Immunotherapy: a new standard of care in thoracic malignancies?

A summary of the European Respiratory Society research seminar of the Thoracic Oncology Assembly

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ABSTRACT In May 2017, the second European Respiratory Society research seminar of the Thoracic Oncology Assembly entitled "Immunotherapy, a new standard of care in thoracic malignancies?" was held in Paris, France. This seminar provided an opportunity to review the basis of antitumour immunity and to explain how immune checkpoint inhibitors (ICIs) work. The main therapeutic trials that have resulted in marketing authorisations for use of ICIs in lung cancer were reported. A particular focus was on the toxicity of these new molecules in relation to their immune-related adverse events. The need for biological selection, currently based on immunohistochemistry testing to identify the tumour expression of programmed death ligand (PD-L)1, was stressed, as well as the need to harmonise PD-L1 testing and techniques. Finally, sessions were dedicated to the combination of ICIs and radiotherapy and the place of ICIs in nonsmall cell lung cancer with oncogenic addictions. Finally, an important presentation was dedicated to the future of antitumour vaccination and of all ongoing trials in thoracic oncology.

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Introduction

Lung cancer, causing 1.6 million annual deaths worldwide [1] is a major health problem. Respiratory medicine specialists play an ever-increasing role in the diagnosis, treatment and follow-up of patients suffering from lung cancer. In view of this, the European Respiratory Society (ERS) Thoracic Oncology Assembly officers designed an action plan in March 2010 which was strongly approved and supported by the ERS executive committee. The first ERS research seminar focusing on targeted therapies in lung cancer took place in Paris (France) on May 6–7, 2015. The aim of the research seminar was to promote exchange of knowledge and interaction between basic scientists and clinicians as well as between different research groups. 85 participants from around the world (Europe, Asia, Africa and North and South America) were present and contributed to making the research seminar a success. 2 years later, on May 4–5, 2017, the second meeting took place in Paris and was entitled "Immunotherapy, a new standard of care in thoracic malignancies?"

To enlarge the scope of the research seminar, four young European pulmonologists attending the sessions were designated to report and summarise the different presentations (table 1). The summaries were compiled into a single document that was reviewed by each speaker in order to validate the following text.

Immunotherapy, the fifth pillar of lung cancer treatment

In 2013, *Science* branded immunotherapy as the breakthrough of the year thanks to the results of anti-cytotoxic T lymphocyte-associated antigen (CTLA)4 therapy in melanoma [2]. Different immune checkpoint inhibitors (ICIs) such as anti-programmed death (PD)-1 or anti-programmed death ligand (PD-L)1 antibodies have since been developed and tested in a variety of cancers (head and neck, lung, bladder, renal and Hodgkin's lymphoma), often showing impressive results and prompting the US Food and Drug Administration and European Medicines Agency to approve these treatments rapidly.

A new fifth pillar has been added for the treatment of lung cancer after surgery, radiotherapy, chemotherapy and targeted therapy. The immunotherapy pillar is unique as it has created a new paradigm, the aim of which is not to target the cancer cells directly, but rather the tumour microenvironment, and especially its immune components. With this change in paradigm, immunotherapy has thus resulted in a novel approach in all areas of cancer, including new mechanisms of tumour escape through immune escape, new original biomarkers in order to anticipate responders, new schemes of treatment, new tumour evaluation methods (*i.e.* iRECIST [3]), new toxicities (*i.e.* immune-related adverse events) and new mechanisms of action of the treatment itself. The T-cell is a complex cell expressing a number of both activator and inhibitory signals, creating many different possibilities of modulating the immune response. It is predicted that the number of trials testing immunotherapy will grow in an exponential fashion, creating a paradox where there will be more drugs and drug combinations than patients to treat, underlining the importance of anticipating optimal treatment regimens. In lung cancer alone, at the date of the ERS seminar, >40 studies were investigating immunotherapy, often in association with one of the other pillars of cancer treatment, such as radiotherapy or chemotherapy.

Cancer immunosurveillance has long been a subject of controversy. It has now been demonstrated [4, 5] that tumours develop in mice after the abrogation of their natural immunity. This phenomenon has also

TABLE 1 Speakers and titles of presentations

Franck Pages (Paris, France)	From ineffective tumour response to immunomodulation in lung cancer
Ming Tsao (Toronto, Canada)	How to evaluate the immune response in the tissue
Frances Shepherd (Toronto, Canada)	Unresolved issues in the use of checkpoint inhibitors in NSCLC
Hasna Bouchaab (Lausanne, Switzerland)	Toxicity of checkpoint inhibitors
Marina Garassino (Milan, Italy)	Check-point inhibitors in advanced non-small cell lung cancer
Jacques Cadranel (Paris, France)	Is there a place for ICIs in the context of oncogenic addiction?
Joachim G.J.V. Aerts (Rotterdam, the Netherlands)	Vaccination in non-small cell lung cancer
Julien Mazières (Toulouse, France)	Check-point inhibitors in peri-operative non-small cell lung cancer strategy
Michele Mondini (Villejuif, France)	Rationale for combined immune-, chemo- and radiotherapy
Thierry Berghmans (Brussels, Belgium)	Current clinical trials

