Immunotherapy and lung cancer: current developments and novel targeted therapies

Non-small-cell lung cancer (NSCLC) is a highly prevalent and aggressive disease. In the metastatic setting, major advances include the incorporation of immunotherapy and targeted therapies into the clinician’s therapeutic armamentarium. Standard chemotherapeutic regimens have long been reported to interfere with the immune response to the tumor; conversely, antitumor immunity may add to the effects of those therapies. The aim of immunotherapy is to specifically enhance the immune response directed to the tumor. Recently, many trials addressed the role of such therapies for metastatic NSCLC treatment: ipilimumab, tremelimumab, nivolumab and lambrolizumab are immunotherapeutic agents of main interest in this field. In addition, anti-tumor vaccines, such as MAGE-A3, Tecetomide, TG4010, CIMAvax, ganglioside vaccines, tumor cell vaccines and dendritic cell vaccines, emerged as potent inducers of immune response against the tumor. The current work aims to address the most recent developments regarding these innovative immunotherapies and their implementation in the treatment of metastatic NSCLC.

Keywords: checkpoint inhibitors • immunotherapies • lung cancer • nivolumab • tremelimumab • tumor vaccines

Background
Lung cancer is the most commonly diagnosed malignancy in less developed regions of the world, and the second in the most developed nations, with 1.8 million new cases in 2012, corresponding to a 12.9% of the global cancer burden. Due to its high lethality, lung cancer is, at the same time, the most common cause of death from cancer [1]. The two main histological subtypes of lung cancer are small-cell lung cancer (SCLC) and non-SCLC (NSCLC), the latter accounting for approximately 85% of all cases [2] and being diagnosed in the locally advanced or metastatic stage at presentation in 70% of patients [3]. Overall, only 16.6% of lung cancer patients survive 5 years or more (3.9% in the metastatic setting) [4]. For patients with advanced-stage NSCLC, chemotherapy with a platinum-doublet yields a median overall survival (OS) of approximately 10 months [5]. Cisplatin-based chemotherapy in the adjuvant setting showed an absolute survival benefit of 5% [6]. Recent introduction of molecular targeted therapies in the metastatic setting resulted in clinically meaningful OS improvements, but only in selected patients with tumors harboring specific genetic profiles, such as activating mutations of the EGFR receptor (EGFR) and the ALK translocations [7]. Therefore, even with the latest advances, lung cancer prognosis remains dismal, mandating research for novel therapies with new mechanisms of action.

Immunotherapy represents a broad class of treatment modalities designed to elicit immune-mediated destruction of tumor cells [8]. Immunotherapy’s encouraging results in other human malignancies hold promise that it may be applied to lung neoplasms [9]. This paper’s main purpose is to provide a comprehensive review about current understanding of immunotherapy for lung cancer.
Lung cancer immunology
A brief description of lung cancer immunology is provided, in order to better understand immunotherapies' mechanisms of action.

Innate immunity
Innate immunity is a nonspecific first line of defense, involving macrophages and neutrophils. A chronic inflammation state induced by smoking, occupational exposures and other environmental factors activates the innate immunity with subsequent release of cytokines. These cytokines may promote tumor destruction, but can also lead to oncogenesis by stimulating tumor proliferation, angiogenesis and metastatic potential. Tumor cells can activate M2 macrophages by releasing IL-10. Sentinel cells from the innate branch of immunity may recognize relatively nonspecific structurally preserved molecules, distinguishable from the host molecules through Toll-like receptors in their surface.

Immunosurveillance
The immunosurveillance hypothesis postulates that malignant cells express antigens that are recognized by the immune system as foreign, eliciting immune responses against the tumor. Antigens are internalized, processed and displayed by APCs, particularly dendritic cells (DCs). The DCs then migrate to the lymph nodes, where they activate T lymphocytes via interaction of the specific T-cell receptors (TCRs) with the processed antigenic determinants bound to the MHC proteins in the DCs surface. CD8+ T cells recognize antigen-MHC class I complexes and, once activated, turn into cytotoxic lymphocytes (CTLs). CD4+ T-helper cells (of the Th1 kind), on the other hand, identify antigen-MHC class II complexes and secrete cytokines, such as IL-2 and IFN-γ, which in turn ease CD8+ T-cell activation. Activated CTLs are able to identify these tumor cells via their complementary TCR, and then induce apoptotic cell death. Finally, a subpopulation of CD4+ CD25+ T lymphocytes, named Tregs, have a fundamental role in maintaining homeostasis by inhibiting excessive immune reactions.

Historically, lung cancer was considered as a non-immune-sensitive neoplasia. However, this notion is beginning to change, since there is increasing evidence that lung tumors can evoke antitumor immune responses (both humoral and cellular-mediated). SCLC patients with clinical features of the immune-mediated Lambert–Eaton paraneoplastic syndrome appeared to have better progression-free survival. Increased stromal infiltration of CD8+ T cells is an independent favorable prognostic indicator in NSCLC. On the other hand, high tumor Treg infiltration is associated with disease recurrence. Actually, the first description of Tregs in the neoplastic setting was made in human lung cancer.

