Immune Checkpoint Modulation for Non-Small Cell Lung Cancer

Jean-Charles Soria1,2,3, Aurélien Marabelle1,4, Julie R. Brahmer5, and Scott Gettinger6

Abstract

Therapies targeting immune checkpoints have recently shown encouraging activity in patients with heavily pretreated advanced non–small cell lung cancer (NSCLC), independently of NSCLC histology or mutational status, with low toxicity profiles when used as monotherapy. Objective response rates of approximately 20% have been reported in patients with advanced NSCLC treated with antagonist antibodies targeting the immune checkpoint, programmed death 1 (PD-1) on activated T cells, or its primary ligand, programmed death ligand 1 (PD-L1) expressed within the tumor microenvironment. Response rates appear to be higher in patients with tumor PD-L1 expression documented by immunohistochemistry, although responses have been appreciated in patients with reportedly PD-L1–negative tumor specimens. Antibodies directed against cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), another immunosuppressive T-cell signaling molecule, are also being evaluated in clinical trials, with one randomized phase II trial demonstrating improved immune-related progression-free survival in lung cancer patients when added to standard chemotherapy. Additional clinical trials are combining anti–CTLA-4 antibodies with either anti–PD-1 or anti–PD-L1 antibodies. Combinations of other immune checkpoint antagonists or agonist antibodies with anti–PD-1 or anti–PD-L1 antibodies are also being pursued. Clin Cancer Res; 21(10): 2256–62. ©2015 AACR.

See all articles in this CCR Focus section, "Progress in Lung Cancer."

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, being responsible for more than 1.5 million deaths per year (1). The majority of patients present with locally advanced or metastatic disease. Approximately 85% of lung cancers are classified as non–small cell lung cancer (NSCLC), and include lung adenocarcinoma, squamous cell carcinoma, and large cell carcinoma histologic subtypes. Over the past decade, major advances have been achieved in our understanding of NSCLC biology (2). Beyond classical histology, analyses of NSCLC cancer genomes and signaling pathways have defined NSCLCs as a group of distinct diseases. Somatic point mutations (i.e., EGFR, B-RAF) and gene fusions (i.e., ALK, ROS1) have been identified as NSCLC oncogenic drivers, and their blockade with specific tyrosine kinase inhibitors can generate dramatic tumor responses (3–5). See also the articles from Gandara and colleagues (6) and Katayama and colleagues (7) in this CCR Focus. Progress has additionally been made in our understanding of the tumor’s surrounding immune microenvironment (8). It has become apparent that some NSCLC tumors are infiltrated by immunosuppressive leukocytes, which, together with the cancer cells, inhibit the host antitumor immune response (9, 10). Targeting molecules expressed by these tumor-infiltrative immunosuppressive cells can generate potent antitumor immune responses in mouse models. The translation of this strategy into patients with lung cancer has been fruitful, with durable responses in some patients with advanced disease who would otherwise have limited systemic options for treatment of their cancer (11).

Paradigm shift in lung cancer therapy: targeting cancer cell immune tolerance rather than the cancer cell itself

The development of therapeutic mAbs in the field of oncology has pioneered the concepts of tumor-targeted therapies, predictive biomarkers, and personalized medicine (12, 13). The aim of such mAbs was originally to target tumor antigens or growth factors to either induce directly or indirectly the death of the cancer cells. Recently, mAbs have been designed to antagonize inhibitory receptors expressed by T cells, either by targeting the receptor itself or its ligand. The concept was simple: Tumor cells and tumor-infiltrative immune cells inhibit antitumor T cells by stimulating coinhibitory receptors such as programmed death receptor 1 (PD-1) or cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) expressed on their membrane. Blocking this interaction by targeting these molecules should relieve inhibition of antitumor T cells, resulting in effective immune attack on tumors. Indeed, PD-1 engagement on the T-cell surface leads to phosphorylation of PD-1 intracytoplasmic tyrosines. It also increases SH2-domain–containing tyrosine phosphatase 2 (SHP-2) associations with the immunoreceptor tyrosine–based switch motif (ITSM) of PD-1. Recruitment of SHP-2 dephosphorylates signaling through the PI3K pathway and downstream signals through Akt. Therefore, PD-1 stimulation upon T-cell receptor ligation ultimately decreases the induction of cytokines, such as IFNγ, and cell survival proteins, such as Bcl-xL, and decreases T-cell proliferation and survival (14). The proof of concept was first seen in patients with refractory/refractory metastatic melanoma treated with ipilimumab, an antibody targeting CTLA-4. Approximately 20% of patients achieved long-term survival with ipilimumab in two phase III trials (15, 16). Notably, some patients showed...
unusual patterns of response, characterized by initial tumor growth followed by regression (so-called "pseudo-progression") or tumor stability, or development of a new lesion in the setting of sustained tumor response at other sites (so-called "mixed response"), or delayed response. These nonconventional types of tumor responses have motivated the elaboration of new immune-related response criteria (irRC) in order to properly assess patients treated with immunotherapy (17). Indeed, classical disease evaluations by WHO criteria do not include the measurement of new lesions, nor do they require new lesion measurements to define an evolving tumor burden. In contrast, in the irRC, index and measurable new lesions are taken into account. Therefore, the total tumor burden is assessed by measuring the sum of the products of the two largest perpendicular diameters of all index lesions and subsequent new lesions.

