Review Article

Upcoming innovations in lung cancer immunotherapy: focus on immune checkpoint inhibitors

Sandrine Aspeslagh[1], Aurélien Marabelle[1,2], Jean-Charles Soria[1], Jean-Pierre Armand[1]

[1]IGustave Roussy, Université Paris-Saclay, F-94805 Villejuif, France; [2]INSERM U1015, GRCC, F-94805 Villejuif, France

Contributions: (I) Conception and design: S Aspeslagh, A Marabelle, JP Armand; (II) Administrative support: S Aspeslagh; (III) Provision of study materials or patients: S Aspeslagh, A Marabelle, JC Soria; (IV) Collection and assembly of data: S Aspeslagh, A Marabelle; (V) Data analysis and interpretation: S Aspeslagh, A Marabelle; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Sandrine Aspeslagh. 114 Rue Edouard Vaillant, 94805 Villejuif Cedex, France. Email: sandrine.aspeslagh@gustaveroussy.fr.

Author's introduction: Sandrine Aspeslagh is an oncologist actually working at the phase I unit in the Gustave Roussy Cancer Centre. She did a PhD in immunology analyzing the potential of iNKT cells in murine cancer models. Therefore she is highly interested in the novel developments in immunotherapy that are currently changing the landscape of oncology.

Jean-Pierre Armand, MD, MSc, is certified in Medical Oncology (University of Toulouse III and Paris XI). He was recently General Director of the Institut Claudius Regaud in Toulouse (2007–2012) and is cancer adviser to the Dean of University of Toulouse. Over the last five years he has been in charge of the construction of a new cancer center, in a European research hub created in the Toulouse cancer campus (Institut Universitaire du Cancer). After a position as research fellow in Columbia University New York, Dr. Armand has joined Institut Claudius Regaud in Toulouse, he was head of Medical oncology until 1984. In the next 23 years, at Institut Gustave Roussy (IGR) in Paris, he was successively CEO of the Hospital IGR3, head of the Department of Medical oncology at IGR2 and finally CMO of IGR&D, Department of Innovation and Development at IGR. Although expert in breast, head & neck, and neuro-oncology, the first field of Dr. Armand was very early drug development in phase 1 and 2. He has been the founder of the IGR phase i unit (Sitep) in the early 80s. He did the first in human phase I in the world at IGR of numerous drugs, including classical cytotoxics, irinotecan, oxaliplatin, taxotere, navelbine, vinflunine, and more recently targeted therapies, sutent, sorafenib, temsirolismus .... Dr. Armand is active in the International Cancer community. He served as President of the European Society for Medical Oncology (ESMO), Medical Director of the Federation of European Cancer Societies (FECS/ECCO), President of the French Cancer Society (SFC), Chairman of the Protocol Review Committee of European Organization of Research and Treatment of Cancer (EORTC), Chairman of Oncology at French EMEA (AFSSAPS), Member of International Boards of the American Association for Cancer Research (AACR), Member of scientific committee of the American Society of Clinical Oncology (ASCO) and AACR, Member of the board of clinical trials at Institut National du Cancer (INCa) and chairman of the president nominating committee of ESMO.

Sandrine Aspeslagh

Jean-Pierre Armand

Abstract: For decades, immunotherapy strategies have failed to succeed in lung cancer. However, the recent success of immune checkpoint inhibitors and the progress in the understanding of the immunobiology of lung cancer have changed this paradigm. Here we review ongoing clinical trials and recent results obtained with these novel lung cancer immunotherapies.

Keywords: Immune checkpoint inhibitors; vaccines; immunotherapy; lung cancer

Submitted Nov 01, 2015. Accepted for publication Dec 18, 2015.
doi: 10.3978/j.issn.2304-3865.2015.12.06
View this article at: http://dx.doi.org/10.3978/j.issn.2304-3865.2015.12.06

Introduction

Lung cancer is one of the leading causes of cancer-related mortality worldwide. It has been categorized into non-small cell carcinoma (NSCLC) and small cell carcinoma (SCLC). SCLC has an aggressive clinical behavior which is characterized by a rapid growth and early metastasis. Although most SCLC patients respond very well to chemotherapies, they present a very high relapse rate and the long-term overall survival (OS) remains poor. NSCLC, on the other hand, represents about 85% of lung cancers and includes squamous cell carcinoma and adenocarcinoma histological subtypes. Squamous cell carcinoma is more closely associated with smoking than adenocarcinoma, which is often driven by activating mutations in oncogenes such as EGFR, KRAS, HER2, BRAF, etc... Most patients are unfortunately diagnosed in a late advanced stage with a locally advanced or metastatic disease (stage IIIB or IV), when no treatment with curative intent is available. Until recently, the median survival of these patients was about 9-12 months with the use of conventional chemotherapy. Especially for patients with an oncogenic driven adenocarcinoma, the advent of molecular targeted therapies has increased the OS (to up to more than 2 years) and quality of life. However long-term survivors were rare and the benefits in OS were limited. Even for early diagnosed patients who underwent complete resection with curative intention, the 5-year survival rate was only around 40% (1). So there is a high unmet medical need for the treatment of lung cancer.

Recent successes with immune checkpoint blockade therapy, such as anti-CTLA4 and anti-PD1/PDL1 monoclonal antibodies (mAbs), demonstrated that manipulation of the immune system is a very potent way to fight cancer (2).

The immune system in cancer

A central problem in oncology is the reduced ability of the immune system to overcome an established tumor. Many studies reported that an effective cancer microenvironment induced immunosuppression that prevented cytotoxic T cells from killing the tumor cells. Immunosuppression in the microenvironment is mainly induced by regulatory T cell (Tregs), myeloid derived suppressor cells (MDSCs) and tumor activated macrophages (TAMs). These cells prevent the activation of anti-tumor T cells through different mechanisms including production of immunosuppressive cytokines, such as IL-10 and TGFb, and expression of co-inhibitory molecules, like CTLA4, PD1 and PDL1. Additionally, cancer cells can hide from the immune system by a diminished expression of major histocompatibility complex one (MHC-I) molecules, and therefore lower presentation of tumor-antigens to immune cells.

Immunotherapeutic approaches

Immunotherapies consist of a broad class of therapeutics that are designed to either provide immune effectors (passive immunotherapies; e.g., tumor targeted antibodies) or activate the patients' immune cells (active immunotherapies; e.g., cytokines) in order to mediate the destruction of tumor cells. Interestingly, immune checkpoint targeted mAbs are an active immunotherapy. They stimulate the patient's own immune system in order to destroy cancer cells. This is a paradigm shift in the treatment of cancer as opposed to conventional chemotherapies or tumor-targeted therapies that were designed to focus directly on the tumor cells.

Immunotherapeutics for lung cancer

Recent discoveries in the lung cancer field highlighted the

mechanisms underlying tumor escape from the immune recognition. As for other cancer types, the presence of different effector T cells subsets seemed to be correlated with long-term OS (3,4). Beside the role of effector cells in antitumor biology in lung cancer, the presence of immunosuppressive cells such as MDSCs was correlated with a bad prognosis (5). Additionally, it was shown that Tregs from lung cancer patients could potentially inhibit autologous T cells activity (6). These data at least suggested that immune cells play a pivotal role in the pathogenesis of lung cancer.

Immunomodulatory agents

There are different classes of immunomodulatory agents: immune checkpoint modulators (anti-CTLA4, anti-PD1 and anti-PDL1), TLR agonists, cytokines, … (*Table 1*, *Table S1*). The hypothesis is that immune checkpoint inhibitors will activate the immune system by blocking the expression of co-inhibitory molecules such as CTLA4, PD1 and PDL1 (*Figure 1*), and as such re-activate the preexisting tumor response. Additionally, there is a strong preclinical rationale for a beneficial effect of agonistic antibodies against other activating co-stimulatory molecules such as OX40, LAG3 and GITR. Preclinical settings showed that antibody derived cellular cytotoxicity (ADCC) played a major role in the outcome of immunomodulatory antibody treatments such as anti-CTLA4 and anti-GITR (17). This means that CTLA4 expressing cells, mostly Tregs, will be killed by natural killer cells or macrophages, after binding to anti-CTLA4 (18). ADCC will depend on the Fc portion of the antibody, which differs according to the antibody IgG subtype. However this observation remains to be proven in patients.