Neoplastic cells may evade immunosurveillance by modulating their tumor-associated antigens, losing MHC expression, escaping apoptosis, inducing T-cell death, increasing Treg or decreasing CD4+ /CD8+ ratios. Lung tumors can also produce a dense stroma, which can thwart infiltration by T cells or therapies. Cigarette smoke exposure may also play a part in this immunosuppressive effect.

Immune checkpoints
Besides the antigen-MHC-TCR interaction, additional co-activation signals must also be present, namely interaction of T cell’s CD28 with the APC’s/tumor cell’s B7 surface molecules (CD80 or CD86).

In order to prevent autoimmunity phenomena, immune checkpoints are set in place. Activated CD8+ T cells express a protein receptor named CTLA-4, which also binds B7 with high affinity, limiting further T-cell activation by CD28. PD1 is another T-cell surface receptor that, upon binding its cognate ligand PD-L1 in the APC/tumor cell, inhibits the immune response. While CTLA-4’s action focuses on limiting the initiation of T-cell activation in the lymph nodes, PD1 acts later by limiting T-cell activity in the tumor microenvironment.

Immunologic effects of irradiation & chemotherapy
Interesting observations from selected case-reports suggest that immunological antitumor effects can be triggered by tumor-cell destruction by means of various treatment modalities. Ionizing radiation induces cell death with consequent release of tumoral antigens. These, in turn, stimulate an inflammatory response that may have antineoplastic activity. In animal studies, radiotherapy is more effective in immunocompetent mice than in their immunodeficient counterparts. Radiotherapy has also been shown to activate innate immunity’s Toll-like receptors. Significant responses have been observed at distant tumor sites after both radiation and administration of Toll-like receptor agonists.

Many chemotherapeutic agents induce cell death mainly by direct necrosis, with spill-over of the intracellular content to the extracellular milieu. This produces an inflammatory response against these unknown components, which can be magnified by immunotherapies. The antigens released during chemotherapy have been used to prime the immune
Figure 1. The immunosurveillance mechanism. Antigens derived from the tumor are processed by APCs and displayed to specific T cells. Activated Th1 cells secrete immunostimulatory cytokines. Activated CD8+ T cells exert cytotoxicity against the tumor. This process is inhibited by Treg cells. Antitumoral vaccines act through this pathway by supplying tumor antigens (and also immunostimulatory adjuvants) to the APCs. CTL: Cytotoxic lymphocyte; IFN: Interferon; TCR: T-cell receptor.

The first immunotherapies developed for NSCLC were recombinant cytokines, namely those secreted by Th1 cells, such as IL-2 and IFN (Figure 1). Phase II trials were not suggestive of clinical benefit for human recombinant IL-2 administration (with or without IFN) [44]. In fact, therapy was not well-tolerated, yielding grade 3–4 cardiac and pulmonary toxicity. A Phase II trial by Correale et al. showed that addition of IL-2 to chemotherapy (gemcitabine plus docetaxel) in patients with advanced NSCLC improved response rates (58.3 vs 28.6%) with good tolerability [41,44]. However, these findings were not replicated in a Phase III randomized trial of IL-2 in combination with chemotherapy with a cisplatinum doublet [42,44]. These results were further challenged by a subsequent study reporting 20% partial response and 50% stable disease among 20 advanced NSCLC patients when IL-2 was administered with the pineal neuro-hormone melatonin [43,44]. Blood concentration of IL-2 seems to follow a circadian pattern, which must be taken into account when defining a therapeutic strategy [45].
Immune checkpoint inhibitors

One of the most promising approaches in immunotherapy for lung cancer is to inhibit the immune checkpoints that harness an effective immune response against the tumor (Figure 2). This is accomplished using T-cell-directed monoclonal antibodies (mAbs). Nevertheless, the same strategy has not been always successful in other tumor types, such as prostate cancer [12,13].

Ipilimumab
Ipilimumab is a fully humanized mAb directed against CTLA-4, which has shown efficacy against metastatic melanoma [46,47]. A Phase II trial for ipilimumab in lung cancer was conducted, but results for NSCLC and SCLC were reported separately.

Lynch et al. [23] enrolled 204 chemotherapy-naive patients with stage IIIIB/IV NSCLC and randomly assigned them (1:1:1) to receive one of the following regimens:

- Paclitaxel-carboplatin chemotherapy with placebo;
- The same chemotherapy with concurrent ipilimumab;
- A phased schedule of 2 chemotherapy cycles followed by ipilimumab with chemotherapy for the next four cycles.

The phased schedule was designed to allow chemotherapy-induced antigen release before ipilimumab administration, whereas the combined schedule meant to guarantee that ipilimumab would be present when said antigen release would have started [9,23].

The study met its primary end point of improved immune-related progression free survival (irPFS) for phased ipilimumab versus the control arm (hazard ratio [HR]: 0.72; p = 0.05), but not for concurrent ipilimumab (HR: 0.81; p = 0.13) [12,23]. A subgroup analysis showed a greater improvement among NSCLC of the squamous subtype.

An equally designed trial was carried out by Reck et al. for extensive disease SCLC. It showed similar results in the sense that the phased schedule, but not the concurrent scheme, increased irPFS when compared with the placebo control (HR: 0.64; p = 0.03) [16]. However, Reck et al. used paclitaxel and carboplatin as chemotherapy, instead of the standard-of-care etoposide-based regimens for SCLC. Preclinical models have shown that anti-CTLA-4 agents act synergistically with etoposide, so further investigation of ipilimumab in SCLC could involve this agent [16,48,49].