Recent results in lung cancer therapy with immune checkpoint blockade mAbs

As opposed to melanoma and renal cell cancer, NSCLC had not been considered a cancer sensitive to immunotherapy. The activity of immune checkpoint inhibitors in NSCLC was indeed an unexpected discovery made during early-phase trials. Four antibodies targeting the coinhibitory receptor PD-1 or its primary ligand, programmed death ligand 1 (PD-L1), are currently in later development for NSCLC. These include the anti–PD-1 mAbs, nivolumab [Bristol-Myers-Squibb (BMS)] and pembrolizumab (Merck Sharp and Dohme, Merck), and the anti–PD-L1 mAbs, MEDI4736 (Astra Zeneca/Medimmune) and MPDL3280A (Roche/Genentech). Response rates in untreated patients across early trials have ranged from 16% to 23% in NSCLC (Table 1). In the majority of trials, response rates appeared higher in patients with increased tumor PD-L1 expression by immunohistochemistry (IHC). However, different antibody assays and thresholds to define PD-L1 positivity used by various pharmaceutical companies, and the small number of specimens available for testing from those treated with drug limit conclusions. Both anti–PD-1 and anti–PD-L1 mAbs were well tolerated, with few grade 3–4 drug-related toxicities, including pneumonitis (0%–3%), pyrexia (0%–1%), fatigue (2%–3%), diarrhea (0%–3%), and rash (0%–1%; refs. 18–21). Notably, no dose-limiting toxicity and evident dose–efficacy correlation were found (above a minimal dose which, for pharmacokinetic and pharmacodynamics reasons, allows for target saturation). Tumor responses could be profound, and were generally prolonged. Additional patients showed significant disease stability with therapy. Mature survival data are available for one of the trials evaluating these agents, in which 129 patients with pretreated advanced NSCLC, untreated for tumor PD-L1 status, received nivolumab. Median overall survival (OS) was 9.9 months, with 1-, 2, and 3-year survival rates of 42%, 24%, and 18%, respectively (22).

Two antagonist antibodies targeting CTLA-4 are currently being evaluated in clinical trials enrolling patients with advanced NSCLC, ipilimumab (IgG1, BMS), and tremelimumab (IgG2, AZ/Medimmune). Ipilimumab has been tested in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV NSCLC in a randomized, double-blind, multicenter phase II study (23). This study demonstrated an immune-related progression-free survival (PFS) benefit and a trend toward improved OS. Benefit was seen primarily in patients with squamous cell NSCLC, prompting an ongoing phase III trial evaluating the same chemotherapy with or without ipilimumab. Based on encouraging activity when combining nivolumab and ipilimumab in advanced melanoma, ipilimumab and tremelimumab are additionally being evaluated in combination with anti–PD-1 or anti–PD-L1 antibodies in patients with advanced NSCLC (24). Many other combination trials of anti–PD-1/PD-L1 mAbs are also ongoing in NSCLC (Table 2).

Are there predictive markers of response to anti–PD-1/PD-L1 therapy in NSCLC patients?

In early-phase trials, PD-L1 tumor expression by IHC appeared to be predictive of response to anti–PD-1/PD-L1 mAbs (Table 1). However, multiple issues remain to be addressed before PD-L1 is considered a robust and definitive molecular predictor of efficacy. Various clones are currently being used in clinical trials to evaluate PD-L1 expression, with no comparative study yet reported.

