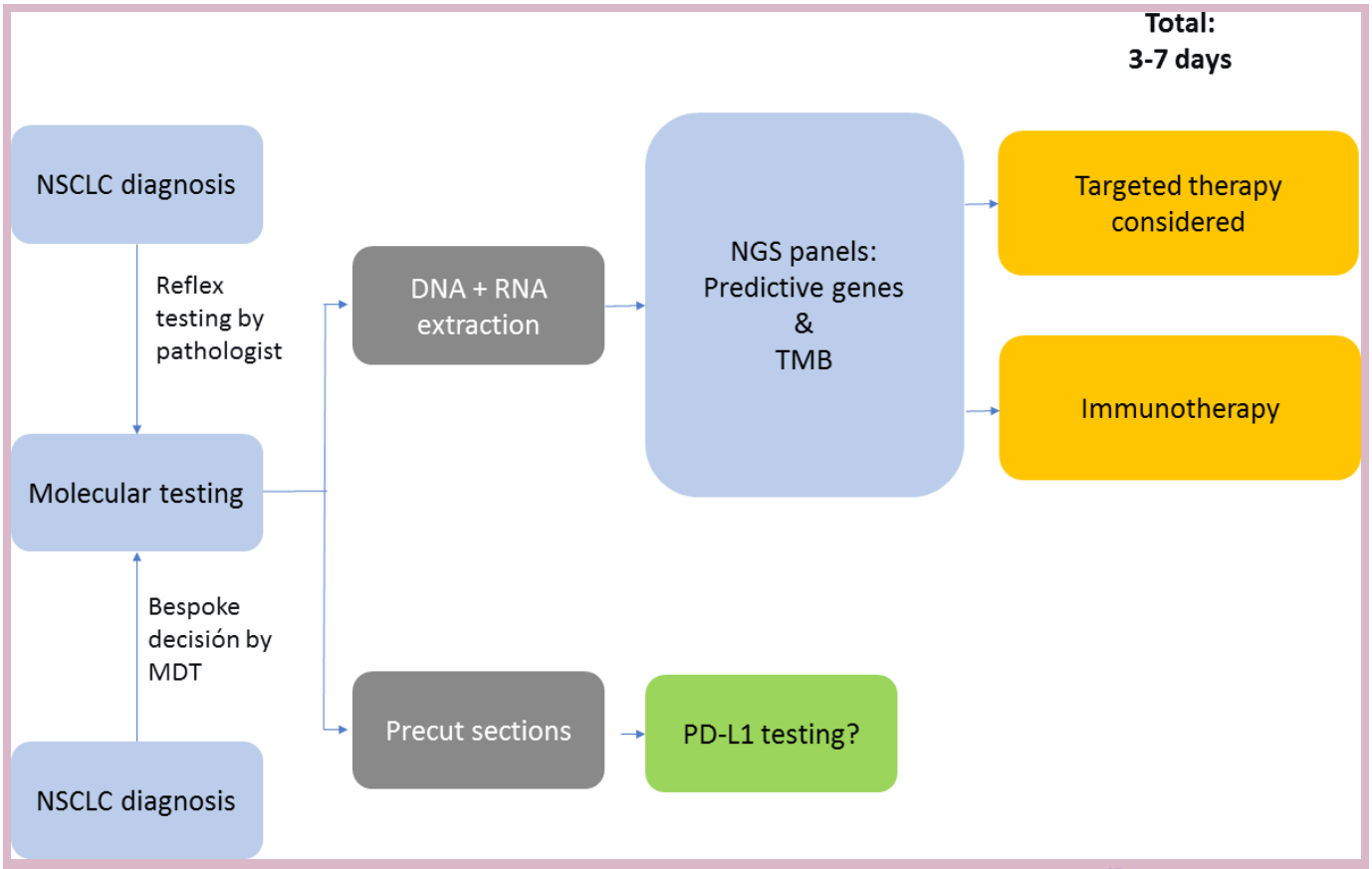

Figure 2 Molecular testing algorithm when NGS is commonplace (adapted from Kerr and López-Rios[17]). MDT, multidisciplinary team; NSCLC, non-small cell lung cancer; NGS, next generation sequencing; PD-L1, programmed death-ligand 1; TMB, tumour mutational burden.

receptor 2 (*HER2*) amplification, *PIK3CA* and *BRAF* mutations and small cell histologic transformation.[36 37] More recently, *CDKN2A* loss, *MTOR* mutations and *FGFR3* alterations including translocations have also been implicated in mediating *EGFR* TKI resistance.[38 39] The specific third-generation *EGFR* TKI osimertinib that targets the mutation p.T790M has been developed and demonstrates high efficacy in most patients.[40]

