Competing Immune Biomarkers in the Selection of First-line Therapy in Non-small Cell Lung Cancer

An Expert Interview with Khaled A Tolba

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After completing a fellowship in hematology-oncology at the University of Rochester Wilmot Cancer Center, (Rochester, NY) in June 1999, Dr Khaled A Tolba stayed on faculty as a physician-scientist working in the lab of Dr Joseph D Rosenblatt. Dr Tolba focused on the development of Herpes simplex virus (HSV) as a therapeutic tool to enhance anti-tumor host immunity. Dr Tolba published his first manuscript on the subject in 2001 in the journal Blood. *Subsequently, he focused on the interface of virus (HSV): host innate immunity, how different aspects of the host innate immunity, namely activation of the Toll-like receptors (TLR) though virus-derived pathogen-associated molecular patterns (PAMP), could be exploited to mount an anti-tumor immune response. In parallel, Dr Tolba continued his clinical work as a medical oncologist focusing on lung and head and neck cancers, his area of clinical expertise. In January 2015 Dr Tolba joined Oregon Health & Science University Knight Cancer Institute, where he manages the lung and head and neck cancer specialties. His current focus is the development of novel clinical trials.*

Immune checkpoint inhibitors have established themselves as bona fide practice-changing agents in the management of several cancers including melanoma and lung cancer. However, selection of individual regimens appropriate for first-line treatment of different subsets of patients with lung cancer remains in flux, and is subject to a number of competing predictive biomarkers. In an expert interview, Khaled A Tolba reviews currently available evidence supporting the use of the two currently available biomarkers, namely programmed death-ligand 1 (PD-L1) protein expression and tumor mutational burden (TMB), as well as technical and biologic limitations confounding the use of these two biomarkers in patient selection.

Q. What are the major limitations of PD-L1 expression as a predictive biomarker in the treatment of non-small cell lung cancer?

PD-L1 expression has emerged as a predictive biomarker to select patients for treatment with anti-programmed cell death protein-1 (PD-1)/PD-L1 immune checkpoint inhibitors.[1] Initial trials with immune checkpoint inhibitors revealed an impressive durable response in a small subset of heavily pre-treated patients,[2] and subsequent work established a link between PD-L1 expression in the tumor micro-environment and response to PD-1/PD-L1 blockade in several malignancies including melanoma, non-small cell lung cancer (NSCLC), and bladder cancer. As a consequence, large randomized NSCLC trials incorporated an assessment of PD-L1 expression level as a potential predictive biomarker.[3] Though a trend towards improved objective response and therapeutic efficacy could be observed in patients with higher PD-L1 expression,[4,5] the results were far from conclusive resulting in an uneven regulatory approval landscape whereby some anti-PD-1/PD-L1 agents were approved independent of PD-L1 expression (nivolumab, atezolizumab, and durvalumab) while others (pembrolizumab) were linked to a certain PD-L1 expression level cut off.

PD-L1 expression is inducible by both type I and type II interferons, produced by infiltrating T-cells and natural killer cells, indicative of an anti-tumor immune response. However, interpretation of PD-L1 expression levels is generally complicated by two major factors: A) the biology of PD-L1 upregulation,[6] and B) technical aspects of the assays employed to detect the protein.[7] The former includes a series of genetic aberrations leading to constitutive PD-L1 expression independent of an

anti-tumor immune attack. These include over-expression of c-Myc; loss of PTEN (phosphatase and tensin homolog); activation of the PI3K/Akt (phosphatidylinositol-3-kinase/protein kinase B) pathway; or activation of the epidermal growth factor receptor (EGFR) tyrosine kinase. Activation of such oncogenic signaling pathways is often associated with high expression levels of PD-L1 that would not adequately respond to PD-1 blockade. This might explain why some PD-L1 positive tumors fail to respond to PD-1 directed therapy.

Technical aspects complicating interpretation of PD-L1 expression include the availability of multiple assays and antibodies of variable sensitivities, heterogeneity of PD-L1 expression within the tumor micro-environment giving rise to sampling errors, and the use of various cut-off points among different studies that make cross comparisons of studies and extrapolation of results rather difficult.

Q. What are the pros and cons of PD-L1 expression compared with tumor mutational burden when selecting treatments for NSCLC?