### Table 1. Response rates of PD-1/PD-L1 blockade antibodies used as a monotherapy in advanced NSCLC

<table>
<thead>
<tr>
<th>Antibody (company)</th>
<th>ORR (RECIST v1.0 or v1.1)</th>
<th>PD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All comers</td>
<td></td>
</tr>
<tr>
<td>Nivolumab (all histologies)</td>
<td>21% (n = 52; ref. 60)</td>
<td>17% (n = 129; ref. 22)</td>
</tr>
<tr>
<td>Nivolumab (squamous, ≥2 prior tx)</td>
<td>15% (n = 117; ref. 61)</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab (Merck-MSD)</td>
<td>20% (n = 194; ref. 27)</td>
<td></td>
</tr>
<tr>
<td>BMS-936559 (BMS)</td>
<td>10% (n = 49; ref. 62)</td>
<td>16% (n = 58; ref. 63)</td>
</tr>
<tr>
<td>MEDI4736 (AZ/Medimmune)</td>
<td>31% (n = 58; ref. 63)</td>
<td></td>
</tr>
<tr>
<td>MPDL3280A (Roche/Genentech)</td>
<td>23% (n = 53; ref. 25)</td>
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</tr>
</tbody>
</table>

### Notes

- **ORR**: objective response rate
- **PD-L1**: programmed death ligand 1
- **RECIST**: Response Evaluation Criteria in Solid Tumors
- **IHC**: immunohistochemistry
- **PD-L1**: programmed death ligand 1
- **PD-1**: programmed death 1
- **PD-L1**: programmed death ligand 1

**Abbreviations**: NA, not available; ORR, objective response rate; squamous, squamous; tx, treatment.

*29 patients regardless of prior treatment were additionally evaluated at different PD-L1 tumor cell thresholds, with ORR in PD-L1 negative, 10% (n = 42); PD-L1+ in 1% to 49% cells, 17% (n = 46); PD-L1+ in ≥50% cells 37 (n = 41).

*Includes 159 pretreated and 42 untreated PD-L1+ patients.
Table 2. Ongoing trials of immune checkpoint blockade therapy in NSCLC

