

Reflections on immune checkpoint inhibition in non-small cell lung cancer

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Submitted Sep 03, 2014. Accepted for publication Sep 04, 2014.

doi: 10.3978/j.issn.2218-6751.2014.09.09

View this article at: <http://dx.doi.org/10.3978/j.issn.2218-6751.2014.09.09>

Introduction

Despite the expanding armamentarium of treatment modalities against metastatic non-small cell lung cancer (NSCLC) this disease remains incurable. The introduction of targeted therapies provides transient control of disease for some molecular subtypes but virtually all patients' progress. Recently immunotherapies have been approved for the treatment of metastatic melanoma and prostate cancer, and have shown promise for the treatment of NSCLC. More specifically, the blockade of immune checkpoints may improve outcomes in the treatment of NSCLC. Immune checkpoints modulate immune responses to effectively balance self-tolerance and tissue destruction. Many tumors express immune checkpoints or their ligands to inhibit anti-tumor immune responses. One of the most important immune checkpoints is programmed cell death ligand 1 (PD-L1), which was discovered at Mayo Clinic (1). PD-L1 was first named B7-H1 due to its homology with the B7 family of co-stimulatory molecules. When PD-L1 was initially discovered in peripheral blood monocytes, it was shown to negatively regulate T cells through IL-10 production after ligation. It was later shown that PD-L1 negatively regulated T cell proliferation through engagement of programmed cell death protein 1 (PD-1), and it has since been called PD-L1 by many groups. Additional work demonstrated that PD-L1 induces apoptosis of tumor specific T-cells (2). The expression of PD-L1 in at least a quarter of patients with NSCLC suggests that blockade of the PD-1/PD-L1 axis may be effective therapy for NSCLC (3).

Pharmaceutical companies have developed antibodies that block PD-1 or its ligand PD-L1. There was noteworthy

clinical activity in one of the first phase I dose-escalation clinical trials with a fully humanized IgG4 anti-PD-1 antibody. This trial included patients with metastatic colorectal cancer, renal cell carcinoma, melanoma, castrate-resistant prostate cancer and NSCLC. Out of 39 patients, one complete response and two partial responses were observed in addition to some mixed responses. Successful treatment was associated with tumor cell surface expression of PD-L1 and significant increases in lymphocyte infiltration into metastatic tumors (4).

PD-1 inhibition with MK-3475 in NSCLC

There has since been an increase in clinical trials targeting the PD-1/PD-L1 axis, especially in NSCLC. At the Annual Meeting of the American Society of Clinical Oncology (ASCO) 2014, an update of one such trial was presented: "safety and clinical activity of MK-3475 in previously treated patients with NSCLC" (5). MK-3475 (also known as pembrolizumab) is a humanized monoclonal IgG4 antibody against PD-1 and was recently approved by FDA for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and a BRAF inhibitor if a BRAF V600 mutation is present. In this clinical trial, previously-treated patients with NSCLC whose tumors expressed any detectable PD-L1 by an immunohistochemical assay were randomized to receive MK-3475 at 10 mg/kg every 2 weeks or every 3 weeks. Some patients who had received 2 or more prior lines of therapy and whose tumors did not express PD-L1 were also treated with MK-3475 at 10 mg/kg every 2 weeks. Responses were determined by investigators using

immune-related response criteria (irRC) in addition to an independent central review using Response Evaluation Criteria in Solid Tumors 1.1. Out of 450 patients who provided tissue, 305 patients' tumors expressed PD-L1 with the antibody that was utilized for immunohistochemistry (68%). Of the 221 patients who were treated with MK-3475, 6% of patients experienced grade 3-4 adverse events, and 48% of patients experienced grade 1-2 adverse events. The most common events were fatigue and decreased appetite, although a few developed pneumonitis. The preliminary confirmed overall response rate was 15% (16% for tumors that expressed PD-L1 and 10% for patients whose tumors did not express PD-L1). The confirmed response rate was 19% for patients treated at 10 mg/kg every 2 weeks, and 15% for patients treated at 10 mg/kg every 3 weeks. Many of the patients were still on treatment at the time of the presentation.