Resistance against third-generation TKI

Third-generation TKI show even higher effectiveness in *EGFR*-mutant patients with a median response rate of 80% in untreated patients, including those bearing the p.T790M mutation.[41] However, resistance development also eventually occurs, although with 18.9 months significantly later than with first-generation and second-generation TKI.[41] The mechanisms of resistance, as with first-generation and second-generation inhibitors, include *EGFR*-dependent and *EGFR*-independent mechanisms.[40] Among the *EGFR*-dependent resistance mechanisms, mutations affecting the binding of the drug such as the p.C797S or the p.E709K, p.L692V and p.L798I mutations have been observed. Of note, regarding resistance to third-generation TKI, it seems that the appearance of resistance mutations, depending on the location—either in cis or trans—has different implications: if C797S and p.T790M mutations are in trans, cells will be resistant to third-generation TKI but remain sensitive to a combination of first-generation and third-generation *EGFR*-TKIs.[42] Tumours with C797S and p.T790M mutations in cis are greatly resistant to *EGFR*-TKI and their combinations.[42] If C797S mutation develops in T790 wild-type cells after administration of third-generation *EGFR*-TKI, the cells retain their sensitivity to first-generation TKI, underscoring the preclinical evidence of TKI sequencing.[42] Among *EGFR*-independent mechanisms of resistance to third-generation TKI, MET amplification as well as amplification of genes involving receptors (such as Insulin-like growth factor 1 receptor (*IGF1R*)) and mutations or amplifications of genes involved in the signalling cascades (such as *BRAF*) have been reported.[43]

Molecular biomarkers for response to ICI therapy

Increasing PD-L1 levels, tumour mutational burden (TMB), CD8 T cell infiltration have been associated with increasing benefit from ICI. However, patient selection by predictive biomarkers remains controversial as no absolute predictive markers reliably differentiating between responding and not responding patients were identified yet.[44 45]

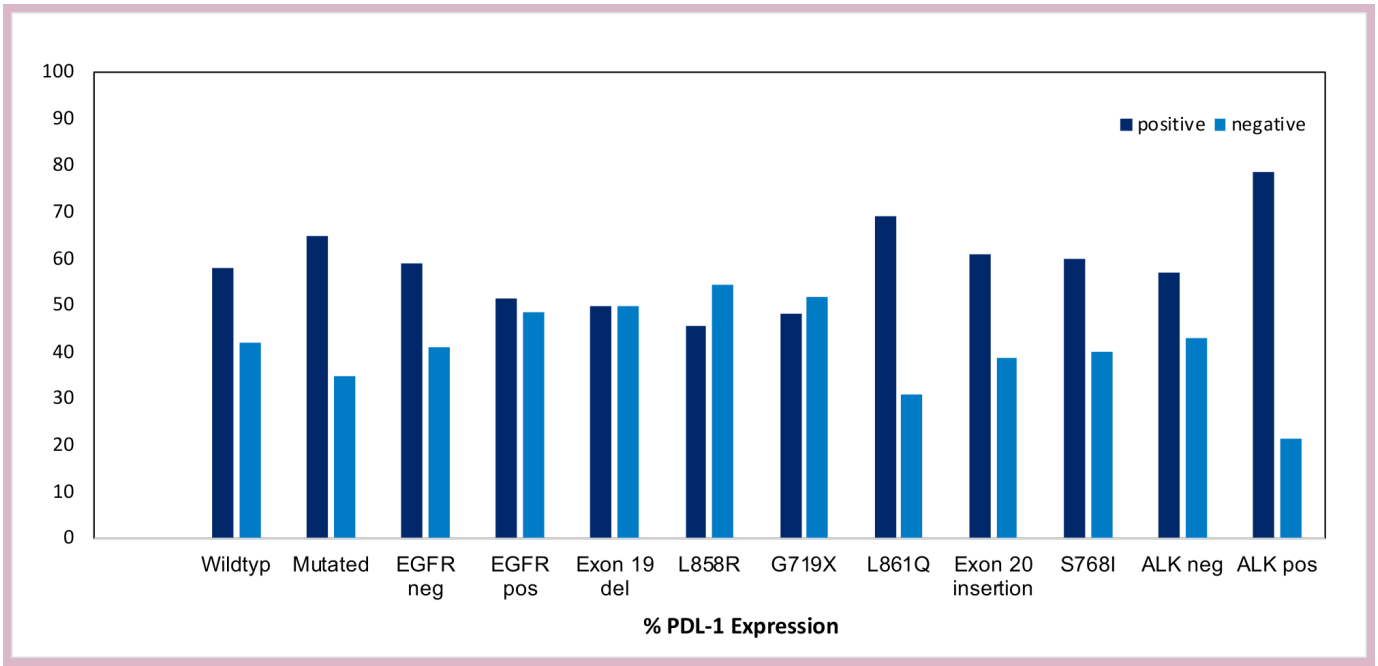

Figure 3 Relationship of programmed death-ligand 1 (PD-L1) expression with oncogene alterations.