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Disease</th>
<th>ID</th>
<th>Phase</th>
<th>Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-PD-1</strong></td>
<td>Nivolumab</td>
<td>Stage IIIB/IV</td>
<td>NCT01454102</td>
<td>Multicenter</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Nivolumab/gemcitabine/cisplatin–pemetrexed/ carboplatin–bevacizumab/erlotinib/pembrolizumab</td>
<td>NCT02220894</td>
<td>Randomized phase III</td>
<td>Jul 2019</td>
</tr>
<tr>
<td>Nivolumab vs docetaxel</td>
<td>Previously treated advanced/M+ SCC</td>
<td>NCT0846416</td>
<td>Phase II</td>
<td>May 2015</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Neo-adj in resectable</td>
<td>NCT09842738</td>
<td>Randomized phase III</td>
<td>Mar 2018</td>
</tr>
<tr>
<td>Nivolumab until disease prog vs nivolumab discontinued at 1 year (re-tmt allowed)</td>
<td>Previously treated advanced or M+</td>
<td>NCT02399537</td>
<td>Phase II</td>
<td>Mar 2018</td>
</tr>
<tr>
<td>Nivolumab vs Inv choice plat-based doublet chemo</td>
<td>First-line stage IV or recurrent PD-L1+</td>
<td>NCT0219533</td>
<td>Phase III</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>Nivolumab after 2 cycles of epigenetic priming with oral azacitidine (CC-486) or s.c. azacitidine + entinostat</td>
<td>Recurrent metastatic</td>
<td>NCT0219533</td>
<td>Phase II</td>
<td>Aug 2015</td>
</tr>
<tr>
<td><strong>Pembrolizumab</strong> (Pembro)</td>
<td>Pembrol vs platinum-based chemotherapy</td>
<td>PD-L1+ advanced or M+</td>
<td>NCT0203129</td>
<td>Phase I</td>
</tr>
<tr>
<td>Pembrol vs platinum-based chemotherapy</td>
<td>Pembrol + cisplatin/pemetrexed or carboplatin/ paclitaxel</td>
<td>Stage IIIB/IV</td>
<td>NCT08145097</td>
<td>Phase I</td>
</tr>
<tr>
<td>Pembrol + paclitaxel and carboplatin or + paclitaxel and carboplatin and bevacizumab or + pemetrexed + carboplatin or + ipilimumab or + erlotinib or + gefitinib</td>
<td>NCT0905657</td>
<td>Phase II/III</td>
<td>Jan 2020</td>
<td></td>
</tr>
<tr>
<td>Pembrol &gt;2 vs docetaxel</td>
<td>Pembrol 1 mg/kg vs 3 mg/kg vs 10 mg/kg</td>
<td>NCT020007070</td>
<td>Phase I</td>
<td>Nos</td>
</tr>
<tr>
<td><strong>Anti-PD-L1</strong></td>
<td>MPDL3280A</td>
<td>Locally adv or M+</td>
<td>NCT02013229</td>
<td>Phase Ib</td>
</tr>
<tr>
<td>MPDL3280A + erlotinib</td>
<td>PD-L1+ locally adv or M+</td>
<td>NCT08846416</td>
<td>Phase II</td>
<td>May 2015</td>
</tr>
<tr>
<td>MPDL3280A vs docetaxel</td>
<td>Locally adv or M+ after first-line platinum</td>
<td>NCT09105939</td>
<td>Randomized phase II</td>
<td>Mar 2016</td>
</tr>
<tr>
<td>MED14736</td>
<td>MED14736 vs placebo after platinum-based CT with RT</td>
<td>Stage III unresectable</td>
<td>NCT0215461</td>
<td>Randomized phase III</td>
</tr>
<tr>
<td>MED14736 + tremelimumab</td>
<td>Locally advanced or M+</td>
<td>NCT02008472</td>
<td>Phase II</td>
<td>Oct 2016</td>
</tr>
<tr>
<td>Adjuvant MED14736 vs placebo</td>
<td>Completely resected</td>
<td>NCT02273375</td>
<td>Phase III</td>
<td>Nos</td>
</tr>
<tr>
<td>Gefitinib + MED14736</td>
<td>Locally advanced or M+</td>
<td>NCT02088112</td>
<td>Phase I</td>
<td>Oct 2017</td>
</tr>
<tr>
<td>MED14736 after gefitinib or AZD9291 or selumetinib + docetaxel or tremelimumab</td>
<td>Locally advanced or M+</td>
<td>NCT02179671</td>
<td>Multicenter</td>
<td>Jul 2017</td>
</tr>
<tr>
<td>AZD9291 + MED14736</td>
<td>MED14736 + tremelimumab</td>
<td>NCT02144666</td>
<td>Phase I</td>
<td>Jun 2017</td>
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<tr>
<td>MED1469/MEDI4736</td>
<td>MED1469/MEDI4736</td>
<td>NCT02225333</td>
<td>Phase II</td>
<td>Jun 2017</td>
</tr>
<tr>
<td><strong>Anti-CTLA-4</strong></td>
<td>Ipilimumab</td>
<td>Stage IV</td>
<td>NCT02221339</td>
<td>Phase II</td>
</tr>
<tr>
<td>Ipilimumab + radiotherapy</td>
<td>III/IV</td>
<td>NCT01454102</td>
<td>Phase I</td>
<td>Jan 2017</td>
</tr>
<tr>
<td>Ipilimumab + nivolumab</td>
<td>EGF/R/LKmut stage IV</td>
<td>NCT09998236</td>
<td>Phase Ib</td>
<td>Dec 2015</td>
</tr>
<tr>
<td>Ipilimumab + erlotinib or crizotinib</td>
<td>Stage III/IV</td>
<td>NCT02039674</td>
<td>Phase I/II</td>
<td>Jun 2019</td>
</tr>
<tr>
<td>Ipilimumab + pembrolizumab</td>
<td>Stage III/IV</td>
<td>NCT02147172</td>
<td>Phase I</td>
<td>Jul 2017</td>
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<tr>
<td><strong>Tremelimumab</strong></td>
<td>Tremelimumab + MEDI14736</td>
<td>Advanced</td>
<td>NCT02000947</td>
<td>Phase I</td>
</tr>
<tr>
<td>Tremelimumab + gefitinib</td>
<td>EGFRmut advanced</td>
<td>NCT02040064</td>
<td>Phase I</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>Tremelimumab/gefitinib/AZD9291/ selumetinib + docetaxel/tremelimumab followed by MEDI14736</td>
<td>Stage III/IV</td>
<td>NCT02179671</td>
<td>Randomized phase II</td>
<td>Nov 2017</td>
</tr>
<tr>
<td>Tremelimumab + MEDI6469</td>
<td>Advanced</td>
<td>NCT02205333</td>
<td>Phase I</td>
<td>Jul 2017</td>
</tr>
</tbody>
</table>

Abbreviations: adv, advanced; Inv choice, investigator's choice; M+, metastatic; Neo-adj, neoadjuvant; prog, progression; re-tmt, retreatment; SCC, squamous cell carcinoma.