These promising results for ipilimumab led to two Phase III trials that are still ongoing (Table 2).
### Table 1. Clinical trials with published data for immunotherapies in lung cancer.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Compound</th>
<th>Comparator</th>
<th>n</th>
<th>Study population</th>
<th>Primary end point</th>
<th>p-value</th>
<th>Ref.</th>
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<tr>
<td>Lynch et al.</td>
<td>2</td>
<td>Ipilimumab + carbo/paclitaxel (concurrent or sequential)</td>
<td>Placebo + carbo/paclitaxel</td>
<td>204</td>
<td>NSCLC (first line)</td>
<td>irPFS: concurrent vs placebo (HR: 0.81)</td>
<td>0.13</td>
<td>[23]</td>
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<td>sequential vs placebo (HR: 0.72)</td>
<td>0.05</td>
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<tr>
<td>Reck et al.</td>
<td>2</td>
<td>Ipilimumab + carbo/paclitaxel (concurrent or sequential)</td>
<td>Placebo + carbo/paclitaxel</td>
<td>130</td>
<td>SCLC (first line)</td>
<td>irPFS: concurrent vs placebo (HR: 0.75)</td>
<td>0.11</td>
<td>[16]</td>
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<td>sequential vs placebo (HR: 0.64)</td>
<td>0.03</td>
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<tr>
<td>Zatloukal et al.</td>
<td>2</td>
<td>Tremelimumab</td>
<td>BSC</td>
<td>87</td>
<td>Locally advanced/metastatic NSCLC</td>
<td>PFS at 3 months: tremelimumab vs placebo 20.9 vs 14.3%</td>
<td>&lt;0.05</td>
<td>[24]</td>
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<tr>
<td>Topalian et al.</td>
<td>1</td>
<td>Nivolumab</td>
<td>Different doses of experimental drug</td>
<td>122</td>
<td>Heavily pretreated NSCLC</td>
<td>ORR: 1 vs 3 vs 10 mg/kg 6 vs 32 vs 18%</td>
<td></td>
<td>[25]</td>
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<tr>
<td>Brahmer et al.</td>
<td>1</td>
<td>Nivolumab</td>
<td>Different doses of experimental drug</td>
<td>75</td>
<td>Heavily pretreated NSCLC</td>
<td>Safety/tolerability</td>
<td></td>
<td>[26]</td>
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<tr>
<td>Brahmer et al.</td>
<td>1</td>
<td>BMS-936559 (anti-PD-L1)</td>
<td>Different doses of experimental drug</td>
<td>75</td>
<td>NSCLC progression after ≥ one line of chemo</td>
<td>Safety/tolerability</td>
<td></td>
<td>[27]</td>
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<tr>
<td>Herbst et al.</td>
<td>1</td>
<td>MPDL3280A (anti-PD-L1)</td>
<td>Different doses of experimental drug</td>
<td>171</td>
<td>Locally advanced or metastatic NSCLC</td>
<td>Safety/tolerability</td>
<td></td>
<td>[28]</td>
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<td>Antitumoral vaccines</td>
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<td>Vansteenkiste et al.</td>
<td>2</td>
<td>MAGE-A3</td>
<td>Placebo</td>
<td>182</td>
<td>Resectable NSCLC with MAGE-A3 expression</td>
<td>DFI: HR: 0.75</td>
<td>0.254</td>
<td>[29]</td>
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<tr>
<td>Butts et al.</td>
<td>2</td>
<td>Tecetomide</td>
<td>BSC</td>
<td>171</td>
<td>Stage IIIb/IV NSCLC (second line)</td>
<td>OS: HR: 0.74</td>
<td>0.112</td>
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<td>START trial</td>
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<td>Tecetomide</td>
<td>Placebo</td>
<td>1.514</td>
<td>Stage III NSCLC after chemorad</td>
<td>OS: HR: 0.88</td>
<td>0.123</td>
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<tr>
<td>Ramlau et al.</td>
<td>2</td>
<td>TG4010 in monotherapy (+ cisplatin double upon progression)</td>
<td>TG4010 + cisplatin doublet</td>
<td>65</td>
<td>Stage IIIb/IV NSCLC</td>
<td>ORR: monotherapy vs concomitant 39.4 vs 0%</td>
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<td>[32]</td>
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<td>Quoix et al.</td>
<td>2b</td>
<td>TG4010 + cisplatin/gemcitabine</td>
<td>Cisplatin/gemcitabine</td>
<td>148</td>
<td>Stage IIIb/IV NSCLC with MUC1 expression (first line)</td>
<td>PFS at 6 months exceeding 40% in the vaccine arm: 43.2%</td>
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<td>[33]</td>
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<tr>
<td>Neninger Vinageras et al.</td>
<td>2</td>
<td>CIM Avax + cyclophosphamide</td>
<td>BSC</td>
<td>80</td>
<td>Stage IIIb/IV NSCLC after first-line chemo</td>
<td>OS: CIM Avax vs placebo 6.47 vs 5.33 months</td>
<td>0.099</td>
<td>[34]</td>
</tr>
</tbody>
</table>