Monotherapy of immune checkpoint modulators (*Table 1*)

CTLA4 inhibitors

Ipilimumab and tremelimumab are both fully humanized anti-CTLA4 mAbs (*Table 2*), which block the binding of CTLA4 to its ligands (the co-stimulatory molecules CD80 and CD86). Two studies (NCT01165216, NCT00527735) in NSCLC patients showed that ipilimumab slightly improved the progression free survival (PFS) and the OS when given after chemotherapy in treatment-naive stage IV NSCLC patients (19,20). A small phase II trial with tremelimumab did not show any benefit as a maintenance therapy after first line chemotherapy (7).

PD1 and PDL1 inhibitors

Currently, two different anti-PD1 molecules (nivolumab, pembrolizumab) and four anti-PDL1 molecules (BMS-936559, atezolizumab, durvalumab and avelumab) are being tested in lung cancer patients (*Table 2*). Although anti-PDL1 and anti-PD1 may inhibit slightly different binding partners (*Figure 1*), it is too early to determine clinical differences between these molecules. Both nivolumab and pembrolizumab have been recently approved for melanoma by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (21,22). The results of the phase I trial with nivolumab showed for the first time long term beneficial effects of anti-PD1 in lung cancer (8,9). Heavily pretreated patients had a 17% objective response rate, a median response duration of 74 weeks, and an ongoing response in more than half of the patients. Nivolumab was very well tolerated as only 14% experienced of the patients grade III or IV toxicity rates, and three therapy-related deaths were reported (pneumonitis). These cases of pneumonitis incited physicians to treat pneumonitis or other immune related side effects earlier with corticoids, which seemed to stop clinical aggravations. These results were confirmed in the recently published phase II trial with nivolumab (Checkmate 063): 14.5% of the patients had an objective response of which most is still ongoing and additionally 26% had stable disease (10). So in contrast to chemotherapy and most molecularly targeted therapies, and in analogy to the responses seen in metastatic melanoma patients, therapy responses are much more long-lasting which is paradigm changing for NSCLC. These revolutionary data were also seen in two recently published phase III trials: Checkmate 057 for non-squamous NSCLC and Checkmate 017 for squamous NSCLC. Both studies compared nivolumab to docetaxel and showed a response rate for nivolumab of about 20% versus about 10% for docetaxel with again long lasting responses. Additionally nivolumab was better tolerated than docetaxel (about 10% grade III-IV toxicity with nivolumab compared to 50% with docetaxel). An ongoing first-line phase III study is also conducted, comparing chemotherapy of choice with nivolumab in PDL1 positive patients (NCT02041533). The response to pembrolizumab in NSCLC corroborated the results from the nivolumab trials as it demonstrated an overall response rate (ORR) of 24% in patients who had

Table 1 Overview of trials using immune checkpoint inhibitors in lung cancer

Inhibitors	Conditions	Interventions/treatments arms	Phases	NCT number/reference
CTLA4	SCLC, limited disease	Ipilimumab	II	NCT02046733
	NSCLC, locally advanced or metastatic	Tremelimumab *vs.* BSC	II	(7)
PD1	NSCLC	Nivolumab	I	NCT00730639/NCT00441337 (8,9)
	Solid tumors (Chinese pts)	Nivolumab	I/II	NCT02593786/Checkmate 077
	NSCLC, squamous, advanced, after 2 or more previous treatments	Nivolumab	II	NCT01721759/Checkmate 063 (10)
	NSCLC, prior to resection	Nivolumab	II	NCT02259621
	NSCLC	Nivolumab	II	NCT02350764
	NSCLC	Nivolumab	II	NCT02582125/NCT02175017
	NSCLC	Nivolumab and (cryo or thermo) ablation	II	NCT02469701/BrUOG317
	NSCLC, squamous, advanced	Nivolumab	II	NCT02409368/Checkmate 171
	NSCLC, advanced	Nivolumab	III	NCT02066636
	NSCLC, squamous, advanced, after platinum based chemotherapy	Nivolumab versus docetaxel	III	NCT01642004/Checkmate 017 (11)
	NSCLC, non-squamous, advanced, after platinum based chemotherapy	Nivolumab versus docetaxel	III	NCT01673867/Checkmate 057 (12)
	NSCLC, early stage	Nivolumab after surgery and adjuvant CT	III	NCT02595944
	NSCLC, PDL1 positive	Nivolumab versus Investigator's choice	III	NCT02041533/CheckMate 026
	NSCLC, advanced, after platinum based chemotherapy	Nivolumab *vs.* docetaxel	III	NCT02613507
	SCLC, relapsed	Nivolumab *vs.* topotecan or amrubicin	III	NCT02481830
	NSCLC, squamous, advanced	Nivolumab	III	NCT02475382
	NSCLC, advanced	Pembrolizumab	I	NCT01295827 (13)
	NSCLC, advanced, PDL1+	Pembrolizumab	I	NCT02007070/Keynote-025
	Solid tumours in HIV+ pts	Pembrolizumab	I	NCT02595866
	NSCLC, stage III unresectable	Pembrolizumab (maintenance after CRT)	II	NCT02343952
	NSCLC, brain metastases	Pembrolizumab	II	NCT02085070
	SCLC, extensive disease	Pembrolizumab	II	NCT02359019
	NSCLC, squamous, 1st line	Pembrolizumab (maintenance after platinum based CT)	II	NCT02564380/PRIMUS
	NSCLC, advanced	Pembrolizumab *vs.* docetaxel	II/III	NCT01905657/Keynote-010
	NSCLC, PDL1 positive	Pembrolizumab *vs.* paclitaxel or carboplatin + pemetrexed	III	NCT02220894/Keynote-042
	NSCLC, PDL1 positive	Pembrolizumab versus SoC	III	NCT02142738/Keynote-024
	NSCLC, after resection	Pembrolizumab *vs.* placebo (with or without adjuvant CT)	III	NCT02504372/Keynote-09/ PEARLS

Table 1 *(continued)*

Table 1 *(continued)*

Inhibitors	Conditions	Interventions/treatments arms	Phases	NCT number/reference
PDL1	Solid cancers	Atezolizumab	I	NCT01375842 (14)
	NSCLC, advanced, PDL1+	Atezolizumab	II	NCT01846416/FIR
	NSCLC, advanced, PDL1+	Atezolizumab	II	NCT02031458/BIRCH
	NSCLC, advanced, failed after platinum	Atezolizumab *vs.* docetaxel	II	NCT01903993/POPLAR (15)
	NSCLC, squamous, advanced	Atezolizumab *vs.* gemcitabine/cis or carbo	III	NCT02409355/IMpower 111
	NSCLC, resectable	Atezolizumab *vs.* BSC after CT and resection	III	NCT02486718
	NSCLC, non-squamous, advanced	Atezolizumab *vs.* carbo or cis/permetrexed	III	NCT02409342/IMpower 110
	NSCLC, advanced, failed after platinum	Atezolizumab *vs.* docetaxel	III	NCT02008227/OAK
	NSCLC	Atezolizumab with vemurafenib or alectinib or trastuzumab emtansine	II	NCT02314481
	Solid tumors	Avelumab	I	NCT01772004/Javelin solid tumor
	NSCLC	Avelumab versus docetaxel	III	NCT02395172/Javelin 200
	NSCLC, advanced, PDL1+	Avelumab *vs.* platinum doublet CT	III	NCT02576574/Javelin 100
	NSCLC	Durvalumab	I/II	NCT01693562 (16)
	NSCLC	BMS 936559	I	Brahmer *et al.*, *NEJM*, 2012, NCT00729664
	NSCLC, resectable	Durvalumab after surgery (and CT) *vs.* placebo	III	NCT02273375
	NSCLC, stage III, unresectable	Durvalumab after CRT *vs.* placebo	III	NCT02125461/PACIFIC
	NSCLC, advanced	Durvalumab	II	NCT02087423/ATLANTIC
	NSCLC, squamous, after failure to platinum therapy	Docetaxel versus MPDL3280A	III	NCT02008227
	NSCLC, stage IIIA, resectable	Durvalumab in the (neo)adjuvant setting	II	NCT02572843

SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; BSC, best supportive care; pts, patients; CT, chemotherapy; PDL1, programmed death ligand 1; CRT, chemoradiotherapy; SoC, standard of care.