(Ventana SP263 clone and SP142 clone, Dako 28-8 and 22C3 clones). Furthermore, there is no consensus on the definition of a PD-L1 "positive" tumor, with different thresholds of cell expression used, e.g., 1%, 5%, 10% of cells or higher. Also, some pharmaceutical companies consider PD-L1 expression only on tumor cells, whereas others consider PD-L1 expression additionally on tumor-infiltrative immune cells (25).
Interestingly, history of smoking appears to have an impact on the probability of response to anti–PD-1/PD-L1 mAbs. Response rates in current/former smokers versus never/light smokers (≤5 pack years) have been reported for nivolumab (20/75, 27% vs. 0/13, 0%; ref. 26), pembrolizumab (27% vs. 6/15 vs. 9%; n = 65; ref. 27), and MPDL3280a (26%, n = 43 vs. 10%, n = 10; ref. 25). This observation may in part be explained by a larger number of somatic point mutations in the lung cancers of smokers, which would in turn generate immunogenic neoepitopes. This has been recently demonstrated in a murine model of colon carcinoma (28) and in patients with melanoma treated by ipilimumab (29).

Is there a link between onecogenic stress and cancer immune suppression in NSCLC?

The expression of PD-L1 by cancer cells seems to be redundantly induced by various tumor (somatic) DNA abnormalities. In Hodgkin disease, 9p24.1 amplification (30) and AP-1 signaling (31) have been linked to the expression of PD-L1. In anaplastic large cell lymphoma, NPM/ALK fusion gene expression induces a STAT3-mediated overexpression of PD-L1 (32). In melanoma, the activation of alternative signaling pathways following resistance to vemurafenib is accompanied with the induction of PD-L1 expression, whereas resistance due to the reactivation of the MAPK pathway has no effect on PD-L1 expression (33). The loss of PTEN has been associated with PD-L1-mediated immune escape in glioma (34) and colorectal cancer (35). In a mouse model of squamous cell carcinoma, the biallelic inactivation of LKB1 and PTEN has also been associated with upregulation of PD-L1 expression (36). Akbay and colleagues (37) have shown a link between the activation of EGFR signaling and the upregulation of PD-L1, PD-1, and CTLA-4 in an EGFR-driven murine model of lung cancer and human NSCLC cell lines. Accordingly, Azuma and colleagues (38) have shown recently a link between activating EGFR mutations and tumor PD-L1 overexpression. Also, at AACR 2013, Lastwika and colleagues (39) reported a correlation between PI3K/AKT/mTOR pathway activation and the expression of PD-L1 in NSCLC.

The mutation status of KRAS might also have an impact on the probability of response to anti–PD-1/PD-L1 mAbs. Indeed, Horn and colleagues (20) reported at IASLC 2013 that patients with a KRAS WT tumor treated with MPDL3280A had a 30% response rate (8/27 patients) as opposed to 10% in KRAS mutant patients (1/10 patients). This trend has also been reported by Geginster and colleagues (21) in patients treated with nivolumab, with a 25% reported response rate (9/36) in patients with KRAS WT tumors versus 14% (3/21) in patients with KRAS mutant tumors. However, the response rate in KRAS mutant with pembrolizumab was 28% (n = 39; ref. 27). No significant difference in response rates has been observed so far between patients with EGFRTKI versus EGFRTKI tumors.