NSCLC: nonsmall cell lung cancer; ICIs: immune checkpoint inhibitors.

been observed in immunosuppressed humans [6]. After the initial attack, an equilibrium phase appears, with mature dendritic cells (DCs), natural killer (NK) cells producing interferon-γ, $CD8^+$ T-cells or T-helper type 1 $CD4^+$ T-cells beneficial to the immune response. The tumour tissue is infiltrated by innate immunity cells, but also adaptive immunity cells, which can be found in the tumour bed and in tertiary lymphoid structures. The immune escape in lung cancer is caused first by the tumour cells themselves, capable of downregulating major histocompatibility complex (MHC) class 1, overexpressing PD-L1 or human leukocyte antigen-G and producing interleukin-10 or transforming growth factor (TGF)-β. Secondly, the tumour microenvironment can express immunosuppressive molecules (vascular endothelial growth factor, hypoxia-inducible factor-1 and TGF-β), and finally, some immune cells have negative effects, such as immature DCs or M2 macrophages. Conversely, the tumour cells create a chronic stimulation of the immune system, resulting in worsening immune response by the exhaustion of effector T-lymphocytes. They become less cytotoxic, less replicative, do not respond to cytokines, decrease expression of activating signals and express inhibitory signals such as PD-L1. This causes a functional disconnection between immune cells and tumour cells, resulting in the passage from equilibrium to tumour escape. However, this state is not a definite one and the equilibrium phase can be restored by ICIs.

The role of ICIs in immune response modulation requires an in-depth understanding of the regulatory mechanisms of T-cell activation. The definition of T-cell co-stimulation continues to evolve through the identification of new co-stimulatory and co-inhibitory receptors. The quality and amplitude of a T-cell response are regulated by a balance of activating and inhibitory signals. For example, negative co-stimulation, also called "co-inhibition" helps to shut down an immune response, in order to prevent damage to healthy tissues. PD-1, CTLA-4 and LAG-3 are the examples of such co-inhibitory "checkpoint" molecules which can limit, or "check" an ongoing immune response. However, sometimes cancer cells make use of these checkpoint molecules to divert certain immune-checkpoint pathways and evade antitumour immunity. PD-1 is a checkpoint protein on immune cells, which normally prevents T-cells from attacking. It acts by binding to PD-L1 on some of the normal and cancer cells. When PD-1 binds to PD-L1, it gives the T-cell the message not to attack the cell. Some cancer cells have large amounts of PD-L1, which helps them escape immune attack. ICIs, which are monoclonal antibodies that target either PD-1 or PD-L1 can obstruct this binding and elicit an immune response against cancer cells. Currently approved PD-1 (pembrolizumab, nivolumab) and PD-L1 inhibitors (atezolizumab, avelumab and durvalumab) enhance antitumour immunity and produce durable clinical responses in the treatment of different cancer types (bladder cancer, nonsmall cell lung cancer (NSCLC) and renal cancer) [7].

Immunotherapy in action in advanced NSCLC; a need for better patient selection

Table 2 offers a brief review of the major clinical trials testing ICIs and the results of the major clinical trials are summarised hereafter. Pembrolizumab has proven its efficacy in the first-line setting in advanced NSCLC in patients with PD-L1 expression >50% [8]. The response rate to first-line nivolumab in the subgroup with ⩾50% PD-L1 expression in Checkmate 026 [9] was lower (34%) than the objective response rate (ORR) to pembrolizumab in Keynote 024 [8] (44.8%), and the negative results observed in the CheckMate 026 study need to be elucidated. Nivolumab and atezolizumab have demonstrated their efficacy in the second-line setting in advanced NSCLC [10–12]. Durvalumab and pembrolizumab [13] demonstrated efficacy in the second-line setting in PD-L1-positive patients.

The importance of biomarkers capable of anticipating treatment response is central in the era of immunotherapy. Some will argue that immunotherapy is well tolerated in comparison to chemotherapy and has few toxicities, rendering the need for biomarkers of little use, especially considering that no biomarkers exist for use in chemotherapy. However, biomarkers could be used to avoid financial toxicity, limit adverse effects and help choose the most appropriate treatment for each patient. They can be used to anticipate the natural progression or aggressiveness of the tumour, anticipate the response to treatment, correlate with response during treatment or at the point of tumour assessment and predict immune-related adverse effects.

However, the possibility of precisely anticipating the immune response remains elusive. The tumour microenvironment presents a complex immune infiltrate composed of T- and B-cells, NK cells, macrophages and mast cells, among others. These cells can be stained using immunohistochemistry (IHC), which enables them to be located in the tumour microenvironment and their cell type to be determined. Since the development of anti-PD-1 and anti-PD-L1 antibodies for the treatment of advanced NSCLC, the PD-1/PD-L1 pathway has been in the limelight. PD-L1 can now be located precisely in various cells using IHC (T-cells, tumour cells or other immune cells).