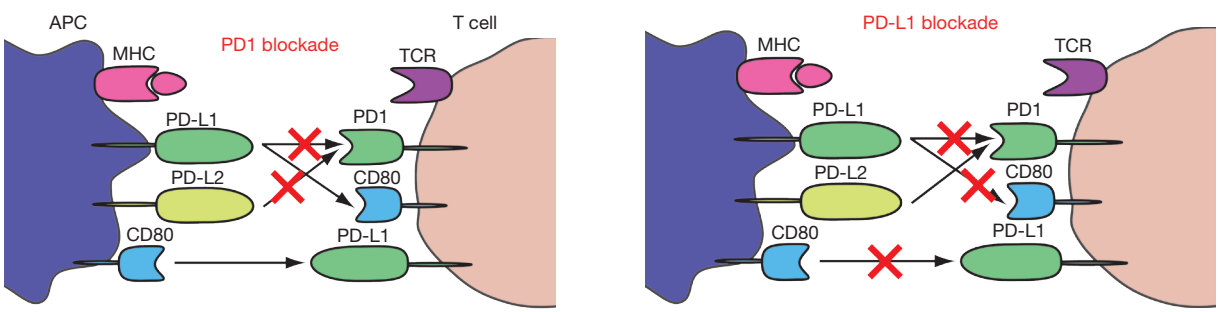

Figure 1 PD1 blockade does affect binding of PDL1 to PD1 and binding of PDL2 to PD1; PDL1 blockade does inhibit binding of PDL1 to PD1 and CD80. PD1, programmed death receptor; PDL1, programmed death ligand 1.

Table 2 Overview of immune checkpoint inhibitors

Name	Inhibitors	Molecule	Ab subtype	Clinical	Company	Development in lung cancer
MDX010	Ipilimumab	Anti CTLA4	IgG1	Yervoy	Bristol-Myers Squibb	×
CP675,206	Tremelimumab/ ticililumab	Anti CTLA4	IgG2	II	Pfizer	×
MK 3475	Pembrolizumab/ lambrolizumab	Anti PD1	IgG4 (humanized)	Keytruda	Merck & Co	Keynote
MDX-1106/BMS-936558	Nivolumab	Anti PD1	IgG4	Opdivo	Bristol-Myers Squibb	Checkmate
CT-011	Pidilizumab	Anti PD1	IgG1 (humanized)	Phase I/II	CureTech/Teva	×
MEDI0680/AMP-514		Anti PD1	IgG	Phase I	MedImmune/ AstraZeneca	
MPDL3280A	Atezolizumab	Anti PDL1	IgG1	Phase I	Roche/Genentech	IMPower
BMS-936559/ MDX1105-01		Anti PDL1	IgG4	Phase I	Bristol-Myers Squibb	×
MEDI-4736	Durvalumab	Anti PDL1	IgG1	Phase I	MedImmune/ AstraZeneca	×
MSB0010718C	Avelumab	Anti PDL1	IgG1	Phase I/II	Pfizer/EMD Serono (Merck Kga)	Javelin
AMP-224		PD-1/B7/Fc Fusion protein			AstraZeneca/ Medimmune	
W014A		PD1 decoy peptide			Pierre Fabre	

CTLA4, cytotoxic T-lymphocyte-associated protein 4; IgG, immunoglobulin; PD1, programmed death receptor; PDL1, programmed death ligand 1.

failed two previous therapy regimen (13,23). Interestingly, these responses towards pembrolizumab seemed to correlate with a mutation burden and smoking history (24). Although further analysis is underway, mutational burden may be a good predictive biomarker for immunotherapy. Additionally, Keynote 010, a phase III trial comparing pembrolizumab *vs.* docetaxel, confirmed the superiority of checkpoint inhibition in treating NSCLC patients with PDL1 positive tumour cells (25). These positive results in a refractory patient group are very promising, prompting different phase III trials in second-line treatment comparing standard chemotherapy versus several anti-PD(L)1 antibodies (NCT02220894, NCT02142738). These paradigm changing results with both nivolumab and pembrolizumab have led to the US-FDA and the EMA approvals of nivolumab for patients with metastatic squamous cell lung cancer, refractory to platinum derivatives (21,22) and the US-FDA approval of pembrolizumab for PDL1 positive NSCLC (26).

The results with atezolizumab, an anti-PDL1 antibody (IgG1 but transformed not to induce ADCC of PDL1 expressing cells), in NSCLC affirm our enthusiasm: 23% of all NSCLC patients have shown a response in addition to 34% who had stable disease (NCT01375842) (14). These data were confirmed in the phase II POPLAR trial (NCT01903993) where it was shown that atezolizumab had an advantage over docetaxel in second line (especially in PDL1 high patients) (15). These data will be further analyzed in the OAK trial (phase III, NCT02008227). Two other anti-PDL1 antibodies (BMS 936559 and durvalumab) have demonstrated their efficacy in the phase I trials with NSCLC patients (NCT00729664, NCT01693562) (16,27). Now, almost 15 phase III trials are ongoing, challenging standard regimen in lung cancer patients: comparison between anti-PDL1 with standard chemotherapy (NCT02395172, NCT02008227), introduction of anti-

PDL1 after chemoradiotherapy for stage III NSCLC patients (NCT02125461), introduction of anti-PDL1 in the adjuvant setting after complete resection in NSCLC patients (NCT02273375) among others.

Results from some clinical trials [e.g., Keynote 001 (23), Poplar (15)] may suggest that expression of PD-L1 on tumor-infiltrating immune cells or tumor cells may potentially be used as a biomarker to predict anti-tumor response to PD-1/PD-L1 inhibitors. Other trials especially with nivolumab (11,12) did not show a clear correlation. However at present, PDL1 staining is not standardized due to heterogeneities of staining, analysis, and timing, among the different industrial partners. Consequently, PDL1 positivity is not a good biomarker.

Combination therapy with immune checkpoint modulators (*Table 3*)

Although these results are very encouraging, monotherapy with checkpoint inhibitors still fail to induce a response in the majority of the metastatic patients. Preclinical research has shown that primary or secondary resistance to single immune checkpoint blockade could be overcome by targeting other immunosuppressive pathways or by combining immune checkpoint inhibitors. Very positive results were already shown in the melanoma field where combining ipilimumab with nivolumab induced response rates in up to 50% of the patients (34). Another strategy includes combinations with conventional treatments that induce antigen release due to cancer cell death (35-37). Therefore, many ongoing clinical trials are investigating combinations between immune checkpoint inhibitors, chemotherapy, radiotherapy, anti-angiogenic and targeted therapies (*Table 3*). Up to now, the results are eagerly awaited as only very few data from ongoing phase I trials have been released. The first results from Checkmate 012 (NCT01454102) and Keynote 021 (NCT02039674), both multi-arm studies which combine anti-PD1 (nivolumab and pembrolizumab) with either chemotherapy, bevacizumab, erlotinib or ipilimumab are very promising. Combining pembrolizumab with ipilimumab could induce response rates of about 60% of the patients (31), and this robust anti-tumour response was confirmed with the combination of pembrolizumab with ipilimumab that showed responses in about 40% of the patients. Compared to the first trials in melanoma the toxicity of the combination could be largely reduced by using intervals of e.g., 12 weeks for ipilimumab. These are very early data that should be interpreted with caution but it clearly demonstrates that combining immune checkpoint inhibitors may be a very powerful therapy in lung cancer. Trials with such combinations in NSCLC (anti-CTLA4 antibodies with anti-PDL1 antibodies) are ongoing [ARTIC (NCT02352948) and Neptune (NCT02542293)]. Even in advanced SCLC patients a combination of ipilimumab and nivolumab could induce long lasting responses in about 25% of the patients (NCT01928394) (29). Checkmate 451 (phase III, NCT02538666) will further analyze the combination of nivolumab with ipilimumab in early stage SCLC after platinum therapy.

Another possible synergistic combination consists of chemotherapy plus checkpoint inhibition. Also here, some early results are very encouraging: the combination of platinum doublets with pembrolizumab induced response rates of about 60% (Keynote 012) (32) and similar results were seen in the phase Ib trial that used a combination of atezolizumab with several chemotherapeuticals (NCT01633970) (33). Many phase III trials combining chemotherapy with immune checkpoint inhibition are underway (NCT02578680/Keynote-189, NCT02477826/Checkmate 227, NCT02367781/IMpower 130, NCT02366143, ...).