Expression of PD-L1

PD-L1 expressed by the tumour cells can be induced not only by the oncogenic pathways, which induce tumour development, but also by the immune response itself, especially after induction by the interferon-gamma pathway.[46] Thus, in case of immune attack, the tumour cell defends itself and upregulates PD-L1. Accordingly, PD-L1 expression on tumour cells was extensively studied as a predictive marker for PD-1 axis targeting ICI. The expression by the tumour cells is heterogenous with areas of expression alternated with areas of absent expression. In line, cut-off values between 1% and 50% of PD-L1 expression tumour cells were investigated as predictive marker for PD-1 axis targeting ICI.[47 48] Analysis of biopsies is challenging in this context as samples could be rated as false negative, potentially inhibiting an effective treatment option.

Furthermore, PD-L1 expression has an imperfect negative predictive value, as also a PD-L1 negative tumour can present with clinically relevant response. In addition, PD-L1 analysis might be challenging due to the expression of PD-L1 not only of tumour cells but also by cells of the microenvironment including macrophages and T cells. In addition to this variability in location, PD-L1 expression was shown to also vary over time, as treatments including chemotherapy and radiotherapy can impact the expression level.[49]

Importantly, oncogenes were shown to not only impact on tumour growth but also on the expression of immunosuppressive molecules including PD-L1 (figure 3). Here,the presence of *ALK* translocation was shown to be associated with PD-L1 expression, while the presence of *EGFR* mutation is inversely correlated with PD-L1 expression.[50–52] In patients harbouring an *EGFR* mutation, those with rare *EGFR* mutations and not harbouring the specific T790M mutation are more likely to express PD-L1 on the tumour cells.[50 53 54]

Tumour mutational burden

TMB was recently shown to be an important predictive marker for ICI response, as cancer entities with higher TMB like melanoma or smoking-associated NSCLC were shown to have higher response rates[55 56] (figure 4). The high TMB and the resulting high rate of pathological or foreign folded proteins is associated with a higher fraction of neo-epitopes potentially triggering an immune response. It is important that most responding patients have mainly clonal mutations, while non-responders have mutations present in tumour subclones, allowing immune evasion and lower response to ICI.[57] Currently, the most suitable cut-off value to define 'high' and 'low' TMB as well as a uniformed method for detection still need to be defined. Recently, patients with NSCLC with a high TMB, defined as ≥10 mutations per megabase using the FoundationOne CDx assay, treated with a combination of the ICI nivolumab and ipilimumab, showed improved progression-free survival (PFS) compared with those treated with conventional chemotherapy in the first-line setting.[58]

Infiltration by CD8 lymphocytes and transcriptomic signature

Another potential biomarker is CD8+ T cell infiltration, which defines the notion of 'hot' tumour and 'cold' tumour based on the density of tumour-infiltrating lymphocytes (TIL). Particularly in metastatic melanoma, CD8+ T cell infiltration is associated with better response to immunotherapy.[59] In lung cancer, T cell infiltrate and tertiary lymphoid structures were reported to be associated with a good outcome in chemotherapy patients.[60] Beyond the presence of T cells, the analysis of the transcriptomic