In lung cancer, nivolumab, an anti-PD-1 fully humanised monoclonal antibody has shown its efficacy in the second-line setting compared to docetaxel in advanced NSCLC, and this effect was correlated with PD-L1 expression on the tumour cells measured by IHC, especially in the nonsquamous setting [10].

TABLE 2 Brief review of pivotal studies evaluating immune checkpoint inhibitors

	Treatment line	Treatment protocol	Population	PD-L1 testing	Primary end-point	Study outcome	Approval
Checkmate 026	First line, phase III	Nivolumab *versus* IC-PT-DC	Stage IV NSCLC	PD-L1 positive (⩾5%)	PFS	Negative	No
Keynote 024	First line, phase III	Pembrolizumab *versus* IC-PT-DC	Stage IV NSCLC	PD-L1 positive (>50%)	PFS	Positive	Yes, FDA
Keynote 021	First line, phase II	Carboplatin-pemetrexed-pembrolizumab *versus* carboplatin-pemetrexed	Advanced NSCLC	PD-L1 stratification	ORR	Positive	No
Checkmate 017	Second line, phase III	Nivolumab *versus* docetaxel	Advanced squamous NSCLC	No	OS	Positive	Yes
Checkmate 057	Second line, phase III	Nivolumab *versus* docetaxel	Advanced nonsquamous NSCLC	No	OS	Positive	Yes
Keynote 010	Second line, phase II–III	Pembrolizumab 2 mg·kg^{-1} *versus* pembrolizumab 10 mg·kg^{-1} *versus* docetaxel	Advanced NSCLC	No	OS and PFS	Positive	Yes
OAK	Second–third line, phase III	Atezolizumab *versus* docetaxel	Advanced NSCLC	PD-L1 stratification	OS	Positive	Yes
1108 study	Phase I/II	Durvalumab	Advanced NSCLC	No	Safety and tolerability	Positive	Yes
ATLANTIC study	Third line, phase II	Durvalumab	Advanced NSCLC	No	ORR	Positive	Yes

PD-L: programmed death ligand; IC-PT-DC: investigator's choice platinum-based doublet chemotherapy; NSCLC: nonsmall cell lung cancer; PFS: progression-free survival; FDA: US Food and Drug Administration; ORR: objective response rate; OS: overall survival.

Overall survival varied, depending on PD-L1 expression in tumour cells: 19.9 months for patients with >10% PD-L1 expression *versus* 9.9 months in patients with a PD-L1 expression <10%. Yet, nivolumab was approved in the second-line setting without PD-L1 expression testing needed. The Keynote 010 [13] and POPLAR [14] studies have found similar results as the Checkmate studies. They all suggest that PD-L1 expression in tumour cells needs to be evaluated in order to select patients that will have longer overall survival when treated with immunotherapy. However, the OAK phase III trial [12] showed that atezolizumab improved overall survival in previously treated NSCLC regardless of PD-L1 expression defined by IHC.

In NSCLC, five different antibody clones for IHC have been developed by different companies and each is associated with a different drug: nivolumab and 28-8 (Dako, Glostrup, Denmark), atezolizumab and SP142 (Ventana, Basel, Switzerland), pembrolizumab and 22C3 (Dako), durvalumab and SP263 (Ventana) and avulumab and 73-10 (Dako). Furthermore, they all have different characteristics, whether it is their origin (mouse or rabbit), the epitope location (extra- or intracellular), the auto-stainer or the detection system used. This complexity grows considering that the different IHC tests stain not only the tumour cells, but some stain the immune and inflammatory cells, and the cut-offs used in clinical trials range from 1% to 50%. Finally, three of these antibodies have been approved as IHC tests for clinical use (nivolumab and 28-8; pembrolizumab and 22C3; and atezolizumab and SP142).

Several studies have been launched to compare the different assays [15–19]. These have shown that the different antibodies used are similar except for the SP142, which seems to be less sensitive than the others to stain PD-L1 on the tumour cells, and presents a different staining pattern of the immune cells. The blueprint project [15] analytically compared four PD-L1 antibodies used in IHC assays in NSCLC and their clinical diagnostic paradigms or selected cut-offs. First, results show that for tumour cell staining, three assays (22C3, 28-8 and SP263) have a similar analytical performance, but the SP142 antibody, used in the OAK study, consistently labels fewer tumour cells. As for the immune cells, the staining is less precise than the staining of tumour cells. One can speculate that the proportion of patients in the OAK study with negative tumour and immune cells might have been less important if another antibody had been used.