Cytokine therapy

Interleukin-2 (IL-2) induces T cells activation and proliferation. It has a long history in melanoma and renal cancer as a successful therapy with durable responses. However, only a minority of patients respond and it is suitable for very few patients due to a high toxicity profile (38). This approach has also been tested in several trials designed for lung cancer patients. However, most of them have failed to show any superiority compared to conventional treatments. Recently a phase I trial has been conducted analyzing the combination of an alternative IL-2 treatment [NHS-IL2 selectikine: human NHS76 (antibody specific for necrotic DNA) fused to genetically modified human IL-2] with local irradiation of a single pulmonary nodule (5×4 Gy) in metastatic NSCLC patients that had stable disease after one line of chemotherapy (39). Beside a possible therapy related thyroiditis in two patients, there were no major side effects. Two out of 13 patients had a long-term response (over 4 years). Thus, the efficacy of this treatment needs to be confirmed in further trials.

Anti-IDO vaccination

A Danish group from Copenhagen has reported a phase

Table 3 Overview of trials combining immune checkpoint inhibitors in lung cancer

Inhibitors	Conditions	Interventions/treatments arms	Phases	NCT number/reference
CTLA4				
Radiotherapy	NSCLC	Ipilimumab + IMRT	II	NCT02221739
	Solid tumours with lung/liver metastasis	Ipilimumab + SBRT	I/II	NCT02239900
Chemotherapy	NSCLC, advanced (Japanese pts)	Ipilimumab + carboplatinum-paclitaxel	I	NCT01165216/CA184-113 (20)
	NSCLC, advanced, CT-naive	Carboplatin-paclitaxel + BSC *vs.* ipilimumab (phased or concurrent)	II	NCT00527735 (19)
	SCLC, advanced, CT-naive	Carboplatin-paclitaxel + BSC *vs.* ipilimumab (phased or concurrent)	II	(28)
	SCLC, advanced	Platinum-etoposide + ipilimumab	II	NCT01331525/ICE
	NSCLC, resectable	Neoadjuvant CT + ipilimumab + adjuvant ipilimumab	II	NCT01820754
	NSCLC, squamous, advanced	Ipilimumab (phased or concurrent) + carbo/paclitaxel or BSC	III	NCT01285609/CA184-104
	NSCLC, squamous, advanced	Ipilimumab + carbo/paclitaxel or BSC	III	NCT02279732
	SCLC, advanced, chemotherapy-naive	Ipilimumab (phased or maintenance) + platinum-etoposide or BSC	III	NCT01450761/CA184-156
TKI	NSCLC, EGFR activating mutation	Tremelimumab + gefetinib	I	NCT02040064/Geftrem
	NSCLC, EGFR or ALK mutated advanced	Ipilimumab + erlotinib or crizotinib	Ib	NCT01998126
	Advanced solid tumors	Tremelimumab + mogamulizumab or durvalumab + mogamulizumab	I	NCT02301130
	SCLC, advanced	Ipilimumab + nivolumab	I/II	NCT01928394/Checkmate 032 (29)
	SCLC, limited stage disease	Ipilimumab + nivolumab	II	NCT02046733/STIMULI
	NSCLC, 1st line, EGFR, ALK WT advanced	Tremelimumab + durvalumab *vs.* SoC	III	NCT02542293/Neptune
	NSCLC, advanced	Tremelimumab + durvalumab	Ib	NCT02000947
	NSCLC, advanced	MGA271 (anti-B7H3) plus ipilimumab	I	NCT02381314
PD1				
Radiotherapy	NSCLC	Pembrolizumab + RT	I	NCT02318771
	NSCLC, advanced	Pembrolizumab + RT	I/II	NCT02444741
	SCLC	Pembrolizumab + RT (+/- CT)	I	NCT02402920
	NSCLC, early stage	Pembrolizumab + RT + carbo-paclitaxel	I	NCT02621398
	NSCLC, advanced	Pembrolizumab + SBRT	I/II	NCT02407171
	NSCLC, advanced	Pembrolizumab + SBRT *vs.* pembrolizumab alone	II	NCT02492568
	NSCLC, advanced	Pembrolizumab + RT	I	NCT02587455
	NSCLC, advanced	Pembrolizumab	I	NCT02608385

Table 3 *(continued)*

Table 3 *(continued)*

Inhibitors	Conditions	Interventions/treatments arms	Phases	NCT number/reference
Chemotherapy	NSCLC	Nivolumab+ nab-paclitaxel + carboplatinum	I	NCT02309177
	NSCLC	Pembrolizumab alone or combined with platinum doublets	I	NCT01840579/Keynote-011
	NSCLC	Pembrolizumab + nab-paclitaxel + carboplatinum	I/II	NCT02382406
	NSCLC, advanced	Pembrolizumab + gemcitabine	I/II	NCT02422381
	Solid tumors	Pembrolizumab + gemcitabine or + docetaxel or +nab paclitaxel or + vinorelbine or + irinotecan or + liposomal doxorubicin	I/II	NCT02331251/PembroPlus
	NSCLC, advanced	Pembrolizumab + carbo-paclitaxel	II	NCT02581943
	SCLC, advanced	Pembrolizumab + paclitaxel	II	NCT02551432
	NSCLC, advanced	Pembrolizumab + docetaxel *vs.* docetaxel alone	II	NCT02574598
	SCLC, advanced	Pembrolizumab + cis/carboplatinum +etoposide	II	NCT02580994
	NSCLC, advanced, 1st line	Pembrolizumab + carbo/paclitaxel or carbo/permetrexed *vs.* CT alone	II	NCT02591615
	NSCLC, non-squamous, advanced, PDL1+ pts	Pembrolizumab +/- platinum + permetrexed	III	NCT02578680/Keynote-189
HDAC-I	NSCLC	Nivolumab alone *vs.* azacitidine and entinostat followed by nivolumab	II	NCT01928576
	NSCLC, advanced	Pembrolizumab + entinostat	I/II	NCT02437136
	NSCLC, advanced	Pembrolizumab + azacitidine or placebo	II	NCT02546986
TKI	NSCLC, advanced	Nivolumab + galunisertib	Ib	NCT02423343
	NSCLC, advanced, ALK+	Nivolumab + ceretinib	I	NCT02393625
	NSCLC, erlotinib resistant	Pembrolizumab + afatinib	I/II	NCT02364609
	NSCLC, advanced	Pembrolizumab + ACP-196 (Btk-inhibitor)		NCT02448303
	NSCLC, advanced, ALK+	Pembrolizumab + crizotinib	I	NCT02511184
	NSCLC, advanced	Pembrolizumab + PLX3397 (kit and CSF1R inhibitor)	I	NCT02452424
	solid tumors	Pembrolizumab + lenvantinib	I/II	NCT02501096
Vaccine	NSCLC	Nivolumab + viagenpumatucel-L	Ib	NCT02439450/DURGA trial
	NSCLC, adenocarcinoma	Nivolumab + GMCD40L vaccine	I/II	NCT02466568
	NSCLC, advanced	Pembrolizumab + modified vaccinia virus ankara vaccine expressing p53	I	NCT02432963