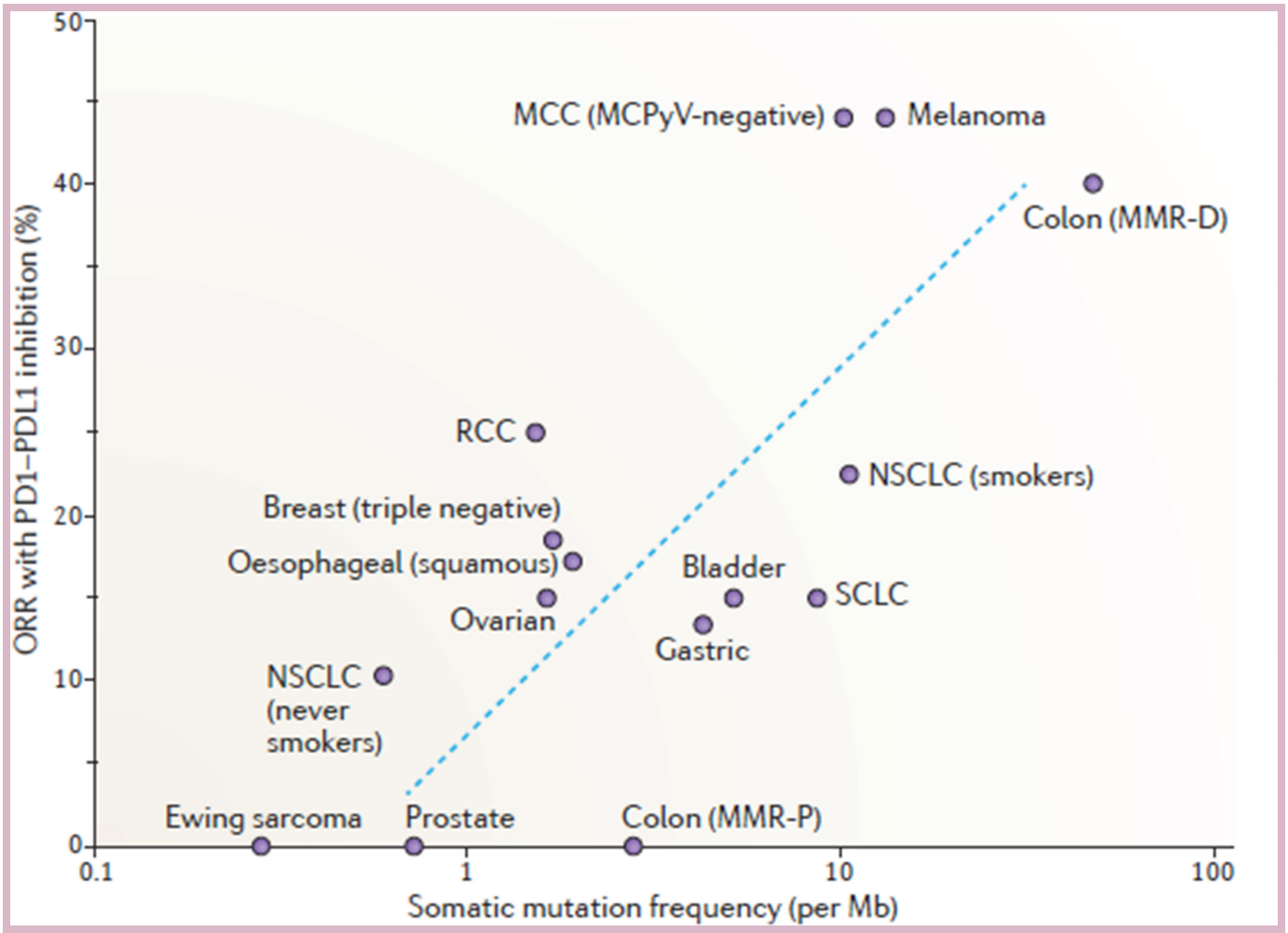

Figure 4 Relationship between mutational load and response to immunotherapies targeting PD-1/PD-L1.[56] Reprinted by permission from Springer Nature. Yarchoan M, Johnson III BA, Lutz ER *et al*. Targeting neoantigens to augment antitumour immunity. *Nat Rev Cancer* 2017. NSCLC, non-small cell lung carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma; SCLC, small cell lung carcinoma.

signature of the whole tumour and the deconvolution of the signals allow to identify transcriptomic signatures of activated T cells. Strong expression of effector T cell and interferon gene signatures was shown to be associated with a better response to immunotherapies targeting the PD-1/PD-L1 checkpoint in patients with NSCLC.[61]

The association of higher CD8+ TIL density and non-synonymous mutation burden was verified in a small cohort of patients with oncogene-addicted NSCLC.[51] However, in general, the *EGFR*-mutated NSCLC harbour a much less inflamed tumour microenvironment compared with *EGFR* wild-type cancers.[62] This might be induced by the expression of the immunosuppressive molecule CD73 in *EGFR*-mutated NSCLC.[63] Indeed, given that most patients with *EGFR*-mutated NSCLC are never smokers, the rate of passenger mutations is lower and in consequence the TMB and the immunogenicity.