Considering the difficulties in harmonising PD-L1 expression, its use has come under scrutiny, especially considering that only pembrolizumab requires PD-L1 expression to be prescribed. However, all studies evaluating anti-PD-1 or anti-PD-L1 antibodies have shown better efficacy with higher PD-L1 expression in IHC apart from the notable exception of the CheckMate 026 study [9] evaluating nivolumab in the first-line setting. For routine practice, samples need to be formalin fixed and paraffin embedded, primary and metastatic tumour sites are acceptable and archival and re-biopsy samples can be analysed [13]; however, all clinical trials have excluded the use of cytology samples for PD-L1 testing. Furthermore, PD-L1 expression is heterogeneous [20] within the tumour, so re-biopsy and multiple biopsies are crucial. Finally, appropriate pathologist training is important to obtain acceptable and reproducible results. Reliable testing requires experienced pathologists and knowledge of the clinical algorithms. Digital methods are currently being developed and may be used in the future for comprehensive quantitative profiling of the tumour immune microenvironment.

Other biomarkers are also currently being evaluated. The Immunoscore study was launched using the immune infiltrate as a biomarker to evaluate the quality of the immune response and its possible response to ICIs. In addition, gene signatures have been explored. The authors of CheckMate026 [9] focused on tumour mutation burden (TMB). However, this was a *post hoc* analysis that concerned ~60% of the total population. The patients that had a high TMB, defined by whole-exome sequencing showed a better progression-free survival with nivolumab: 9.7 months compared to 4.1 months in patients with low/medium TMB. However, there was no difference between the two groups regarding overall survival. Although potentially linked, it remains unclear whether TMB always correlates directly with the most effective response to immune checkpoint blockade.

Immune-related adverse events, a new category of drug toxicity

Immune-related adverse events (ir-AEs) can affect all organs and they are more frequent when ICIs are combined. The digestive system is mostly affected by anti-CTLA-4 (5–8%) therapy and less by PD-1/PD-L1 blockade (1–3%), both of which can lead to perforation. In contrast, the lung and the endocrine system are more frequently affected by PD-1/PD-L1 (10%) blockade than by anti-CTLA-4 (5%) therapy. The other, rare ir-AEs described are neurological autoimmune diseases, pancreatitis and renal and ocular toxicities.

Patients suspected to be suffering from toxicity should undergo thorough physical examination, a series of basic tests evaluating the heart (ECG) and blood (routine blood tests, inflammatory markers, heart

markers, thyroid-stimulating hormone, liver function and renal function), as well as a computed tomography scan in order to detect tumour progression, infection or pulmonary embolism, for example. More specialised investigations such as bronchoscopy, colonoscopy or skin biopsies can be performed, but should be discussed with the organ specialist first. Biopsies should be performed as often as possible as to document and prove the diagnosis of toxicity. The first step in the management of ir-AEs is assessing the severity of the toxicity. In case of grade 1 toxicity, treatment can be continued. In case of toxicities graded $\geqslant$3, immunotherapy should be discontinued. The treatment of ir-AEs must be initiated as soon as possible and is based on corticosteroids such as prednisone or prednisolone; the dose can reach 3 mg·kg^{-1} depending on the severity of the toxicity and should be maintained for $\geqslant$2 weeks followed by slow tapering. Steroids can be stopped when the patient has reached grade 1–2 toxicity. Toxicities need to be closely monitored and reported in patient charts. Some toxicities might require treatment combining immunosuppressive agents such as corticosteroids with other agents such as tumour necrosis factor-α antagonists and mycophenolate mofetil, depending on severity. Its use should always be discussed with the organ specialist first. Finally, the reintroduction of immunotherapy needs to be discussed with the patient and a multidisciplinary team. Usually, in case of grade 3 toxicity, ICIs will not be reintroduced. In all, cases, if ICIs are reintroduced, steroids should have been tapered down to a minimum (<10 mg·day^{-1}).

A summary of the main ir-AEs and proposed associated diagnostic tests is presented in table 3.

To improve the management of ir-AEs, patients should be educated as well as general practitioners, emergency-room doctors and intensivists. In all cases, the management of ir-AEs requires a multidisciplinary approach including the oncologist and organ specialists. The question of where the patient should be handled (at home, intensive care unit, *etc.*) is essential and should be discussed early in the management of toxicities. Finally, physicians should bear in mind that toxicity is not always the main diagnosis and that other more frequent diagnoses need to be discussed and eliminated before confirming toxicity. These include, but are not limited to tumour progression, infection, pulmonary embolism and metabolic disorders.