These are very promising results in this developing era of immunomodulating agents for the treatment of NSCLC. First of all, MK-3475 seems relatively well tolerated. The most concerning events were the cases of pneumonitis seen in just over 1% of patients. Thus, MK-3475 may pose a risk of pneumonitis similar to that seen with erlotinib. The 15% response rate in a heavily pre-treated patient population is encouraging for a novel therapy and holds promise for use in a subsequent line of therapy strategy. The ongoing clinical trial comparing MK-3475 to docetaxel after prior treatment with a platinum doublet will be critical to defining the role of PD-1 blockade in second line therapy for patients with NSCLC whose tumors express PD-L1 (NCT01905657).

Detection of PD-L1 expression

There are a number of issues that will hopefully be clarified in the clinical trials moving forward. The presented data suggest that there is a relationship between PD-L1 expression on tumor cell surfaces and objective responses; however 10% of patients whose tumors did not express PD-L1 responded to MK-3475. These responses could possibly be related to tumor heterogeneity, meaning the biopsied tumor did not express PD-L1 but non-sampled areas of tumor possibly did. Alternatives to small biopsies may need to be considered for determination of PD-L1 status. In this regard, some groups are investigating circulating markers of PD-L1 expression by tumors, such as our efforts to determine if downstream signaling of CD8+/PD-1+ T cells predict engagement with PD-

L1 (6). Additionally, the 68% of patients with PD-L1 expression in this clinical trial is higher than that of other reports (4). Questions have been raised about the validity of the currently used immunohistochemical assays. Indeed, evaluation of PD-L1 expression in NSCLC samples using multiple validated antibodies that target different PD-L1 domains produced discordant patterns of expression (7). These findings could possibly be due to different antibody affinities, cross reactivity, or variable expression of distinct target epitopes. Another study compared PD-L1 expression by immunohistochemistry to in situ hybridization (ISH) in squamous cell carcinoma of the lung, and found a higher percentage of PD-L1 expression in tumors by ISH (8). Tumor heterogeneity in NSCLC (9) may confound the importance of biomarkers, and obfuscate markers of treatment selection. A better understanding of how to select patients for immune checkpoint inhibition is needed.

Dynamics of PD-L1 expression

The expression of PD-L1 under normal circumstances is dynamic and influenced by cytokines such as interferon- γ . Recent studies suggest that PD-L1 expression by tumor cells can be influenced by cytotoxic agents and targeted therapies (10). Thus, the timing of the biopsy to determine PD-L1 expression may be critical to patient selection. Additionally, as we learn how treatments modulate PD-L1 expression we may begin to test for optimal sequences or combinations of immune checkpoint inhibitors and other approved or experimental therapies. For example, another anti-PD-1 antibody is being studied as front line therapy for patients with metastatic NSCLC whose tumors express PD-L1 (NCT02041533), and a separate trial is combining anti-PD-1 therapy with an immune checkpoint inhibitor against LAG-3 (NCT01968109).

Response evaluation with immunotherapeutics

The use of standard response criteria can be challenging with immunotherapies. Some immune checkpoint inhibitors promote infiltration of tumors with lymphocytes which is associated with a delayed response, but radiographically may present as progressive disease. It is difficult for clinicians to distinguish tumor progression from immune infiltration. Although this issue seems to affect a minority of patients, clinicians and patients would likely prefer to continue therapy resulting in immune infiltration and a likely subsequent response. Some novel imaging technologies,

such as technetium-linked IL-2 single-photon emission computed tomography are being explored in the setting of patients with metastatic melanoma receiving a different immune checkpoint inhibitor against CTLA-4, ipilimumab (NCT01789827). Detection of IL-2 receptor in this setting may help distinguish immune infiltration from tumor progression. Accordingly, this strategy may complement standard imaging modalities in the setting of progression on immune checkpoint inhibitors, providing a rationale to continue with immunotherapy when IL-2 is detected at tumor sites.

Conclusions

Immune checkpoint blockade is a very promising development for the treatment of metastatic NSCLC. We still have much to learn about PD-L1 expression, the detection of PD-L1, the selection of patients for anti-PD-1/PD-L1 therapies, the optimal combination or sequences of therapies, and the use of novel imaging modalities for the appropriate definition of responses.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Leventakos K, Mansfield AS. Reflections on immune checkpoint inhibition in non-small cell lung cancer. *Transl Lung Cancer Res* 2014;3(6):411-413. doi: 10.3978/j.issn.2218-6751.2014.09.09