Tumour molecular alterations

Certain molecular alterations affecting the tumour cell such as the β-catenin and phosphatase and tensin homologue (PTEN) pathways have been recently linked to response to immunotherapy in melanoma. When the β-catenin pathway is activated in patients with melanoma, there is little infiltration of CD8+ T cells, whereas this infiltration is important when the β-catenin pathway is not activated.[64] Similarly, the loss of anti-tumour protein PTEN is associated with a lack of response to immunotherapy in patients with melanoma.[65] However, currently no data exists on the relevance of these pathways in oncogene-addicted NSCLC.

Clinical efficiency of ICI in patients with oncogene-addicted NSCLC

Beyond the already approved indications in the first-line and second-line setting of advanced NSCLC, only relatively little data is available regarding anti-PD-1 and anti-PD-L1 efficacy in patients with oncogene-addicted NSCLC. Most of the available data is for patients harbouring an *EGFR* mutation or *ALK* rearrangement, while data for the other even more rare NSCLC subtypes is mostly lacking.

The phase 1 study CA209-012 of PD-1 inhibitor nivolumab (n=52) as first-line treatment in patients with metastatic NSCLC reported an impaired overall efficacy in patients with *EGFR* mutation patients as compared with patients with *EGFR* wild-type NSCLC. The overall response rate (ORR) was only 14% in patients with *EGFR* mutation (ie, one of seven) versus 30% in patients with wild-type NSCLC (ie, nine of 30). Further, the PFS at 24 weeks was only 14% in patients with *EGFR* mutation versus 51% in wild-type NSCLC, respectively.[9]

Study CA209-153 is a phase 3b/4 safety trial of nivolumab in patients with advanced or metastatic squamous or non-squamous NSCLC who received at least one prior line. The *EGFR* mutation status was available in 549 patients and 103 patients presented with an activating *EGFR* mutation. However, partial response rate was 11% (n=55 patients available for response assessment) in the *EGFR*-mutated cohort compared with 16% (n=300 patient available for response assessment) in the *EGFR* wild-type cohort.[10]

The phase 1 KEYNOTE-001 trial found that PD-1 inhibitor pembrolizumab provides promising long-term OS benefit with a manageable safety profile for PD-L1-expressing treatment-naive advanced NSCLC, with greatest efficacy observed in patients with PD-L1 tumour proportion score (TPS) ≥50%.[66] The best objective response rate based on mutation status was 16% in patients with *EGFR* mutation (n=19) versus 37% without mutation (n=89) and 60% in patients (n=5) with unknown *EGFR* status. Across all PD-L1 subgroups, patients with *EGFR*-mutant had a lower objective response rate than patients with *EGFR* wild-type tumour.[11] In the 3-year follow-up of the KEYNOTE-001 trial, the median overall survival (OS) in patients with *EGFR* mutation was 6 months (95% CI 4.4 to 8.8) compared with 12 months (95% CI 9.2 to 14.3) in wild-type patients.[67] A recent phase 2 trial investigated pembrolizumab in TKI-naive patients with PD-L1 positive *EGFR*-mutant NSCLC. No responses were observed in the first 11 included patients and the trial had to be discontinued.[68]

The phase 2 BIRCH study on PD-L1 inhibitor atezolizumab[12] showed higher response rates in patients with higher expression of PD-L1 (on tumour cells (TC) ≥50%) (ORR 35% vs 26% (for all treated patients)). Overall, 13 patients with activating *EGFR* mutation were included and the ORR was 31% for mutant *EGFR* versus 23% for wild-type EGFR patients (n=103).

The ImPOWER 150 study compared the use of bevacizumab plus atezolizumab plus carboplatin plus paclitaxel versus carboplatin plus paclitaxel plus bevacizumab.[13] Eighty patients (35 in the intervention and 45 in the control arm) with *EGFR* mutation and 34 patients (13 in the intervention and 21 in the control arm) with *ALK* rearrangement were included after progression on established TKI treatment. PFS was also longer in those patients with oncogene addicted NSCLC in the intervention arm containing atezolizumab compared with the standard arm (median, 9.7 months vs 6.1 months; unstratified HR, 0.59; 95% CI 0.37 to 0.94)