The emergence of immunotherapy in the setting of early stage NSCLC

ICIs have shown a clear benefit in the advanced setting of NSCLC; in addition, they are currently being investigated in the perioperative setting. Historically, the treatment of early-stage NSCLC has been surgery, but the 5-year survival for patients treated with surgery alone remains low, ranging from 23% (stage IIIA) to 67% (stage IA). Several randomised trials have shown that adjuvant chemotherapy after complete

TABLE 3 Immune checkpoint inhibitor toxicities

	Symptoms	Features	Suggested tests
Lung	Cough, dyspnoea, shortness of breath	COP, ground-glass opacities, interstitial, hypersensitivity, pneumonitis not otherwise specified	High-resolution CT scan, bronchoscopy, BAL, bronchial biopsies
Skin	Rash	Vitiligo, bullous pemphigoid	Dermatology consult, skin biopsies
Colon	Diarrhoea, abdominal pain	Colitis	Colonoscopy, biopsies, CT scan
Liver	Asymptomatic, fever, abdominal pain	Elevated liver enzymes	Liver function tests, ultrasound, CT scan, virology, liver biopsy
Endocrine	Fatigue, headache, tachycardia, weight gain or loss	Hyper- or hypothyroidism, hypophysitis	Hormonal tests (TSH, cortisol), anti-TPO and -TGO, brain MRI, thyroid ultrasound
Rare			
Neurological	Headache, fatigue	Autoimmune pancreatitis	Brain MRI
Pancreatic	Abdominal pain	Renal failure	Lipase, abdominal ultrasound or CT scan
Renal	Asymptomatic		Renal function tests, biopsy
Ocular	Modified vision		Ocular consult

COP: cryptogenic organising pneumonia; CT: computed tomography; BAL: bronchoalveolar lavage; TSH: thyroid-stimulating hormone; TPO: thyroperoxidase; TGO: thyroglobulin; MRI: magnetic resonance imaging.

resection in early-stage NSCLC improves survival. Therefore, combination cisplatin-based doublet adjuvant chemotherapy became a standard of care for stage II and IIIA patients. However, this approach reports a modest absolute overall survival benefit of 5.4% [21]. Likewise, other randomised trials have demonstrated that neo-adjuvant chemotherapy improves survival, and has become accepted in many countries [22]. Despite the established benefit of perioperative chemotherapy after curative surgery for NSCLC, 30–60% of patients will eventually relapse [23]. Furthermore, not all patients with early-stage disease are eligible or willing to undergo chemotherapy following complete surgical resection. These data highlight the need to further investigate novel therapies to improve the clinical outcomes of completely resected NSCLC. The efficacy of targeted therapies in early-stage NSCLC is less well established, despite their good toxicity profiles. Routine molecular profiling is not recommended in localised NSCLC, therefore few data on targeted therapies are available. Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) in wild-type patients with early-stage NSCLC have shown no efficacy in phase III trials [24, 25]. Although TKIs hold promise as adjuvant therapy in patients harbouring EGFR mutations [26], ongoing prospective phase III trials are needed to draw conclusions. Several trials assessing anti-angiogenic therapy efficacy are planned or underway in early-stage NSCLC. In analogy with the indication of bevacizumab in advanced NSCLC, ongoing clinical trials of anti-angiogenic therapy in this setting have focused on nonsquamous NSCLC [27]. For the moment, there are no data on its efficacy. Pazopanib, an oral anti-angiogenic drug used as adjuvant therapy in resected stage I patients failed to improve relapse-free survival [28]. In this context, ICIs, which can induce both cell-mediated immunity against proliferating cancer cells following complete resection and establish immunological memory that may guard against future recurrences through active immune surveillance are a particularly attractive therapeutic option [29], especially as early-stage disease may have fewer mechanisms of resistance to ICIs. Inhibition of the PD-1 checkpoint pathway by antibodies targeting either PD-1 or its ligand PD-L1 has been efficient in pretreated metastatic tumours and more recently in chemo-naive selected NSCLC patients (table 2). Moreover, immunotherapy is generally well tolerated. Perioperative immunotherapy can be undertaken in either the neoadjuvant or adjuvant setting. Nivolumab has been tested in the neoadjuvant setting in early-stage resectable NSCLC in a feasibility and safety clinical trial showing promising results, with the majority of patients benefitting from a major pathological response [30]. Therefore, neoadjuvant strategies may allow a better understanding of tumour response and biomarker predictive value and further randomised clinical trials assessing this approach are needed (table 4).

The combination of ICIs with radiotherapy is an actively growing field of investigation. Preclinical studies have shown that radiotherapy modulates tumour cell phenotypes leading to an increase in peptide pool production presented by MHC class I molecules, and in consequence enhancing cytotoxic T-cell recognition [31]. It has been shown that radiotherapy efficacy relies, at least in part, on $CD8^+$ T-cell activity [32], in particular when radiotherapy is combined with immunotherapies [33]. The activation tumour antigen specific T-cell immunity involves the secretion of HMGB1 alarmin protein on TLR4 expressed by DCs [34]. The secretion of HMGB1, together with other features, such as the release of ATP and the translocation of calreticulin, defines the so-called immunogenic cell death that can be elicited by radiotherapy and chemotherapy. The induction of an immune response by radiotherapy may explain the observation of clinical cases of an abscopal effect (antitumor effect on nonirradiated distant metastases), which has been reported in patients with metastatic cancer treated with radiotherapy. This phenomenon is