Table 3 *(continued)*

Table 3 *(continued)*

Inhibitors	Conditions	Interventions/treatments arms	Phases	NCT number/reference
Immunomodulator	SCLC, extensive diseaese	Nivolumab + ulocuplumab (anti-CXCR4)	I	NCT02472977/CXCessoR4
	NSCLC, advanced	Nivolumab + INCB24360 (IDO-inhibitor)	I/II	NCT02327078
	NSCLC, advanced	Nivolumab + INCB24360 (IDO-inhibitor)	I/II	NCT02178722
	NSCLC, advanced	Nivolumab + FPA008 (anti-CSF1R)	I	NCT02526017
	NSCLC	Nivolumab + ALT-803 (IL-15)	Ib/II	NCT02523469
	NSCLC, advanced	Pembrolizumab + AM0010 (pegylated recombinant human IL-10)	I	NCT02009449
	NSCLC	Nivolumab + varlilumab	I/II	NCT02335918
	HIV associated solid tumours	Nivolumab + ipilimumab	I	NCT02408861
	Solid tumors	Pembrolizumab + MGA271 (anti-B7H3)	I	NCT02475213
	SCLC, extensive disease after 1st line CT	Nivolumab alone or with ipilimumab or placebo after completion of platinum CT	III	NCT02538666/Checkmate 451
Diverse	NSCLC, treatment-naive stage III/IV	Nivolumab alone or combined with gemcitabine, cisplatin, pemetrexed, paclitaxel, carboplatin, bevacizumab, erlotinib, ipilimumab	I	NCT01454102/CheckMate 012 (30)
	NSCLC, advanced	Nivolumab alone or combined with gemcitabine, carboplatin, pemetrexed, paclitaxel, bevacizumab, erlotinib, palliative RT, nab-paclitaxel, docetaxel, crizotinib	I/II	NCT02574078/Checkmate 370
	NSCLC, advanced	Nivolumab alone or with ipilimumab or with platinum CT *vs.* platinum CT	III	NCT02477826/Checkmate 227
	NSCLC, advanced	Nivolumab + temsirolimus or irinotecan or irinotecan + capecitabine	I/II	NCT02423954/NivoPlus
	NSCLC, advanced	Pembrolizumab + paclitaxel or + carboplatin or + bevacizumab or + pemetrexed or + ipilimumab or + erlotinib or + gefitinib	I/II	NCT02039674, Keynote-021 (31,32)
	NSCLC, advanced	Pembrolizumab + ramucirumab	I	NCT02443324
	NSCLC, advanced	Pembrolizumab + necitumumab (anti-EGFR)	I	NCT02451930
	NSCLC, advanced	Pembrolizumab + PEGPH20 (pegylatd recombinant human hyaluronidase)	Ib	NCT02563548
PDL1				
Radiotherapy	NSCLC, stage I (inoperable)	Atezolizumab + SBRT	I	NCT02599454
	NSCLC, advanced	Atezolizumab + SBRT	I	NCT02400814
	NSCLC, unresectable	Atezolizumab + CRT (first line)	II	NCT02525757/DETERRED
Chemotherapy	NSCLC, non-squamous	Atezolizumab with carbo/Nab-paclitaxel +/- bevacizumab	III	NCT02367781/IMpower 150
	NSCLC, squamous, advanced	Atezolizumab with carbo/paclitaxel or carboplatin/ Nab-paclitaxel versus carboplatin/Nab-paclitaxel	III	NCT02367794/IMpower 131
	NSCLC, non-squamous	Atezolizumab with carbo/Nab-paclitaxel *vs.* carbo/ Nab-paclitaxel alone	III	NCT02367781/IMpower 130
	sSolid tumours	Atezolizumab with bevacizumab or bevacizumab/ folfox or carbo/paclitaxel or carbo/pemetrexed or carbo/nabpaclitaxel or nabpaclitaxel	Ib	NCT01633970 (33)

Table 3 *(continued)*

Table 3 *(continued)*

Inhibitors	Conditions	Interventions/treatments arms	Phases	NCT number/reference
Vaccine	NSCLCL	Atezolizumab + CDX-1401 (DEC-205/NY-ESO-1 fusion protein)	II	NCT02495636
Immunomodulator	NSCLC, advanced	Atezolizumab + INCB24360 (IDO-inhibitor)	I	NCT02298153
	NSCLC, advanced	Atezolizumab + varlilumab	I/II	NCT02543645
	Solid tumours	Durvalumab +/– tremelimumab	I	NCT02537418
	NSCLC, advanced	Durvalumab + tremelimumab	I/II	NCT02000947
	NSCLC, 1st line, EGFR, ALK WT advanced	Durvalumab + tremelimumab *vs.* soc	III	NCT02542293/Neptune
	NSCLC, 1st line, EGFR, ALK WT advanced	Durvalumab +/– tremelimumab *vs.* soc	III	NCT02453282/Mystic
	NSCLC, advanced	Durvalumab +/– tremelimumab *vs.* soc	III	NCT02352948/ARTIC
	Solid tumours	Avelumab + PF-05082566 (anti-4-1BB)	I/II	NCT02554812/Javelin Medley
TKI	NSCLC, EGFR, ALK mutated	Atezolizumab + alectinib or erlotinib	Ib	NCT02013219
	NSCLC	Durvalumab with gefitinib	I	NCT02088112
	NSCLC, ALK mutated	Avelumab + crizotinib or PF-06463922 (ALK inhibitor)	I	NCT02584634/Javelin 101
	NSCLC	Durvalumab + selumetinib	I	NCT02586987
	Solid tumors	Durvalumab + ibrutinib	I/II	NCT02403271
	NSCLC, advanced	Durvalumab + AZD9291 (EGFR-inhibitor)	I	NCT02143466
Diverse	NSCLC	Atezolizumab with vemurafenib; alectinib; trastuzumab emtansine	II	NCT02314481
	NSCLC, squamous, stage IIIB-IV	Durvalumab with PI3 kinase inhibitor GDC-0032; palbociclib isethionate; FGFR inhibitor AZD4547; rilotumumab; docetaxel; erlotinib hydrochloride	II/III	NCT02154490
	NSCLC, non-squamous	Atezolizumab with carboplatin; paclitaxel with or without bevacizumab	III	NCT02366143
	NSCLC, advanced	Durvalumab + ramucirumab	I	NCT02572687
	NSCLC, advanced	Gefitinib + durvalumab (sequential), AZD9291 + durvalumab (sequential), selumetinib + docetaxel + durvalumab (sequential),tremelimumab+durvalumab (sequential)	II	NCT02179671
	NSCLC, ATM deficient	AZD6738 (ATR inhibitor)	I/II	NCT02264678

CTLA4, cytotoxic T-lymphocyte-associated protein 4; NSCLC, non-small cell lung cancer; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiation therapy; BSC, best supportive care; CT, chemotherapy; SCLC, small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; SoC, standard of care; RT, radiotherapy; PDL1, programmed death ligand 1; pts, patients; CSF1R, colony stimulating factor 1 receptor; CXCR4, C-X-C motif receptor 4; IDO, indoleamine 2,3 dioxygenase; IL, interleukin.

I trial with a very original approach by targeting an immunosuppressive enzyme indoleamine 2,3 dioxygenase (IDO). Because they had previously shown that anti-IDO T cells may exist in human beings, they wanted to boost this anti-inhibitory Tcells with a vaccine consisting of an IDO peptide. The ultimate goal is to setup anti-IDO T cells that should have a boosting effect on the immune system. In the 15 treated patients with NSCLC, no toxicity was seen and there was a median OS of 25 months which was superior to the 7 months for the non-vaccinated group (excluded because not HLA-A2 positive) (40). These interesting results need confirmation in a double blind trial.

Vaccine treatments (*Table S2*)

The aim of a vaccine treatment in tumor biology is to mount an effective immune response by the host in order to eliminate the cancer cells by specific recognition by cytotoxic CD8 T cells. However, in contrast to healthy subjects, cancer patients are already in an immunosuppressed status. So it might be even more difficult to find an effective vaccination strategy in a cancer patient. Different types of vaccines exist: rather aspecific whole tumor or tumor lysate vaccination versus strategies where one epitope of a tumor antigen is the target. The latter strategy includes RNA and DNA vaccines, specific gangliosides or peptide vaccines and autologous dendritic cell vaccines. The actual timing of a vaccine in the anti-cancer treatment is mostly in the adjuvant setting: after successful surgery accompanied with or without chemotherapy. In general and despite many efforts in lung cancer research, therapeutical vaccinations did not lead to a breakthrough [reviewed by (41)]. Nevertheless, many studies found a niche or a genetic signature of patients who might benefit from a vaccine (*Table S2*). The reason for these failures might reside on the fact that these vaccines did not address the issue of tumor antigen tolerance in cancer patient. Indeed, cancer cells are "self" cells and have therefore multiple pathways to hamper immune cells from attacking them. Therefore, it might be very interesting to combine a vaccine with an immune checkpoint modulator, as CD8 T cell response might be boosted directly via the vaccine and indirectly by relieving immunosuppression. This strategy is supported by a lot of preclinical rationale and should soon be tested in lung cancer patients. Some trials have already been set up (NCT NCT02495636, NCT02466568, …*Table S2*).

Adoptive T cell therapy approaches (*Table S3*)

In order to evade the formation of an effective CD8 T cell response upon vaccination, one step further is to inject directly tumor specific T cells. Most approaches hereby consist in isolating T cells from the initial tumor, let them exponentially grow and reinfuse them in much larger quantities into cancer patients. This strategy was very effective in a well selected population with metastatic melanoma (42) and is ongoing in lung cancer (NCT00569296, NCT02133196). Another T cell based strategy is the use of CAR T cells. These T cells are transfected with a transformed hybrid molecule between a single chain Fv directed against a tumor antigen and a T-cell receptor intracellular signaling. Such CAR T-cells can directly recognize a tumor antigen without the need of MHC molecules. This strategy turned out to be very effective in CD19 malignancies with CD19 CAR T cells (43). A similar strategy using CARs directed against VEGFR2 is underway in lung cancer patients (NCT01218867).