	Cohort 1, *EGFR*+/*ALK*+	
	<25%†	≥25%†‡
Patients evaluable for response per independent central review§		
Total	28	74
Confirmed objective response	1 (3·6%, 0·1–18·3)	9 (12·2%, 5·7–21·8)
Confirmed disease control at 6 months¶	2 (7·1%, 0·9–23·5)	15 (20·3%, 11·8–31·2)
Best overall response		
Complete response	0	0
Partial response	1 (4%)	9 (12%)
Stable disease‖	5 (18%)	23 (31%)
Progressive disease	22 (79%)	40 (54%)
Not evaluable	0	2 (3%)
TTR, months	1·8 (1·8–1·8)	1·8 (1·8–1·8)
DoR, months	7·9 (7·9–7·9)	7·4 (5·6–9·2)
Full analysis set**		
Total	30	77
PFS, months	1·9 (1·8–1·9)	1·9 (1·8–3·6)
OS, months	9·9 (4·2–13·0)	13·3 (8·1–NC)
OS at 1 year	40·0% (22·1–57·4)	54·8% (41·5–66·3)
OS follow-up, months	8·2 (3·0–13·3)	6·5 (2·5–10·9)

Figure 5 Response after durvalumab treatment in cohort 1 of the ATLANTIC trial (*EGFR*+/*ALK*+).[14] Reprinted with permission from Elsevier. DOR, duration of response; OS, overall survival; PFS, progression-free survival; TTR, time to response.

ATLANTIC is a phase 2, open-label, single-arm trial studying the efficacy of durvalumab, a PD-L1 inhibitor, in pretreated NSCLC including 111 patients with *EGFR* or *ALK* alteration.[14] Eligible patients had advanced NSCLC with disease progression following at least two previous systemic regimens, including platinum-based chemotherapy. Patients with *EGFR* or *ALK* alteration had received standard treatment with TKI before. Among the 111 oncogene-addicted patients, 77 presented with PD-L1 expression in at least 25% of tumour cells. The objective response rate was 12.2% (95% CI 5.7 to 21.8) in the oncogene-addicted patients with PD-L1 expression >25% of tumour cells, while patients with <25% PD-L1 expression the objective response rate was only 3.6% (95% CI 0.1 to 18.3). PFS was not different according to PD-L1 expression in the *EGFR* or *ALK* altered patients (1.9 months). In summary, the proportions of patients who achieved a response were generally lower in patients with *EGFR* or *ALK* positive NSCLC than in those with *EGFR* negative and *ALK* negative NSCLC and higher PD-L1 expression appears to enrich for response. The figure 5 shows response after durvalumab treatment in cohort 1 of the ATLANTIC trial (*EGFR*+/*ALK*+)

A recent systematic review and meta-analysis of five randomised trials comparing ICI (nivolumab, pembrolizumab and atezolizumab) versus docetaxel in the second-line setting after chemotherapy showed an OS benefit

Table 1 Anti-PD-1 and anti-PD-L1 efficacy in patients with wild-type NSCLC versus patients with *EGFR*-mutated NSCLC

Study	Treatment	*EGFR*-mutated n (%)	HR OS wild-type versus mutated patients who received anti-PD-1 or PD-L1
Check Mate 057[44]	Nivolumab versus docetaxel	82 (14%)	0.66 (0.51–0.85) versus 1.18 (0.45–2.07)
KEYNOTE-010[82]	Pembrolizumab versus docetaxel	86 (8%)	0.66 (0.55–0.79) versus 0.88 (0.45–1.72)
OAK[83]	Atezolizumab versus docetaxel	85 (10%)	0.69 (0.57–0.83) versus 1.24 (0.71–2.18)
POPLAR[61]	Atezolizumab versus docetaxel	18 (6%)	0.70 (0.47–1.04) versus 0.99 (0.29–3.40)
ImPOWER 150[13]	Atezolizumab plus bevacizumab and chemotherapy versuschemotherapy plus bevacizumab	80 (10%)	0.62 (0.52–0.74) versus 0.41 (0.22–0.78)

NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

for *EGFR* wild-type NSCLC with an impressive HR of 0.67 (p<0.001) for ICI compared with chemotherapy.[8] However, in contrast, no OS advantage was observed for patients with *EGFR*-mutant NSCLC, although the small sample size needs to be considered (HR of 1.11, p=0.54). Only 12% (n=271) of the included patients indeed presented with an *EGFR* mutation. The major limitation of the study is that *EGFR* mutation was not determined by centralised testing and in 764 patients (25%) *EGFR* status was not assessed. The different types of mutations are also unknown.

Table 1 gives an overview on efficacy of anti-PD-1 and anti-PD-L1 in patients with wild-type NSCLC versus patients with EGFR-mutated NSCLC.