TABLE 4 Current clinical trials testing immune checkpoint inhibitors in early-stage nonsmall cell lung cancer (NSCLC)

	Phase	Treatment protocol	Population	Primary end-point	Status
Checkmate 816	III	Nivolumab and ipilimumab *versus* chemotherapy doublet	Early-stage NSCLC	MPR rate	Recruiting
IoNESCO	II	Durvalumab	Early-stage NSCLC	Rate of complete resection	Recruiting
BR31 NCI-IFCT trial	III	Durvalumab *versus* placebo	Early-stage NSCLC PD-L1 positive	DFS	Recruiting

MPR: major pathological response; PD-L: programmed death ligand; DFS: disease-free survival.

described more frequently when radiotherapy is performed in association with ICIs, and ICIs may thus enhance a general antitumour response [35].

Unfortunately, relapses after radiotherapy often occur, indicating that a radiotherapy-induced response is insufficient to maintain antitumour immunity. The microenvironment plays a role in tumour cell survival, as tumour-associated macrophages and myeloid-derived suppressor cells are increased after radiotherapy [36]. Also, radiotherapy induces up-regulation of PD-L1 [37]. In a retrospective analysis of NSCLC patients treated by pembrolizumab, previous radiotherapy was associated with better outcomes than patients who had not received previous radiotherapy [38]. These evidences establish the basis for clinical trials assessing combination therapy such as the PACIFIC trial [39] evaluating durvalumab or placebo after chemoradiotherapy in stage III NSCLC and showing prolonged progression-free survival (16.8 months *versus* 5.6 months) in favour of durvalumab.

Is there a place for ICIs in the context of oncogenic addiction?

Another question surrounding ICIs is their use in patients with oncogene addiction, especially EGFR mutation or anaplastic lymphoma kinase (ALK) rearrangement.

A meta-analysis assessing the role of ICIs as second-line therapy in EGFR-mutant advanced NSCLC found that they do not improve overall survival compared to docetaxel. Three studies included in this analysis compared ICIs (nivolumab, pembrolizumab and atezolizumab) to docetaxel and showed that ICIs significantly prolonged overall survival compared to docetaxel in the entire study population and in the EGFR wild-type subgroup, but not in the EGFR-mutant subgroup.

Another study sought to determine the activity of PD-1/PD-L1 inhibitors within clinically relevant molecular subgroups by retrospectively evaluating response patterns among EGFR-mutant, ALK-positive and EGFR wild-type/ALK-negative patients. Findings revealed that NSCLC harbouring EGFR mutations or ALK rearrangements are associated with low ORRs to PD-1/PD-L1 inhibitors, which might be explained by low rates of concurrent PD-L1 expression and $CD8^+$ tumour-infiltrating lymphocytes within the tumour microenvironment. The lack of an inflamed tumour microenvironment in the majority of such patients, suggested by a death of tumour-infiltrating $CD8^+$ lymphocytes may explain the low response rate to PD-1 axis inhibitors observed among EGFR- and ALK-driven NSCLC. PD-L1 tumour expression found in the minority of patients is primarily driven by intrinsic (*i.e.* constitutive oncogenic signalling) rather than adaptive processes (induction by local inflammatory signals), considering a lack of significant concomitant $CD8^+$ lymphocyte infiltrate. Finally, the ATLANTIC study [40] evaluated durvalumab in locally advanced or metastatic EGFR-mutant/ALK^+ NSCLC treated in the third-line setting or more. Results were encouraging, with ORR in the mutant PD-L1-high cohort close to that found in the wild-type PD-L1-high cohort (12.2% and 16.4%, respectively). Overall survival favoured high PD-L1 expression groups, but the short duration of follow-up limits these data. Finally, the safety profile of durvalumab in the mutant group was positive.

There is a bulk of data supporting the need for genomic testing to determine whether tumours harbouring specific alterations are associated with hyperprogression in patients for whom anti-PD-1/PD-L1 monotherapy is planned. EGFR activation is associated with upregulation of PD-1, PD-L1 and CTLA-4, which facilitates immune escape and might explain resistance in EGFR-mutated tumours, and in some cases, hyperprogression.

The primary interest in using PD-1 axis inhibitors in EGFR- and ALK-driven NSCLC was ignited after preclinical studies reported that EGFR and ALK signalling drives PD-L1 expression, and that *in vitro* treatment with PD-1 axis inhibitors compromised tumour viability. Moreover, therapy with a PD-1 axis inhibitor in EGFR mutant mouse models indicated improved survival. No less important is that treatment with TKI therapy in cell-line models has caused PD-L1 downregulation, questioning the idea of combining a TKI with a PD-1 axis inhibitor. Currently the focus has shifted to patients with TKI-naïve EGFR- and ALK-driven NSCLC and multiple ongoing studies are assessing combination therapy with respective TKIs combined with a PD-1 axis inhibitor.