Mechanism of action of immunomodulatory mAbs: truth is more complicated

The initial paradigm of PD-1/PD-L1 blockade therapy was originally presented in a simplistic way: cancer cells express PD-L1 and inhibit antitumor PD-1 pos T cells. Although lung cancer cells might express PD-L1 in a constitutive way as a consequence of oncogenic stress (32, 34, 37, 40), PD-L1 is primarily expressed in response to IFNγ stimulation that is released by immune cells within the tumor microenvironment (mostly T cells; refs. 41, 42). Importantly, PD-L1 expression is limited to cancer cells but can also be upregulated on tumor-associated macrophages, dendritic cells, fibroblasts, and activated T cells (43). Taking into account this diversity of PD-L1–expressing cells, the dynamic process of tumor–immune interaction over time, and the heterogeneity of immune infiltrates within primary tumors and within metastases, a single tumor biopsy might be insufficient to provide a clear PD-L1 status for a given patient.

Moreover, PD-1 has two known ligands: PD-L1 and PD-L2. In addition, PD-L1 has two known receptors: PD-1 and CD80 (B7.1). Importantly, PD-L1 expression is limited to cancer cells but can also be upregulated on tumor-associated macrophages, dendritic cells, fibroblasts, and activated T cells (43). Taking into account this diversity of PD-L1–expressing cells, the dynamic process of tumor–immune interaction over time, and the heterogeneity of immune infiltrates within primary tumors and within metastases, a single tumor biopsy might be insufficient to provide a clear PD-L1 status for a given patient.

Further complicating our understanding of the PD-1 axis, PD-L1 is not only membrane bound but also secreted as a soluble form. The level of blood-soluble PD-L1 (sPD-L1) has been associated with poorer prognosis in renal cell cancer and diffuse large b-cell lymphoma (48, 49). In lung cancer, the source of sPD-L1 could be the tumor cell itself (50), or the tumor-infiltrating immune cells (51). Of importance, soluble PD-L1 may have a scavenger effect on the activity of anti–PD-L1 antibodies, or compete for PD-1 ligation with anti–PD-1 mAbs. CD80 can also be secreted in a soluble form (52) and has been associated with a negative prognosis in some patients with hematologic malignancies (53). Soluble CD80 (sCD80) can bind to CD28, PD-L1, and CTLA-4. However, some preclinical data suggest that the overall effect of sCD80 may promote stimulation of T cells in the context of...
of PD-L1 immunosuppression (54) and activation of antigen-presenting cells (55). Also, sCD80 could compete with anti–PD-L1 mAbs for ligation to PD-L1, or with anti–CTLA-4 mAbs for ligation to CTLA-4. The impact of sPD-L1 and sCD80 in anti–PD-1, anti–PD-L1, and anti–CTLA-4 therapy in NSCLC remains to be studied.

The PD-1/PD-L1 mAbs that are the most advanced in the clinic have been designed (engineered IgG1 or IgG4; Table 1) to avoid antibody-dependent cell-mediated cytotoxicity or phagocytosis (ADCC/ADCP) function, thereby preventing killing of activated antitumor T cells. However, the rationale for anti–PD-1/PD-L1 therapy has been built in mouse tumor models with ADCC/ADCP-prone antibody isotypes (Rat IgG2a/b or Hamster IgG anti–PD-1/PD-L1 mAbs that, in mice, are equivalent to IgG1 human isotypes). It will be interesting to see how the ADCC/ADCP-prone IgG1 anti–PD-1 and anti–PD-L1 mAbs currently in development in the clinic will compare to the IgG4 or engineered IgG1 mAbs (56,57).

Besides constitutive PD-L1 expression on all cancer cells secondary to oncogenic stress (minority of cases), PD-L1 upregulation is a dynamic process that fluctuates over time, as it occurs in response to IFNγ secreted by immune cells. It happens as a physiologic process on self-cells to prevent against autoimmunity (12). It occurs heterogeneously in tumors when IFNγ–secreting immune cells interact with cancer cells (40). Therefore, it cannot be considered as a fixed biomarker like somatic DNA mutations and should be considered as a prognostic rather than predictive biomarker as it provides information on the host natural antitumor immunity rather than the cancer cell biology. Accordingly, the prognostic value of PD-L1 that has been identified under anti–PD-1 monotherapy disappears when anti–PD-1 is combined with anti–CTLA-4 treatment in melanoma (22).