Conclusions and future perspectives

One of the major challenges in the field of lung cancer immunotherapy is to overcome primary and secondary resistance towards anti-PD(L)1 antibody therapy. Preclinical research showed that a combination of checkpoint inhibition with radiotherapy, chemotherapy, anti-angiogenesis, and targeted therapy, could increase the cure rate (44). However early results from a combination of TKI and checkpoint inhibition in renal cancer (45) did show major liver toxicity, slowing down the development of these combinatorial regimens. Recently, two trials combing a TKI with durvalumab were suspended due to interstitial lung disease (46). Therefore innovating trials with different timing of the treatments (sequential, alternating days) or different administration routes (e.g., intratumoral) are highly awaited. The first results of the combination of nivolumab and ipilimumab showed increased OS rates both in patients with NSCLC and SCLC with manageable toxicity (29,31). About 20 trials have started to address this question (*Table 3*). Preclinical studies combining radiotherapy with checkpoint inhibition showed increased occurrence of abscopal effect [tumor response outside radiotherapy field due to immunological induced anti-cancer response (47)]. Therefore, up to 12 trials combining immune checkpoint blockade with radiotherapy are under

way (*Table 3*), including trials conducted at our institute (personal communication Dr. Deutsch). Up to now, only very disperse results on abscopal effect in patients were reported (48). Another promising strategy is to combine chemotherapy with immunotherapy. However, as chemotherapy may be deleterious for lymphocytes, this may diminish the formation of an immunological memory, which is important for long term immunological memory (20 trials ongoing *Table 3*). Last but not least, several preclinical studies suggest that it could be very interesting to repeat some of the vaccination studies with our current knowledge of immune checkpoint inhibitors, even if our clinical experience with the combination of gp100 with ipilimumab did not confirm this hypothesis (49). Several studies are ongoing to evaluate if PD(L)1 antibodies have a better profile (NCT02439450, NCT02466568, NCT02432963). In addition to the results of the ongoing clinical trials that evaluate the feasibility and efficacy of these combinations, the results of the ancillary studies are of interest to find novel biomarkers in responding patients, in order to tailor immunotherapy to each patient and diminish side effects. Therefore are awaiting highly interesting times in the field of immuno-oncology.

Acknowledgements

Sandrine Aspeslagh is an ESMO fellow (Georges Mathé grant 2014).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Rosell R, Skrzypski M, Jassem E, et al. BRCA1: a novel prognostic factor in resected non-small-cell lung cancer. PLoS One 2007;2:e1129.
2. Couzin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy. Science 2013;342:1432-3.
3. Zikos TA, Donnenberg AD, Landreneau RJ, et al. Lung T-cell subset composition at the time of surgical resection is a prognostic indicator in non-small cell lung cancer. Cancer Immunol Immunother 2011;60:819-27.
4. Djenidi F, Adam J, Goubar A, et al. CD8+CD103+ tumor-infiltrating lymphocytes are tumor-specific tissue-resident memory T cells and a prognostic factor for survival in lung cancer patients. J Immunol 2015;194:3475-86.
5. Huang A, Zhang B, Wang B, et al. Increased CD14(+) HLA-DR (-/low) myeloid-derived suppressor cells correlate with extrathoracic metastasis and poor response to chemotherapy in non-small cell lung cancer patients. Cancer Immunol Immunother 2013;62:1439-51.
6. Woo EY, Yeh H, Chu CS, et al. Cutting edge: Regulatory T cells from lung cancer patients directly inhibit autologous T cell proliferation. J Immunol 2002;168:4272-6.
7. Zatloukal P, Heo DS, Park K, et al. Randomized phase II clinical trial comparing tremelimumab with best supportive care following first-line platinum-based therapy in patients with advanced non-small cell lung cancer. J Clin Oncol 2009;27:abstr 8071.
8. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28:3167-75.
9. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.
10. Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol 2015;16:257-65.
11. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
12. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.
13. Garon EB, Leighl NB, Rizvi NA, et al. Safety and Clinical Activity of Pembrolizumab (MK-3475) in Previously Treated Patients With Non-Small Cell Lung Cancer. J Clin Oncol 2014;32:abstr 8002.
14. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563-7.
15. Spira A, Park K, Mazières J, et al. Efficacy, safety and predictive biomarker results from a randomized phase II study comparing MPDL3280A vs docetaxel in 2L/3L NSCLC (POPLAR). J Clin Oncol 2015;33:abstr 8010.
16. Khleif SN, Lutzky J, Segal NH, et al. MEDI4736, an anti-PD-L1 antibody with modified Fc domain: preclinical evaluation and early clinical results from a phase I study

in patients with advanced solid tumors; Proceedings from the European Cancer Congress 2013; 2013 Sep 27-Oct 1; Amsterdam, The Netherlands. Abstract No. 802.
17. Bulliard Y, Jolicoeur R, Windman M, et al. Activating Fc receptors contribute to the antitumor activities of immunoregulatory receptor-targeting antibodies. J Exp Med 2013;210:1685-93.
18. Simpson TR, Li F, Montalvo-Ortiz W, et al. Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti-CTLA-4 therapy against melanoma. J Exp Med 2013;210:1695-710.
19. Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol 2012;30:2046-54.
20. Horinouchi H, Yamamoto N, Fujiwara Y, et al. Phase I study of ipilimumab in phased combination with paclitaxel and carboplatin in Japanese patients with non-small-cell lung cancer. Invest New Drugs 2015;33:881-9.
21. FDA expands approved use of Opdivo to treat lung cancer. Available online: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436534.htm
22. Opdivo. Available online: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003985/human_med_001876.jsp&mid=WC0b01ac058001d124
23. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018-28.
24. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124-8.
25. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2015. doi: 10.1016/S0140-6736(15)01281-7.
26. FDA approves Keytruda for advanced non-small cell lung cancer. Available online: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm465444.htm
27. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455-65.
28. Reck M, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol 2013;24:75-83.
29. Antonia S, Bendell J, Matthew T, et al. Phase I/II Study (CheckMate 032) of Nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC). J Clin Oncol 2015;33:abstr 7503.
30. Rizvi N, gettinger S, Goldman JW. Safety and efficacy of first-line nivolumab and ipilimumab in non-small cell lung cancer. World Conf Lung Cancer. 2015:abstr orla 02.05.
31. Patnaik A, Socinski M, Gubens M, et al. Phase 1 study of pembrolizumab (pembro; MK-3475) plus ipilimumab (IPI) as second-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021 cohort D. J Clin Oncol 2015;33:abstr 8011.
32. Papdimitrakopoulou V, Patnaik A, Borghaei H, et al. Pembrolizumab (pembro; MK-3475) plus platinum doublet chemotherapy (PDC) as front-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021 Cohorts A and C. J Clin Oncol 2015;33:abstr 8031.
33. Liu S, Powderly JD, Camidge DR, et al. Safety and efficacy of MPDL3280A (anti-PDL1) in combination with platinum-based doublet chemotherapy in patients with advanced non-small cell lung cancer. J Clin Oncol 2015;33:abstr 8030.
34. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373:23-34.
35. Marabelle A, Kohrt H, Sagiv-Barfi I, et al. Depleting tumor-specific Tregs at a single site eradicates disseminated tumors. J Clin Invest 2013;123:2447-63.
36. Brody J, Kohrt H, Marabelle A, et al. Active and passive immunotherapy for lymphoma: proving principles and improving results. J Clin Oncol 2011;29:1864-75.
37. Le Mercier I, Poujol D, Sanlaville A, et al. Tumor promotion by intratumoral plasmacytoid dendritic cells is reversed by TLR7 ligand treatment. Cancer Res 2013;73:4629-40.
38. Rosenberg SA. IL-2: the first effective immunotherapy for human cancer. J Immunol 2014;192:5451-8.
39. van den Heuvel MJ, Garg N, Van Kaer L, et al. NKT cell costimulation: experimental progress and therapeutic promise. Trends Mol Med 2011;17:65-77.
40. Iversen TZ, Engell-Noerregaard L, Ellebaek E, et al. Long-lasting disease stabilization in the absence of toxicity in metastatic lung cancer patients vaccinated with an epitope derived from indoleamine 2,3 dioxygenase. Clin Cancer Res 2014;20:221-32.
41. Declerck S, Vansteenkiste J. Immunotherapy for lung