From immunotherapy by ICIs to future vaccination against lung cancer

With the success of checkpoint inhibition, the vaccination approach to treat NSCLC has surfaced again as only a subgroup of patients suffering from advanced NSCLC successfully responds to ICIs. The main reason for the absence of immune response is the absence of tumour-directed T-cells. In order to increase the number of tumour-directed T-cells, vaccination seems an appropriate option. Tumour vaccines can elicit an *in vivo* immune response specifically towards a tumour-associated antigen incorporated in the vaccine. Such therapy is considered safe and successful in inducing or enhancing a tumour-directed T-cell

TABLE 5 Selection of recruiting clinical trials summarising the main research directions

	Identifier	Phase	Protocol	Stage	Primary outcome	State
Early-stage NSCLC	NCT02927301	Phase II	Atezolizumab as neoadjuvant and adjuvant therapy	IB, II and IIIA untreated NSCLC	MPR	Recruiting
	NCT02273375	Phase III	Durvalumab *versus* placebo	Early-stage NSCLC PD-L1-positive	DFS	Recruiting
	NCT03030131	Phase II	Durvalumab	Early-stage NSCLC	RSR	Recruiting
	NCT02504372	Phase III	Pembrolizumab *versus* placebo	IB/II–IIIA	DFS	Recruiting
	NCT02595944	Phase III	Nivolumab	Adjuvant IB–IIIA NSCLC	DFS	Recruiting
	NCT03053856	Phase II	Pembrolizumab	Adjuvant in IIIA NSCLC patients treated with neoadjuvant chemotherapy and curative resection	DFS	Recruiting
	NCT02259621	Phase II	Nivolumab *versus* nivolumab + ipilimumab	Resectable NSCLC	Safety	Recruiting
	NCT02998528	Phase II	Nivolumab + ipilimumab *versus* chemotherapy doublet	Neoadjuvant early-stage NSCLC	MPR	Recruiting
	NCT02768558	Phase III	Cisplatin + etoposide followed by nivolumab *versus* placebo	Locally advanced unresectable NSCLC	OS, PFR	Recruiting
	NCT02621398	Phase I	Pembrolizumab, paclitaxel, carboplatin and radiotherapy	II–IIIB NSCLC	MTD and DLT	Recruiting
	NCT02987998	Phase I	Chemoradiation + pembrolizumab followed by consolidation pembrolizumab	IIIA	Safety	Recruiting
First-line advanced NSCLC	NCT02848651	Phase II	Atezolizumab	Advanced or metastatic NSCLC	RECIST PFS	Recruiting
	NCT02879617	Phase II	Durvalumab	Advanced NSCLC	PFS, safety	Recruiting
	NCT03001882	Phase II	Nivolumab + ipilimumab	Advanced NSCLC	ORR	Recruiting
	NCT02576574	Phase III	Avelumab *versus* platinum-based doublet	Advanced NSCLC	PFS, OS	Recruiting
	NCT02542293	Phase III	Durvalumab + tremelimumab *versus* platinum-based doublet	Advanced NSCLC	OS	Recruiting
	NCT02659059	Phase II	Nivolumab + ipilimumab + chemotherapy *versus* chemotherapy alone	Advanced NSCLC	ORR, OS	Recruiting
	NCT02477826	Phase III	Nivolumab, nivolumab + ipilimumab, nivolumab + platinum doublet *versus* platinum-based doublet	Advanced NSCLC	OS, PFS	Recruiting
	NCT02775435	Phase III	Carboplatin-paclitaxel/ nab-paclitaxel with or without pembrolizumab	Metastatic squamous NSCLC	PFS, OS	Recruiting
Maintenance	NCT02486718	Phase III	Atezolizumab *versus* BSC following chemotherapy	Stage IB–IIIA following resection and adjuvant chemotherapy	DFS	Recruiting
	NCT02564380	Phase II	Pembrolizumab	Metastatic squamous NSCLC following first-line chemotherapy	PFS	Recruiting
	NCT02705820	Phase II	Pembrolizumab	Metastatic NSCLC following first-line chemotherapy	irPFS	Recruiting
	NCT02316002	Phase II	Pembrolizumab	After curative intent for oligometastatic NSCLC	PFS	Recruiting
Stereotactic body radiation therapy	NCT02599454	Phase I	Atezolizumab + SBRT	Inoperable stage I NSCLC	MTD	Recruiting
	NCT03050554	Phase I–II	Avelumab + SBRT	Early NSCLC	Safety, RFS	Recruiting
	NCT02904954	Phase II	Durvalumab with or without SBRT	IB–II NSCLC	DFS	Recruiting
	NCT02444741	Phase I–II	Pembrolizumab and SBRT	Advanced NSCLC	MTD	Recruiting
	NCT02239900	Phase I–II	Ipilimumab and SBRT	Advanced solid malignancies	MTD	Recruiting