Perspectives

Combinations

The promising results of anti–PD-1/PD-L1 mAbs in the clinic have initiated a new era in NSCLC therapy. Several ongoing clinical trials are now evaluating anti–PD-1/PD-L1 mAbs in combination with chemotherapies, tyrosine kinase inhibitors, or other immunotherapies such as anti–CTLA-4 mAbs discussed above. Combinations need to be considered carefully, with particular attention to sequencing and anticipation of potential antagonistic effects and synergistic toxicities (58). In attempts to further release suppression of and mobilize the antitumor immune response, combinations of additional immunotherapies are actively being pursued, including anti–KIR, anti–LAG3, anti–CD137, anti–OX40, and anti–CD40 mAbs administered concurrently with anti–PD-1 or anti–PD-L1 mAbs. Also, pairing NSCLC vaccines, which to date have been largely unsuccessful in clinical trials, with anti–PD-1/PD-L1 mAbs may allow silent immune responses generated by such vaccines to finally be realized. That is, anti–PD-1/PD-L1 mAbs may relieve immune suppression in the tumor microenvironment mediated by PD-L1 induced by infiltrating antigen-specific T cells primed by vaccine.

Uncharted territory

The use of immune checkpoint blockade has mainly focused on the metastatic setting of NSCLC. However, there is growing interest in evaluating such therapies in earlier-stage NSCLC and extensive-stage small cell lung cancer. A phase III trial evaluating MEDI4736 as consolidation therapy in stage IIIB NSCLC after completing definitive chemoradiotherapy is already under way (PACIFIC trial; NCT02125461). Another trial evaluating adjuvant MEDI4736 after complete resection of stage IB, II, and III NSCLC is soon to open (BR31 IFC1401 trial, NCT02273375). Ipilimumab is currently being evaluated in a phase III trial in combination with first-line chemotherapy for patients with extensive-stage SCLC, and multiple phase I trials are evaluating anti–PD-1/PD-L1 therapies in patients with pretreated extensive-stage small cell lung cancer (NCT01375842, MPDL3280a; NCT01928394). Perspectives for treatment of small cell lung cancer are discussed in this CCR Focus by Pietanza and colleagues (59).

Words of caution

Although anti–PD-1 and anti–PD-L1 therapies have shown encouraging activity with good tolerability in patients eligible for clinical trials, caution will need to be exercised when treating patients in clinical practice. The potential for severe immune-mediated toxicity needs to be recognized, with clear algorithms in place to assist in rapid identification, evaluation, and treatment of such toxicities. Considering only roughly 20% of unselected patients treated with anti–PD-1/PD-L1 antibodies will have a meaningful response to therapy, other therapies will need to be pursued in most patients, and efforts to identify predictive biomarkers of response to this new class of drugs remain of paramount importance.

Conclusions

Anti–PD-1/PD-L1 mAbs will be added to our pharmaceutical armamentarium for advanced NSCLC. The FDA recently granted approval for an anti–PD-1 single-agent therapy in patients who have progressed after standard chemotherapy for advanced (metastatic) squamous NSCLC. The European Medicines Agency approval is expected for 2015 in NSCLC. The role of tumor PD-L1 expression as a predictive biomarker is still uncertain, with differences in PD-L1 antibody assays, thresholds of “positivity” (% of cells positive), and actual cells considered (tumor cells vs. stromal cells) between agents. Furthermore, identifying tumor PD-L1 expression may not be necessary in the future because its predictive value might disappear upon combination regimen, or because other therapies may induce PD-L1 expression. Although PD-1/PD-L1 blockade therapy provides clinical benefits to approximately 20% of patients with advanced NSCLC, about 80% of patients still remain refractory to this treatment. Therefore, new molecules and combinations are urgently needed to address primary and secondary resistance to these new agents.

Preclinical/translational studies on tumor specimens collected from our patients will help to identify predictive immune biomarkers and synergistic combinations of anti–PD-1/PD-L1 mAbs with standard therapies for NSCLC and other immunotherapies, and build the rationale for future clinical trials. It is too early to know if gains in survival for NSCLC will be obtained with incremental approaches where we will just add anti–PD-1/PD-L1 mAbs on top of existing NSCLC therapies. We might also discover that disruptive strategies only focusing on immunomodulation would do better.

Disclosure of Potential Conflicts of Interest

J.-C. Soria is a consultant/advisory board member for AstraZeneca, Yamanouchi, Roche/Genentech, and Janssen. A. Marabelle is a consultant/advisory board member for AstraZeneca and Janssen. J.R. Brahmer reports receiving a commercial research grant from Bristol-Myers Squibb.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.-C. Soria

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Development of methodology: J.-C. Soria
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.-C. Soria

References