*Bolding shows statistically significant p-values.*

**Legend:**
- BSC: Best supportive care
- Chemo: Chemotherapy
- Chemorad: Chemoradiotherapy
- Comp: Compassionate study
- DC: Disease control
- DFI: Disease-free survival
- HR: Hazard ratio
- irPFS: Immune-related PFS
- NSCLC: Non-small-cell lung cancer
- ORR: Objective response rate
- OS: Overall survival
- PFS: Progression-free survival
- SCLC: Small-cell lung cancer

**Notes:**
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<th>Study population</th>
<th>Primary end point</th>
<th>p-value</th>
<th>Ref.</th>
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<td><strong>Antitumoral vaccines (cont.)</strong></td>
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<td>EORTC 08971–08971B; Silva study</td>
<td>3</td>
<td>BEC2/BCG</td>
<td>BSC</td>
<td>515</td>
<td>Limited-disease SCLC</td>
<td>OS: BEC2/BCG vs BSC 14.3 vs 16.4 months</td>
<td>0.28</td>
<td>[35]</td>
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<tr>
<td>Alfonso et al.</td>
<td>Comp</td>
<td>Racotumomab</td>
<td>N/A</td>
<td>71</td>
<td>Stage IIIb/IV NSCLC</td>
<td>OS: 9.9 months (95% CI: 8.6–11.3)</td>
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<td>Nemunaitis et al.</td>
<td>1/2</td>
<td>GVAX</td>
<td>N/A</td>
<td>49</td>
<td>Stage III/IV NSCLC</td>
<td>Safety/tolerability 2) PFS: 4.4 months; OS: 7 months</td>
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<td>Nemunaitis et al.</td>
<td>2</td>
<td>Belgenpumatucel-L</td>
<td>Different doses of experimental drug</td>
<td>75</td>
<td>Stage II/III/IV NSCLC</td>
<td>Partial response &gt;15% achieved in 61 patients OS associated with dose level</td>
<td>0.0069</td>
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<td><strong>Talactoferrin-α</strong></td>
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<tr>
<td>Digumarti et al.</td>
<td>2</td>
<td>Talactoferrin-α + carboplatin/paclitaxel</td>
<td>Placebo + carboplatin/paclitaxel</td>
<td>110</td>
<td>Stage IIIb/IV NSCLC</td>
<td>ORR: talactoferrin-α vs placebo 47 vs 29%</td>
<td>0.05</td>
<td>[38]</td>
</tr>
<tr>
<td>Parikh et al.</td>
<td>2</td>
<td>Talactoferrin-α</td>
<td>Placebo</td>
<td>100</td>
<td>Stage IIIb/IV NSCLC</td>
<td>OS: talactoferrin-α vs placebo 6.1 vs 3.7 months (HR: 0.61)</td>
<td>0.04</td>
<td>[39]</td>
</tr>
<tr>
<td>FORTIS-M</td>
<td>3</td>
<td>Talactoferrin-α</td>
<td>Placebo</td>
<td>742</td>
<td>Stage IIIb/IV NSCLC</td>
<td>OS: talactoferrin-α vs placebo 7.49 vs 7.66 months (HR: 1.04)</td>
<td>0.66</td>
<td>[40]</td>
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<td><strong>Cytokines</strong></td>
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<tr>
<td>Correale et al.</td>
<td>2</td>
<td>IL-2 + GM-CSF + gemcitabine/docetaxel</td>
<td>Placebo + gemcitabine/docetaxel</td>
<td>26</td>
<td>Advanced NSCLC</td>
<td>ORR: IL-2 vs placebo 58.3 vs 28.6%</td>
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<td>[41]</td>
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<td>Ridolfi et al.</td>
<td>3</td>
<td>IL-2 + gemcitabine/cisplatin</td>
<td>gemcitabine/cisplatin</td>
<td>241</td>
<td>Stage IIIb (unresectable) or IV NSCLC</td>
<td>OS: IL-2 vs chemo alone 10.5 vs 12 months</td>
<td>0.46</td>
<td>[42]</td>
</tr>
<tr>
<td>Lissoni et al.</td>
<td>2</td>
<td>Melatonin ± IL-2</td>
<td>BSC</td>
<td>846</td>
<td>Stage IV NSCLC</td>
<td>DC: IL-2 + melatonin vs melatonin vs BSC66 vs 46 vs 7%</td>
<td>&lt;0.001</td>
<td>[43]</td>
</tr>
</tbody>
</table>

Bolding shows statistically significant p-values.
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**Tremelimumab**

Tremelimumab is, as ipilimumab, another humanized mAb that binds to CTLA-4, inhibiting this immune checkpoint. It was tested in a randomized Phase II trial, enrolling 87 patients with locally advanced or metastatic NSCLC. Progression-free survival (PFS) at 3 months was not significantly improved by tremelimumab compared with best supportive care (BSC), even though there was a 4.8% radiological response rate [19,24]. There are, to our knowledge, no additional trials with tremelimumab to date.

**Nivolumab**

Unlike ipilimumab, nivolumab (formerly known as BMS-936558 or MDX1106b) is a mAb directed at the PD-1 receptor. Phase I studies [25,26] demonstrated remarkable regressions in various advanced solid tumors, namely heavily pretreated NSCLC. Objective response rates of 17% (95% CI: 11–25%) were observed and even though the median PFS was just 2.3 months, the median duration of response reached 17 months [19,25]. Of note, nivolumab exhibited a remarkably favorable toxicity profile, since maximum tolerated doses were not defined [19,26]. Phase III studies of this promising agent in advanced NSCLC are underway (Table 2).