The retrospective multicenter Immunotarget Cohort study reviewed data on the efficacy of ICI in 527 patients with stage IV NSCLC harbouring various activating molecular alterations including *KRAS* (n=252), *EGFR* (n=110), *BRAF* (n=38), *MET* (n=36), *HER2* (n=23), *ALK* (n=18), *RET* (n=14), *ROS1* (n=5) and multiple drivers (n=31).[7] Outcomes by molecular subtypes are shown in table 2. Overall, *EGFR*-mutant patients presented with a shorter PFS after ICI-based therapy compared with *KRAS*-mutant patients (p<0.001). The *EGFR* p.T790M mutation was associated with a shorter PFS than other *EGFR* mutations (p=0.0001). Among patients with *MET* alterations, exon 14 mutations were shown to present with the highest response rate to ICI. Also, among patients harbouring an oncogene alteration, smoking status (p=0.003) and PD-L1 expression (p=0.02) were associated with PFS.

Radiological methods for response evaluation during ICI treatment in NSCLC

Response Evaluation Criteria in Solid Tumours (RECIST) and immune-related response criteria (irRC) are size-based response assessment methods. However, during ICI treatment, lesions can initially increase in size due to an influx of immune cells. When subsequent radiological follow-up shows a decrease in tumour size after initial increase in size or even lesion frequency, this pattern of response is called 'pseudoprogression'. It is associated with a favourable response to immunotherapy. However, early during treatment pseudoprogression cannot be radiologically discriminated from tumour progression. The resolution limitation of CT, ranging typically around 1 mm,[69] can even cause the appearance of 'new

Table 2 Immune checkpoint inhibitor efficacy outcomes in various molecular alterations

		Best response (%)			PFS			OS
Driver	n	CR/PR	SD	PD	Median (months)	6 month PFS (%)	1 year PFS (%)	Median (months)
BRAF	38	28.1	28.1	43.8	3	35	19	13.6
KRAS	252	27.2	23.1	49.8	3.2	39	26	13.5
ROS1	5	20	0	80	NA	NA	NA	NA
MET	36	15.6	34.4	50	3.4	33	23	18.4
EGFR	110	11	18	71	2	16	6	8.8
HER2	23	9.5	28.6	61.9	3.5	34	17	10
RET	14	7.1	21.4	71.4	2.2	16	8	6.5
ALK	18	0	21.4	78.6	2.1	16	8	17

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CR, complete response; NA, not available; PFS, progression-free survival; PR, partial response.

Category	RECIST v1.1	irRC
Measurement of tumor burden	Unidimensional	Bidimensional
Target lesions	Maximum, 5*	Maximum, 15 index lesions
New lesion	Results in progressive disease at first appearance	Up to 10 new visceral lesions and 5 cutaneous lesions may be added to the sum of the products of the two largest perpendicular diameters of all index lesions at any time point
Complete response	Disappearance of all target and nontarget lesions Nodes must regress to < 10 mm short axis No new lesions Confirmation required	
Partial response	≥ 30% decrease in tumor burden compared with baseline Confirmation required	≥ 50% decrease in tumor burden compared with baseline† Confirmation required
Progressive disease	≥ 20% + 5-mm absolute increase in tumor burden compared with nadir Appearance of new lesions or progression of nontarget lesions	≥ 25% increase in tumor burden compared with baseline, nadir, or reset baseline† New lesions added to tumor burden Confirmation required
Stable disease	Neither partial response nor progressive disease	

Abbreviations: irRC, immune-related response criteria; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.
*For the present analyses, the maximum number of target lesions was 10.
†If an increase in tumor burden is observed at the first scheduled assessment, the baseline is reset to the value observed at the first assessment.

Figure 6 Comparison of key differences in Response Evaluation Criteria in Solid Tumours (RECIST) V.1.1 and immune-related response criteria (irRC). Reprinted with permission from American Society of Clinical Oncology, Copyright 2016. All rights reserved.[70]

lesions' as a result of pseudoprogression. Lesions just below the resolution limitation of the CT can grow due to immune cell influx and become large enough to be visible on a CT. With RECIST, this would be classified as progressive disease, while with irRC, the diameters of the new lesion(s) are added to the sum of all diameters and when this sum remains below 20% increase as compared with the baseline value, the response will be classified as stable disease (figure 6). In melanoma, it was estimated that conventional RECIST underestimates the benefit of single agent PD-1 treatment with pembrolizumab in approximately 15% of patients and that the use of irRC better classifies patients according to survival benefit and prevents premature cessation of a potentially successful treatment.[70]