cancer: ongoing clinical trials. Future Oncol 2014;10:91-105.
42. Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. Science 2015;348:62-8.
43. Maus MV, Grupp SA, Porter DL, et al. Antibody-modified T cells: CARs take the front seat for hematologic malignancies. Blood 2014;123:2625-35.
44. Antonia SJ, Larkin J, Ascierto PA. Immuno-oncology combinations: a review of clinical experience and future prospects. Clin Cancer Res 2014;20:6258-68.
45. Amin A, Plimack E, Infante J, et al. Nivolumab (anti-PD1) in combination with sunitib or pazopanib in patients with metastatic renal cell carcinoma (mRCC). J Clin Oncol 2014;32:abstr 5010.
46. AstraZeneca PLC (AZN) Halts Two Lung Cancer Drug Combination Trials After Lung Disease Reports. Available online: http://www.biospace.com/News/astrazeneca-plc-halts-two-lung-cancer-drug/394464
47. Frey B, Rubner Y, Wunderlich R, et al. Induction of abscopal anti-tumor immunity and immunogenic tumor cell death by ionizing irradiation - implications for cancer therapies. Curr Med Chem 2012;19:1751-64.
48. Golden EB, Demaria S, Schiff PB, et al. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer Immunol Res 2013;1:365-72.
49. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.

Cite this article as: Aspeslagh S, Marabelle A, Soria JC, Armand JP. Upcoming innovations in lung cancer immunotherapy: focus on immune checkpoint inhibitors. Chin Clin Oncol 2015;4(4):48. doi: 10.3978/j.issn.2304-3865.2015.12.06

Supplementary

Table S1 Aspecific immunomodulatory agents for the treatment of lung cancer

Conditions	Interventions/treatments arms	Phases	NCT number/reference
Diverse			
NSCLC	Docetaxel|Biological: HyperAcuteÂ®-Lung immunotherapy; gemcitabine; pemetrexed	II/III	NCT01774578
Lung cancer	MVA-brachyury-TRICOM	I	NCT02179515
Lung cancer	OBI-833 (Globo H-CRM197)/OBI-821	I	NCT02310464
Lung cancer	INO-1400; INO-9012 (Inovio TRT-001: Telomerase DNA Immunotherapy)	I	NCT02327468
NSCLC, stage IIIB-IV, after failure of 2 or more regimen	1.5 g talactoferrin BID (recombinant form of human talactoferrin alfa) po *vs.* placebo BID	III	Fortis trial/Ramalingam *et al.*, 2013, *Ann Oncol*
Stage III-IV NSCLC, stable disease after chemotherapy	Anti-IDO vaccine (IDO5 peptide, sequence ALLEIASCL, formulated in Montanide)	I	NCT01219348
Lung cancer/adenocarcinoma	GM.CD40L.CCL21 vaccinations	I/II	NCT01433172
TLR agonist			
SCLC	MGN1703	II	NCT02200081
Cytokine			
NSCLC, stage III-IV	Recombinant interleukin-15	I	NCT01727076
Solid tumour (oligometastatic), after SBRT	L19-IL2	I	NCT02086721
Radiotherapy + cytokine			
NSCLC, disease control following 1st line CT	NHS-IL2 (selectikine: human NHS76 (antibody specific for necrotic DNA) fused to genetically modified human IL-2) IV infusion on 3 consecutive days, every 3 weeks + local irradiation of a single pulmonary nodule (5×4 Gy)	Ib	NCT00879866, Van den Heuvel *et al.*, 2015, *J of Transl Medicine*
Chemotherapy + cytokine			
NSCLC, stage IIIB-IV	Gemcitabine (1,000 mg/m^2) day 1&8, cisplatin (100 mg/m^2) day 2, every 3 weeks with or without low dose SC IL-2 (3.10×10^6 IU on day 3–5, 9–11, 15–17)	III	Ridolfi et al, 2011, *Int J Oncol*
SCLC	Carboplatin (5.5 mg/m^2) day 1, ifosfamide (3.5 mg/m^2) day 1, etoposide 200 mg/m^2 day 1–3, every 28 days + 3 weekly IFNa (3.10×10^6 U) or 3 weekly IFNg (3.10×10^6 U) or 3 weekly IFNg & IFNa (both 1.5×10^6 U)		
Cytokine induced killer cells			
NSCLC	Paclitaxel + cisplatin *vs.* CIK cell therapy	I/II	NCT01902875
NSCLC, stage IIIB-IV, following navelbine-cisplatin CT	HLA haploididentical donor-derived CIK cells *vs.* BSC	I/II	Wang *et al.*, 2014, *Oncology Letters*
NSCLC, stage IIIB-IV	More than 2 rounds of DC-CIK therapy *vs.* two rounds of DC-CIK therapy	I/II	Zhong *et al.*, 2014, *Tumor Biol*
NSCLC, stage IIIB-IV	4 cycles navelbine (25 mg/m^2) day 1&8, cisplatin (80 mg/m^2) day 1+4 cycles of autologous CIK cells activated by antigen loaded DC (monthly)	I/II	Yang *et al.*, 2013, *Cancer Immunol Immunoth*
SCLC	Autologous CIK	II	NCT01592422

Table S1 *(continued)*

Table S1 *(continued)*

Conditions	Interventions/treatments arms	Phases	NCT number/reference
Lung cancer	CIKI + cisplatin + paclitaxel *vs.* arm 2: cisplatin + paclitaxel	II/III	NCT01631357
NSCLC, stage IIIB-IV, after 1-2 chemotherapy or anti-EGFR therapy	Autologous *ex vivo* expanded NK cell enriched lymphocytes with docetaxel (35 mg/m^2) both treatment on d1and d8, cycle of 3 weeks	IIA	Yang *et al.*, 2013, *Anticancer Research*
NSCLC, stage IIIA/B	Hsp70-peptide TKD/IL-2 activated, autologous NK cells	II	NCT02118415

NSCLC, non-small cell lung cancer; IDO, indoleamine 2,3 dioxygenase; SCLC, small cell lung cancer; SBRT, stereotactic body radiation therapy; IL, interleukin; CT, chemotherapy; IFNa, interferon alfa; IFNg, interferon gamma; CIK, cytokine induced killer cells; BSC, best supportive care; DC, dendritic cell; EGFR, epidermal growth factor receptor; NK cell, natural killer cell.

Table S2 Vaccination strategies in lung cancer

Strategies	Conditions	Interventions/treatments arms	Phases	NCT number/reference
Tumor lysate vaccination	Lung cancer/ mesothelioma	H1299 lysate vaccine; cyclophosphamide; celecoxib	I/II	NCT02054104
	Lung cancer	MV mix vaccine	I/II	NCT02333474
	Lung cancer	cancer stem cell vaccine	I/II	NCT02115958
Whole tumor cell vaccination				
Monotherapy	NSCLC stage II, III or IV	Lucanix™ vaccine therapy (=belagenpumatucil-L) 1.25×10^7, 2.5×10^7 or 5.10×10^7 cells/injection, intradermally, every 1 or 2 months up to a total of 16 injections	II	Nemunaitis *et al.*, 2006, *JCO*
	NSCLC stage III/IV with disease stabilization after platinum based CT	BSC + Lucanix™ vaccine therapy (=belagenpumatucel-L) (18× monthly 2.5×10^7 cells + 2×3 monthly 2.5×10^7 cells) *vs.* BSC + placebo	III	NCT00676507, Giaconne *et al.*, 2013, *Annal Oncol*, abstract LBA2, STOP trial
Combination	NSCLC	FANG, Bi-shRNA-furin and granulocyte macrophage colony stimulating factor (GMCSF) augmented autologous tumor cell vaccine	I	NCT01061840
	Lung cancer/ mesothelioma after resection	Allogeneic tumor cell vaccine (K562); celecoxib; cyclophosphamide	I	NCT01143545
	Lung cancer/ mesothelioma after or before resection	Celecoxib; tumor cell vaccine ISCOMATRIX adjuvant	I	NCT01258868
	NSCLC, non squamous; after resection	Epigenetically modified autologous tumor; cyclophosphamide; celecoxib	I	NCT01341496
RNA/DNA/viral vector type vaccination				
Monotherapy	NSCLC	semi-allogeneic human fibroblasts (MRC-5) transfected with DNA	I	NCT00793208
	NSCLC, expressing NY-ESO-1	ID-LV305, intradermal	I	NCT02122861
	NSCLC, non squamous	Ad-sig-hMUC-1/ecdCD40L vector vaccine	I	NCT02140996