**Lambrolizumab**

Like nivolumab, lambrolizumab (MK-3475) is a humanized anti-PD1 mAb, but of the IgG4 subtype. The IgG4 immunoglobulin does not bind to Fc receptors or trigger the complement cascade, thus avoiding cytotoxic effects against the T cells that it is intended to activate. It was well-tolerated in a Phase I study and one unconfirmed partial response was reported in one squamous NSCLC patient [19,50]. New trials with lambrolizumab for NSCLC have opened (Table 2).

**Anti-PD-L1 mAbs**

An alternative to directly block PD-1 is to target its ligand PD-L1 which is expressed by the tumor cell. The theoretical advantage of this mechanism of action is that it keeps the T-cell PD-1 receptor available to interact with APCs (Figure 2). However, additional mechanisms of resistance could emerge, since NSCLC can express other PD-L1 ligands, such as PD-L2 [19]; however, the latter may act by promoting Th1-mediated pro-immunological responses while inhibiting Th2 pro-tumoral responses [11]. BMS-936559 is a high-affinity, fully human, PD-L1-specific, IgG monoclonal antibody.

MPDL3280A is a human monoclonal antibody that targets PD-L1, blocking PD-L1 from binding its receptors, including PD-1 and B7.1. In a Phase I expansion study [51], MPDL3280A was administered in patients with locally advanced or metastatic NSCLC at doses between 1 and 20 mg/kg. The drug exhibited a favorable toxicity profile since maximum tolerated dose could not be defined. Responses were observed at all dose levels. The PFS at 6 months was 46%. Additional anti-PD-L1 agents are under investigation (to date, four have been reported) [19,27,28].

**Antitumoral vaccines**

Antitumoral vaccines use the patient’s own immunosurveillance mechanism to induce immune responses against the tumor. This is achieved through the administration of immunogenic tumor-associated antigens or cells in conjunction with an immunoadjuvant that potentiates the immune response.

**MAGE-A3 vaccine**

MAGE-A3 is a protein almost exclusively expressed by malignant cells (the only normal tissues that express it, like testis and placenta, do not bear MHC molecules) and has been documented in 35–50% of NSCLCs [8,9]. MAGE-A3 is one of the few immunotherapies being investigated in the adjuvant setting [52] because previous pilot studies showed that clinical responses were more frequent in patients with limited tumor burden [10,29]. In a Phase II trial Vansteenkiste et al. randomized 182 completely-resected, MAGE-A3 positive, stage I/II NSCLC patients to receive MAGE-A3 vaccine versus placebo (2:1) [29]. There was a 25% relative risk reduction for relapse after a median post-resection period of 44 months, but with nonsignificant benefits for OS or PFS [29]. The results from the Phase III study in the adjuvant setting were recently announced, but not published yet [53] (accessed 1 July 2014), and failed to show any survival benefit, resulting in the suspension of further clinical development of the drug.

**Tecetomide**

Tecetomide (L-BLP25) is a liposomal vaccine with the exposed peptide core of mucin 1 (MUC1) [8], which is overexpressed by 86% of lung adenocarcinomas [9]. Even though MUC1 is also present in normal epithelial tissues, it differs structurally when expressed by malignant cells (the only normal tissues that express it, like testis and placenta, do not bear MHC molecules). MUC1 is overexpressed by 86% of lung adenocarcinomas [9]. Even though MUC1 is also present in normal epithelial tissues, it differs structurally when expressed by malignant cells (the only normal tissues that express it, like testis and placenta, do not bear MHC molecules) and has been documented in 35–50% of NSCLCs [8,9]. MAGE-A3 is one of the few immunotherapies being investigated in the adjuvant setting [52] because previous pilot studies showed that clinical responses were more frequent in patients with limited tumor burden [10,29]. In a Phase II trial Vansteenkiste et al. randomized 182 completely-resected, MAGE-A3 positive, stage I/II NSCLC patients to receive MAGE-A3 vaccine versus placebo (2:1) [29]. There was a 25% relative risk reduction for relapse after a median post-resection period of 44 months, but with nonsignificant benefits for OS or PFS [29]. The results from the Phase III study in the adjuvant setting were recently announced, but not published yet [53] (accessed 1 July 2014), and failed to show any survival benefit, resulting in the suspension of further clinical development of the drug.

**Anti-PD-L1 mAbs**

An alternative to directly block PD-1 is to target its ligand PD-L1 which is expressed by the tumor cell. The theoretical advantage of this mechanism of action is that it keeps the T-cell PD-1 receptor available to interact with APCs (Figure 2). However, additional mechanisms of resistance could emerge, since NSCLC can express other PD-L1 ligands, such as PD-L2 [19]; however, the latter may act by promoting Th1-mediated pro-immunological responses while inhibiting Th2 pro-tumoral responses [11]. BMS-936559 is a high-affinity, fully human, PD-L1-specific, IgG monoclonal antibody.