Positron emission tomography (PET)-CT using 18F-fluorodeoxyglucose (^{18}F-FDG) (FDG-PET) visualises and quantifies glucose metabolism of tumour lesions. Metabolic responses after chemotherapy have been associated with favourable outcome in terms of PFS and can precede size-based responses.[71 72] A FDG-PET study in patients with NSCLC treated with atezolizumab showed that FDG-PET 6 weeks after treatment initiation is able to classify patients according to survival benefit.[73] However, FDG-PET did not seem to outperform the predictive value of CT. This could be due to the nature of FDG-PET, not discriminating between metabolic activity of immune cells and tumour cells. After 6 weeks of PD-L1 directed treatment, it is likely that tumour FDG uptake is the result of a mixture of an increase in FDG metabolism due to influx of immune cells and a decrease due to tumour cell death, hampering response evaluation. Therefore, an earlier time point after treatment initiation aiming at quantifying the metabolic activity of the influx of immune cells and preceding tumour cell death might be a better discriminator of responders and non-responders.

The balance between the a priori probabilities of progression and pseudoprogression should guide treatment decision. For patients with molecularly driven NSCLC, response rates are generally low to very low and therefore progression according to RECIST and irRC is expected to represent real tumour progression in most cases and rarely pseudoprogression. In patients with molecularly driven NSCLC, RECIST-based response evaluation is expected to be the best discriminator between patients who derive benefit from PD-L1 directed therapy and those who do not. Treatment beyond progression is therefore currently not advised, as well as the use of irRC.

Sequence of treatments in molecularly mutated NSCLC: is there a place for ICI?

The introduction of mutation-specific TKI revolutionised the treatment of patients with NSCLC harbouring an oncogene addiction. However, at some point, resistance occurs in almost all patients. Durable responses can be observed in patients treated with ICI; however, the response in patients with oncogene-addicted NSLCC was shown to be impaired compared with wild-type patients.[8–11] To offer patients with oncogene addiction the chance of immune induced long-term control of their disease, new combinations are most certainly the only clinical possibility. Here, the ATLANTIC trial proposed that the quartet combination therapy could be a promising approach in patients' progression on all available generations of oncogene-specific TKI.[14] Given the potential negative impact of the oncogene on the activity of the inflammatory tumour microenvironment, the combination of TKI with ICI is of potential clinical interest. Certainly, side effects would increase as seen by the combination of ICI with TKI in other entities like melanoma.[74–77] However, in theory, the rapid antigen release through dying tumour cells by the TKI could enhance the inflammatory response.

First phase I trials combining ICI with *EGFR* mutation directed TKI show acceptable side effect profiles.[78–81] Several clinical trials investigating the combination of TKI with ICI are currently recruiting (eg, NCT02364609, NCT01454102, NCT01998126).

CONCLUSION

Lung cancer is becoming a more diverse disease with regard to management with a wide range of targets and treatment options. Recent clinical data on ICI in NSCLC harbouring activating mutations reviewed at the round-table discussion and summarised in this article shows overall low efficacy, although interpretations have to be drawn carefully due to the limited amount of data available. However, promising subgroups needing further clinical investigation were identified. For example, the clinical activity of durvalumab late line salvage therapy in patients with *EGFR*-mutated NSCLC showing PD-L1 expression in ≥25% of tumour cells is encouraging.[14] Here, the clinical challenge is to further understand the biological drivers of inflammation in NSCLC and to identify subgroups driving the benefit as well as defining the optimal treatment sequence with established TKI. In addition, further research is needed to address the heterogeneity of *EGFR*-mutant lung cancer and to assess whether changes in the biology of the disease following different lines of therapy might increase the sensitivity to ICI.

To offer patients with oncogene addiction the chance of immune induced long-term control of their disease, new combinations are probably the only clinical possibility. A combination strategy as recently analysed in the ImPOWER 150 study[13] including platin-based chemotherapy, bevacizumab and atezolizumab showed a clinically meaningful efficacy also in patients with oncogene-addicted NSCLC progressing on all available generations of TKI. However, several other trials reported no significant increase in response rate or PFS in patients with oncogene-addicted NSCLC.[9–11 67] Given the potential negative impact of the oncogene on the activity of the inflammatory tumour microenvironment, the combination of TKI with ICI is of potential clinical interest. Several clinical trials investigating the combination of TKI with ICI are currently recruiting (eg, NCT02364609, NCT01454102, NCT01998126). Due to the overall low clinical efficiency of ICI in patients with oncogene-addicted NSCLC based on the so far available data from prospective clinical trials, the round-table panel concluded that ICI should currently only be considered after exhaustion of targeted therapies including standard and salvage chemotherapies in these patients.

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