Continued

TABLE 5 Continued

	Identifier	Phase	Protocol	Stage	Primary outcome	State
Radiotherapy	NCT02525757	Phase II	Atezolizumab + chemotherapy and radiotherapy	Unresectable NSCLC	Time to toxicity	Recruiting
	NCT02888743	Phase II	Durvalumab + tremelimumab alone or in combination with high- or low-dose radiotherapy	Metastatic colorectal and NSCLC	RECIST	Recruiting
	NCT03044626	Phase II	Nivolumab + radiotherapy	Advanced NSCLC	ORR	Recruiting

Information is based on a selection of recruiting studies available on the clinicaltrials.gov website at time of the meeting (May 2017). NSCLC: nonsmall cell lung cancer; MPR: major pathological response: PD-L: programmed death ligand; DFS: disease-free survival; RSR: R0 surgical resection; OS: overall survival; MTD: maximum tolerated dose; DLT: dose-limiting toxicity; RECIST: Response Evaluation Criteria in Solid Tumours; ORR: objective response rate; irPFS: immune-related progression-free survival; SBRT: stereotactic body radiation therapy; RFS: relapse-free survival.

response in different cancers, including NSCLC. Synergy of vaccination and checkpoint blockade might unleash the full potential of immunotherapy and ensure more patients respond to it.

The generation of an immune response directed against tumour antigens is a multi-step process. First, tumour-associated antigens (TAAs) must be directly presented by tumour cells or captured, processed and presented by DCs. Then DCs differentiate and migrate to present TAAs to the T-cells, which in turn recognise and eliminate tumour cells, into the so-called immune cycle. Based on whether the tumour has been infiltrated by T-cells, it can be described as hot or cold. The infiltration reflects whether the immune system recognises the tumour. Cold tumours are not responsive and can even be highly resistant to immunotherapy with PD-(L)1 checkpoint inhibition. While the mechanisms underlying this are not fully understood, the primary objective is to destroy the immune barriers and convert a cold phenotype (non-T-cell inflamed) into a hot one (T-cell inflamed). A few studies report that a sequence of treatments could make tumours more responsive to immune cell infiltration, resulting in immunological growth control. For instance, a combination of radiotherapy and vaccination may enhance tumour T-cell infiltration and help overcome checkpoint blockade resistance.

Vaccines can be either peptidic (short or long peptides), comprised of proteins or genetic (DNA or mRNA constructs). Adjuvants are also added (chemical or biological). Finally, different types of vaccinations such as pure antigen vaccination, dendritic cell vaccination or viral vector vaccination also exist.

Increasing immune activation is a promising direction in overcoming the immunotherapeutic resistance of cold tumours. Peptide or tumour cell vaccines are designed to deliver tumour antigens to DCs, which can subsequently induce a tumour specific immune response by the adaptive immune system. These vaccines can consist of tumour-specific antigens or can be composed of manipulated tumour cells. Cellular immunotherapy includes the adoptive transfer of autologous or allogeneic activated immune cells. The goal of this approach is to induce a tumour-specific immune response *via* the infusion of, *e.g.* tumour-antigen loaded DCs or specifically activated T-cells.

Recent results of phase III clinical trials of cancer vaccines have been disappointing so far [41] and were not translated into clinical benefits. According to a comprehensive meta-analysis, cellular immunotherapies turned out to be more effective than tumour vaccines for all outcome measures. Due to their potent antigen-presenting capacity, DCs are acknowledged as a promising agent in immunotherapeutic approaches in a number of malignancies. However, when tumours grow and establish a tumour microenvironment, several factors impair the functions of DCs (hypoxia, tumour metabolites, cytokines/chemokines, skewing differentiation to macrophages and endothelial cells and inhibition by regulatory T-cells). These impaired DCs secrete immunosuppressive cytokines and upregulate the cell surface expression of T-cell suppressive molecules. In such cases, as has been demonstrated in the treatment of mesothelioma, administration of *ex vivo* maturated autologous DCs into a patient might be an option, resulting in antigen presentation in the lymph nodes and a specific cytotoxic antitumour response.

More therapeutic combination options and trials than patients

At the time of the meeting, ICIs (anti-PD-1 and anti-PD-L1) demonstrated significant clinical activity in stage IV NSCLC, whether considering first-line (pembrolizumab) or salvage therapy (nivolumab,

atezolizumab, *etc.*). Different approaches are now under investigation: is it possible to improve the effectiveness of ICIs by combining anti-PD-(L)1 and other agents acting on the immunity? Are ICIs effective in early-stage NSCLC and in small cell lung cancer? Is it possible to combine radiotherapy and ICIs? Can ICIs be given in specific populations (with oncogenic driver mutations, HIV patients, *etc.*)? A selection of studies on these different topics currently recruiting was retrieved from clinicaltrials.gov in May 2017 and is summarised in table 5.

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