MPDL3280A is a human monoclonal antibody that targets PD-L1, blocking PD-L1 from binding its receptors, including PD-1 and B7.1. In a Phase I expansion study [51], MPDL3280A was administered in patients with locally advanced or metastatic NSCLC at doses between 1 and 20 mg/kg. The drug exhibited a favorable toxicity profile since maximum tolerated dose could not be defined. Responses were observed at all dose levels. The PFS at 6 months was 46%. Additional anti-PD-L1 agents are under investigation (to date, four have been reported) [19,27,28].

**Antitumoral vaccines**

Antitumoral vaccines use the patient’s own immunosurveillance mechanism to induce immune responses against the tumor. This is achieved through the administration of immunogenic tumor-associated antigens or cells in conjunction with an immunoadjuvant that potentiates the immune response.

**MAGE-A3 vaccine**

MAGE-A3 is a protein almost exclusively expressed by malignant cells (the only normal tissues that express it, like testis and placenta, do not bear MHC molecules) and has been documented in 35–50% of NSCLCs [8,9]. MAGE-A3 is one of the few immunotherapies being investigated in the adjuvant setting [52] because previous pilot studies showed that clinical responses were more frequent in patients with limited tumor burden [10,29]. In a Phase II trial Vansteenkiste et al. randomized 182 completely-resected, MAGE-A3 positive, stage I/II NSCLC patients to receive MAGE-A3 vaccine versus placebo (2:1) [29]. There was a 25% relative risk reduction for relapse after a median post-resection period of 44 months, but with nonsignificant benefits for OS or PFS [29]. The results from the Phase III study in the adjuvant setting were recently announced, but not published yet [53] (accessed 1 July 2014), and failed to show any survival benefit, resulting in the suspension of further clinical development of the drug.
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<tr>
<th>Trial</th>
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<td>Phase 2: PFS Phase 3: OS</td>
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<td>OS</td>
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BSC: Best supportive care; Chemo: Chemotherapy; Chemorad: Chemoradiotherapy; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; SCLC: Small-cell lung cancer.
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<td>Talactoferrin+ carboplatin/paclitaxel</td>
<td>Placebo + carboplatin/paclitaxel</td>
<td>Unresectable locally advanced/metastatic NSCLC</td>
<td>OS/PFS</td>
<td>1100</td>
<td>Mar 2016 (halted in 2014)</td>
</tr>
</tbody>
</table>

BSC: Best supportive care; Chemo: Chemotherapy; Chemorad: Chemoradiotherapy; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; SCLC: Small-cell lung cancer.
responding/stable unresectable NSCLC were randomized (2:1) to receive tecetomide versus placebo. Median OS was significantly improved by tecetomide in patients who received previous sequential chemoradiotherapy (30.8 vs 20.6 months; p = 0.0123), but not concurrent chemoradiotherapy [31]. However, results are still premature for the clinical practice.

TG4010 vaccine
TG4010 also targets MUC1 antigen expressed on malignant cells, but unlike tecetomide (which directly targets the MUC1 epitope), TG4010 uses a recombinant *Vaccinia* virus.

Two randomized Phase II studies were conducted using TG4010 with first-line chemotherapy in patients with IIIb/IV stage NSCLC [32,33]. Ramlau et al. compared TG4010 with concomitant cisplatin-doublet versus TG4010 in monotherapy followed, upon disease progression, by TG4010 plus cisplatin-doublet. The median OS was 12.7 and 14.9 months, respectively [32]. The other trial, by Quoix et al., compared TG4010 with chemotherapy versus chemotherapy alone in 148 patients. There were no statistically significant differences for PFS or OS, but patients who demonstrated an objective response to TG4010 had a longer OS [33]. Also, increased numbers of CD16+CD56+CD69+ NK cells (NKC) prior to treatment correlated negatively with OS. A larger Phase III trial, taking the pretreatment level of NKC into account, is underway (Table 2).

CIMAvax vaccine
EGF-targeted therapies (e.g., gefitinib, erlotinib) have shown significant results in NSCLC, so a vaccine therapy targeting EGF has been developed. CIMAvax contains human recombinant EGF conjugated to the P64K *Neisseria meningitidis* carrier protein. It was developed in Cuba and has been tested thoroughly in Phase I/II trials [9]. Particularly, Neninger Vinageras et al. (a Phase II trial) randomized 80 stage IIIb/IV NSCLC patients to receive either CIMAvax or BSC after first-line chemotherapy completion. A nonsignificant trend towards better OS with CIMAvax was observed (12.7 vs 8.5 months). In a subgroup analysis, patients younger than 60 years old had significantly better OS with CIMAvax (11.5 vs 5.3 months, p = 0.0124) [34]. CIMAvax is approved in Cuba, Venezuela and Peru for second-line treatment of advanced NSCLC. A Phase III study is being carried out outside the USA (Table 2).

Ganglioside vaccines
One of the earliest attempts at an antitumoral vaccine used the GD3 ganglioside as antigen and the bacille Calmette-Guérin (BCG) as immunoadjuvant. It had the distinctiveness of being used in SCLC rather than NSCLC. After a very promising pilot study [8,35], this BEC2/BCG vaccine did not prove a survival or quality of life benefit in a Phase III trial with 515 patients by the European Organization for the Research and Treatment of Cancer (EORTC 08971–08971B; Silva Study) [8,35].