Table S2 *(continued)*

Table S2 *(continued)*

Strategies	Conditions	Interventions/treatments arms	Phases	NCT number/reference
Combination	NSCLC stage IV	CV9202 (RNActive derived cancer vaccine), local radiation	I	NCT01915524
	Treatment-naive MUC1 positive stage IIIB/IV NSCLC	TGA40 [poxvirus (MVA) coding for the MUC1 tumor-associated antigen and IL-2] plus cisplatin + gemcitabin *vs.* placebo plus cisplatin + gemcitabin	IIB	NCT00415818/Quoix *et al.*, 2011, *Lancet Oncol*
	Treatment-naive MUC1 positive stage IV NSCLC	TGA40 [poxvirus (MVA) coding for the MUC1 tumor-associated antigen and IL-2] plus CT *vs.* placebo plus CT	IIB/III	NCT01383148, TIME trial
Peptide/ganglioside/protein vaccination				
Monotherapy	SCLC, HLA-A*24-positive	HLA-A*2402-restricted CDCA1 and KIF20A peptides	I	NCT01069653
	NSCLC, HLA-A*24-positive	HLA-A*2402restricted URLC10, CDCA1, and KIF20A peptides	I	NCT01069575
	NSCLC, HLA-A*02-positive	HLA-A*0201 or HLA-A*0206-restricted URLC10 peptides	I	NCT01069640
	NSCLC, HLA-A*02 positive	HLA-A*0201restricted URLC10 peptides with adjuvant	I/II	NCT01949701
	NSCLC, HLA-A*24 positive	HLA-A*2402restricted URLC10, CDCA1, and KIF20A peptides with adjuvant	I/II	NCT01950156
	HER2+ cancer	AVX901	I	NCT01526473
	Cancer	WT2725	I	NCT01621542
	NSCLC	Mucin1 (MUC1) peptide vaccine + PolyICLC	I/II	NCT01720836
	NSCLC	UV1 synthetic peptide vaccine and GM-CSF	I/II	NCT01789099
	NSCLC	Vx-001; placebo	II	NCT01935154
	NSCLC stage IV	P10s-PADRE vaccine (carbohydrate mimotope vaccine); placebo	II	NCT02264236
	NSCLC stage III, inoperable	GV1001 (telomerase vaccine); normal saline	III	NCT01579188
	NSCLC, stage IIIB-IV, after first-line CT	L-BLP-25 (tecemotide, stimuvax®) vaccine (including one IV dose cyclophosphamide 300 mg/m^2) plus BSC *vs.* BSC alone	II	NCT00157209, Butts *et al.*, 2011, *J Cancer Res Clin Oncol*
	NSCLC, stage III, after (concurrent or sequential) CRT, Asian patients	L-BLP-25 (tecemotide, stimuvax®) (including one IV dose cyclophosphamide 300 mg/m^2) vaccine *vs.* placebo	III	NCT00409188, Butts *et al.*, 2015, *Lancet Oncol*, START trial
	NSCLC, stage III, after concurrent CRT, Asian patients	L-BLP-25 (tecemotide, stimuvax®) (including one IV dose cyclophosphamide 300 mg/m^2) vaccine *vs.* placebo	III	NCT01015443, Wu *et al.*, 2011, *BMC Cancer,* INSPIRE
	NSCLC, stage IIIA or IIIB, no progression after two cycles of platinum based CRT	L-BLP-25 (tecemotide, stimuvax®) (including one IV dose cyclophosphamide 300 mg/m^2) vaccine *vs.* placebo	III	NCT02049151, START2
	Completely resected MAGE-A3-positive stage IB to II NSCLC	MAGE-A3 protein combined with an immunostimulant (AS02B) (13 doses over 27 months)	II	Vansteenkiste *et al.*, *JCO*, 2013, Ulloa-Montoya *et al.*, *JCO*, 2013/MAGRIT

Table S2 *(continued)*

Table S2 *(continued)*

Strategies	Conditions	Interventions/treatments arms	Phases	NCT number/reference
Monotherapy	NSCLC, stage IB, II or IIIA, completely resected MAGE-A3 positive (cohorts +/- adjuvant CT)	MAGE-A3 vaccine *vs.* placebo	III	NCT00480025
	NSCLC stage IIIB/IV after standard CT and/or RT	Five biweekly vaccination with racotumumab (1×10^{10}, anti-idiotype ganglioside vaccine) followed by monthly maintenance	II	Alfonso *et al.*, 2007, *Cancer Biol Ther*
	Stage III/IV NSCLC after standard CT and/or RT	Racotumumab (1×10^{10}, anti-idiotype ganglioside vaccine) plus BSC *vs.* BSC alone	III	NCT01460472
	SCLC-limited disease after a major response to CT and chest RT	Bec2 (anti-idiotypic antibody mimicking GD3, a ganlioside)/bacille calmette-guerin (BCG) vaccination *vs.* placebo	III	Silva Study/Giaccone *et al.*, 2005, *JCO*
Combination	NSCLC	Viagenpumatucel-L (HS-110); metronomic cyclophosphamide; physician's choice regimen	II	NCT02117024
	NSCLC, stage IIIB or IV after conventional 1st line CT	cyclophosphamide plus (CIMAVax) EGF vaccine plus BSC *vs.* BSC alone	II	Neninger Vinageras *et al.*, 2008, *JCO*
	NSCLC, stage IV after conventional 1st line CT, EGFR WT	cyclophosphamide plus (CIMAVax) EGF vaccine plus BSC *vs.* BSC alone	III	NCT02187367
	NSCLC	Racotumumab	III	NCT01460472
	Advanced NSCLC	racotumumab (1×10^{10}, anti-idiotype ganglioside vaccine) plus BSC *vs.* BSC alone plus docetaxel if 2nd line therapy indicated	II	NCT01240447
	NSCLC, stage IIIA or IIIB, no curative surgery possible, after CRT	Bevacizumab; emepepimut-S (BLP25 liposome vaccine) ; carboplatin; cyclophosphamide; paclitaxel; radiation therapy	II	NCT00828009
	NSCLC, stage III	Cyclophosphamide; DRibble vaccine; Imiquimod; GM-CSF; HPV vaccine	II	NCT01909752
	Recurrent lung carcinoma, stage IIB lung carcinoma, NY-ESO-1 positive	DEC-205/NY-ESO-1 fusion protein CDX-1401; sirolimus	I	NCT01522820
Dendritic cell vaccination	NSCLC, stage IIIB-IV, expressing either HER-2, CEA, MAGE-1 or WT-1, after CRT	Autologous DC pulsed with HLA-A2 molecules restricted to WT1 peptide, CEA-peptide, MAGE-1 peptide and HER-2 peptide, SC and IV on day 0 and 14	I	Perroud *et al.*, 2011, *JECCR*
	NSCLC, stage IIB-IIIA, after curative tumorectomy	Autologous DC pulsed with lyophilized autologous tumor cells: day 2, 6, 10 and 14	III	Skachkova *et al.*, 2013, *Exp Oncol*
	HER2+ cancer	Autologous Ad HER2 dendritic cell vaccine	I	NCT01730118

NSCLC, non small cell lung cancer; CT, chemotherapy; BSC, best supportive care; IL, interleukin; CRT, chemoradiotherapy; SCLC, small cell lung cancer; RT, radiotherapy; EGFR, epidermal growth factor receptor; DC, dendritic cell.

Table S3 T cell therapy in lung cancer

Conditions	Interventions/treatments arms	Phases	NCT number
Lung cancer	EGFRBi-armed autologous activated T cells; aldesleukin; sargramostim	I	NCT00569296
	Anti-VEGFR2 CAR CD8 plus PBL; cyclophosphamide; aldesleukin; fludarabine	I/II	NCT01218867
	Aldesleukin; fludarabine; cyclophosphamide; young TIL	II	NCT02133196

EGFR, epidermal growth factor receptor.