Another vaccine, named racotumomab, consists of a mAb that mimics gangliosides with a glycosilation pattern almost exclusive of neoplastic cells. Racotumomab was given to 71 patients with NSCLC in a compassionate use study. The 1-year survival rate was 34% and the OS was 9.9 months [36]. Recently, a Phase III trial by Alfonso et al. showed a median OS of 8.23 months when compared with placebo, 6.8 months, p = 0.004 [36] (Table 2).

Tumor cell vaccines
Tumor cell vaccines are composed of malignant cells harvested from the tumor of a patient which are subsequently processed and administered to that patient (autologous vaccines) or another patient (allogeneic vaccines) in order to stimulate cytotoxic immune responses to a similar tumor cell type.

An autologous vaccine, named GVAX, was isolated from 49 NSCLC patients in a Phase I/II trial. Seven patients attained stable disease during 12 weeks or more following first vaccination, but no patients attained a remission (complete or partial) [8,36].

Belangenpumatucel-L, on the other hand, is an allogeneic vaccine that targets TGF-β2. It is produced from four NSCLC cell lines by transfecting them with a plasmid vector with the TGF-β2 gene [8]. A Phase II trial by Nemunaitis et al. randomized 75 patients with stages II/III/IV NSCLC (1:1:1) to receive Belangenpumatucel-L in different doses. OS was significantly better in the low-dose than in the high-dose cohorts (252 vs 581 days, respectively). There was a partial response in 15% of patients [37].

Dendritic cell vaccines
Dendritic cell (DC)-based vaccines work by administering activated autologous DCs to the patient, producing a specific immune response against the neoplasia. A Phase III trial demonstrated a lower recurrence rate in patients treated with surgery with adjuvant DC vaccine than in patients treated with surgery alone (10 vs 25%, respectively) [57]. A translational study was conducted during the aforementioned trial, in order to detect valid biomarkers for successful DC vaccine therapy (reduction of MMP-1α, increase of RANTES mRNA expression levels, normal CD4+CD8+ ratio, NKC counts) [57].

NK-cell-related therapies
As previously noted in an article by Chang et al., the main immune response in NSCLC may be related
to NKC action against the tumor [17]. The next section will consider immunotherapies that use the NKC branch of immunity.

**Lirilumab**

NSCLC cells evade NKCs by expressing certain KIR receptors that inhibit killer cell action. Lirilumab is a fully human mAb specific against certain inhibitory KIRs. It has demonstrated efficacy in preclinical trials, when in combination with nivolumab [19]. Phase I trials of lirilumab in combination with immune checkpoint-related mAbs (nivolumab and ipilimumab) are currently underway in solid tumors, including NSCLC patients (Table 2).

**Cytokine-induced killer cells**

Cytokine-induced killer (CIK) cells are a heterogeneous population of *ex vivo* engineered T lymphocytes, with a mixed T-NK phenotype and a MHC-independent antitumor action [58]. Adoptive transfer of CIK cells has been shown as a promising technique both in preclinical and clinical studies with hematological and solid malignancies (including NSCLC). CIK cell efficacy, on the other hand, was disappointing in certain clinical trials due to tumor cell escape from the immune-mediated destruction promoted by CIK cells [59].

One potential mechanism of tumor resistance to CIK cell therapy is inhibition of CIK cell infiltration into the tumor site by the abnormal microvasculature. Administration of antiangiogenic drugs (such as endostatin [58] or bevacizumab [60]) prior to CIK cell therapy leads to microvasculature normalization, improving its efficacy in animal models [58,60].

**Other immunomodulators**

Talactoferrin-α is a recombinant form of human lactoferrin that binds to the gut epithelium, stimulating the digestive mucosa dendritic cells and, thus, the immune system, via activation of the immunosurveillance mechanism [40]. Talactoferrin-α has demonstrated antitumor activity both *in vitro* and *in vivo*. Two Phase II placebo-controlled trials enrolling stage IIIb/IV NSCLC patients showed encouraging results: Digumarti *et al.* demonstrated that, when given in conjunction with carboplatin/paclitaxel, talactoferrin-α increased response rate when compared with chemotherapy with placebo (47 vs 29%; *p* = 0.05) [38]. On the other hand, Parikh *et al.* showed that oral talactoferrin-α as monotherapy significantly increased OS compared with placebo (3.7 vs 6.1 months; one-tailed *p* = 0.04 log rank) [39]. However, a recent randomized Phase III trial (FORTIS-M trial) did not show statistically significant benefit in OS, PFS or response rate for talactoferrin-α compared with placebo [40]. In the latter FORTIS-M trial [40] authors noted that results seemed to favor talactoferrin-α in the Asian subpopulation (the previous Phase II trials were carried out in India) and that a selection bias may have occurred (50% of FORTIS-M patients received three or more prior lines of treatment, compared with first/second-line talactoferrin treatment in the Phase II trials) [38–40]. On the basis of this data, further clinical development of talactoferrin in NSCLC has been halted [39].

Other drugs, such as Toll-like agonists (drugs that stimulate Toll-like receptors, i.e., receptors involved in innate immunity), *Corinebacterium parvum* or levamisole (an anthelmintic that has shown immunostimulant properties) have been disappointing so far [8,13,61–65].

**Current limitations & future perspective**

As commented by Chang *et al.*, human organism’s immunological response to lung cancer is still poorly understood [17]. Thorough investigation to determine the immune mechanisms against this particular tumor should be pursued to guide the design of new drugs.

New tumoral antigens, with the potential of being converted into antitumoral vaccines, are continuously being proposed [66,67]. Furthermore, certain tumoral antigens are commonly co-expressed, so that polyvalent vaccines with multiple antigens could be a reality in the future [67]. Likewise, drugs that block other immune checkpoints besides CTLA-4 or PD-1 (e.g., CD137, LAG-3) are currently being developed [19].

One of the ‘hottest’ topics in lung cancer immunotherapy concerns biomarkers for these newly developed drugs [68,69]. Biomarker research has inclusively been defined by an international panel as one of the main hurdles in cancer immunotherapy [70]. Certain polymorphisms in the *CTLA-4* gene augment the susceptibility to solid tumors, namely lung cancer [12]. As for PD-L1 inhibitors, such as nivolumab, tumor biopsies show that PD-L1 expression may be predictive of responsiveness to PD-1 blockade, but this does not mean that patients whose tumors do not overexpress PD-L1 may not derive benefit from such treatments [25,26,51]. Efforts have been made to design a gene signature predictive of MAGE-A3 vaccine efficiency [71].

Others concerns relates to the definition of response to therapy. Ipilimumab investigation in melanoma showed that in certain cases immunotherapy response patterns were dissimilar from those of standard therapies, even though there was indeed a response to treatment [12]. By promoting lymphocyte infiltration and inflammatory edema in the tumor, ipilimumab may transiently increase the lesion size while maintaining antitumoral efficacy. Also, tumor growth continues as the immune response takes time to develop. Response Evaluation Criteria in Solid Tumors (RECIST) are,
therefore, not fully adequate to measure response to ipilimumab. The immune-related response criteria (irRC) have been developed to fill this gap. In irRC, the patient’s total tumor burden is calculated and used as baseline for future comparative imaging [12].

The ipilimumab trials for lung cancer used irRC to evaluate response [12,16,23], but unfortunately irRC hasn’t been prospectively validated for this neoplasm (or for other immunotherapies in the lung cancer setting, for that matter). As such, irRC should be validated for lung cancer if accurate inferences from clinical trials are to be made [12].

Immunotherapies with distinct pathways may act synergistically (e.g., co-administration of both anti-CTLA-4 and anti-PD1 agents has shown promise in melanoma). A trial with concomitant ipilimumab and nivolumab is currently underway for NSCLC (Table 2). The proper way to combine these novel immunotherapies with the standard available treatment for cancer – such as chemotherapy, targeted therapy, radiotherapy and surgery – is a matter of actual research.

Immunoadjuvants can also be developed into immunotherapies. GM-CSF can stimulate immune response in a number of immune-related drugs. Lirilumab may increase ipilimumab or nivolumab response. Antiangiogenics normalize tumor microvasculature and allow a better access of the immune cells to the tumor. Recent data have even implied that bevacizumab decreases the number of protumoral M2 macrophages in the neoplasm [72].

Conclusion
Immunotherapy for lung cancer treatment is now a reality [10]. Monoclonal antibodies targeting immune checkpoints and antitumor vaccines are, at present, the most promising representatives of this treatment modality. Clinical investigation is intense at this point and novel drugs are being developing and tested. Many clinical trials are ongoing and will eventually give further insight into immunotherapy’s proper place in lung cancer treatment, either alone or in combination with other already existing treatment modalities. A deeper understanding of the physiopathology of lung cancer immunology, a better definition of the clinical response criteria and the finding of adequate biomarkers are certainly among the future directions of this intriguing field.

Financial & competing interests disclosure
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Executive summary
Lung cancer immunology
• A chronic inflammation state induced by smoking, occupational exposures and other environmental factors, activates the innate immunity with subsequent release of cytokines. These cytokines may promote tumor destruction, but can also lead to oncogenesis by stimulating tumor proliferation, angiogenesis and metastatic potential.

Immune effect of radiation & chemotherapy
• Ionizing radiation induces cell death with consequent release of tumoral antigens. These, in turn, stimulate an inflammatory response that may have antineoplastic activity.

Immune checkpoint inhibitors
• One of the most promising approaches in immunotherapy for lung cancer is to inhibit the immune checkpoints that harness an effective immune response against the tumor.

Antitumoral vaccines
• Antitumoral vaccines use the patient’s own immunosurveillance mechanism to induce immune responses against the tumor. This is achieved through the administration of immunogenic tumor-associated antigens or cells in conjunction with an immunoadjuvant that potentiates the immune response.

NK-cell-related therapies
• The main immune response in non-small-cell lung cancer may be related to NK cell action against the tumor. However, the NK cell-related therapies are still premature in this setting, although they have a promising role in future combination therapies.

Current limitations & future trends
• Immunotherapies with distinct pathways may act synergistically (e.g., co-administration of both anti-CTLA-4 and anti-PD1 agents has shown promise in melanoma). A trial with concomitant ipilimumab and nivolumab is currently underway for non-small-cell lung cancer. The proper way to combine these novel immunotherapies with the standard available treatment for cancer – such as chemotherapy, targeted therapy, radiotherapy and surgery – is a matter of actual research.
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