Blockade of the PD-1/PD-L1 axis in itself does not generate an anti-tumor immune response; instead it allows a pre-existing T cell-mediated immune response against the tumor neo-antigens to proceed.[8] Precise identification of such tumor-specific antigens remains an elusive goal, but a search for surrogate marker for such neo-antigens has led to the identification of non-synonymous somatic mutations used to calculate the tumor mutational burden. The concept has taken off following the identification of such mutations as a predictive biomarker of response in patients with melanoma treated with cytotoxic T-lymphocyte associated protein 4 (CTLA-4),[9] and later in patients with NSCLC treated with pembrolizumab.[10] It was further studied as an exploratory endpoint in CheckMate-026 when PD-L1 expression failed to predict response to the anti-PD-1 antibody nivolumab.[11] This study is widely accepted as the first proof that PD-L1 and TMB serve as independent predictive biomarkers for response to immune checkpoint inhibitors. From that point on, a series of prospective[12–14] and retrospective[15,16] analyses established the role of TMB in predicting response to immunotherapy, as well as patient selection for such treatment.

Adoption of TMB as a predictive biomarker for patient selection to receive immune checkpoint inhibitor therapy is still largely hampered by the lack of homogenization among different assays that use different gene panels and employ different arbitrary cut-off values.

Q. How would you choose between single-agent pembrolizumab and pembrolizumab combined with chemotherapy in patients with a PD-L1 expression of ≥50%?

Currently, pembrolizumab has received three US Food and Drug Administration (FDA) approvals in the first-line NSCLC setting. The first came out in October 2016, when the FDA approved single-agent pembrolizumab for the first-line treatment of patients with metastatic NSCLC whose tumors have ≥50% PD-L1 expression, who do not harbor EGFR or ALK aberrations, based on KEYNOTE-024.[17] The second approval came in May 2017, for use in combination with pemetrexed plus carboplatin as a first-line treatment for patients with metastatic or advanced non-squamous NSCLC, regardless of PD-L1 expression, based on KEYNOTE-189.[18] The third approval came in October 2018 for use in combination with

carboplatin and either paclitaxel or nab-paclitaxel (Abraxane®; Celgene, Summit, NJ, US) for the first-line treatment of patients with metastatic squamous NSCLC, based on KEYNOTE-407.[19] This leaves patients with non-actionable NSCLC regardless of histology whose tumors have ≥50% PD-L1 expression with two options: A) pembrolizumab monotherapy according to KEYNOTE-024 or B) pembrolizumab plus platinum doublet, according to KEYNOTE-189/407. Selection between these two options is often left to the treating physician since there is currently no direct comparison of the two regimens. A number of factors including disease volume, symptoms at presentation that might dictate the need for rapid response, the patient's performance status, organ function, and co-morbidities among others might settle the argument in favor of chemotherapy plus pembrolizumab versus pembrolizumab monotherapy.

Q. What factors would you take into account when selecting between immuno-chemotherapy combinations and dual immunotherapy regimes (e.g. nivolumab plus ipilimumab, when it is approved)?

Immuno-chemotherapy combinations have already gained FDA-approval for first-line therapy in both adeno- and squamous histology NSCLC based on two large randomized registration trials, KEYNOTE-189 and -407, respectively, where the comparator arm was histology-specific platinum doublet. As a result, these combinations have not been directly compared to an immuno-oncology (IO)-doublet such as nivolumab-ipilimumab. The CheckMate-227 trial,[20] which has completed accrual, will offer a head-to-head comparison of platinum doublet chemotherapy, immuno-chemotherapy (using nivolumab instead of pembrolizumab) and the IO-doublet of nivolumab-ipilimumab. CheckMate-227 incorporated two predictive biomarkers, PD-L1 of ≥1% versus PD-L1 negative, and high TMB of ≥10 mutations/mega-base versus low TMB.

Preliminary results from CheckMate-227 showed the combination of nivolumab plus low-dose ipilimumab in the first-line treatment of patients with advanced NSCLC with tumor TMB of ≥10 mutations/mega-base was associated with a 1-year progression-free survival rate of 43% compared with 13% for those assigned to platinum doublet chemotherapy. The median overall survival for the IO combination in patients with TMB of ≥10 mutations/mega-base was 23.03 months compared with 16.72 months for the chemotherapy arm (0.77; 95% confidence interval [CI]: 0.56–1.06). Among patients with TMB of <10 mutations/mega-base, the median overall survival was 16.20 months versus 12.42 months, respectively (hazard ratio: 0.78; 95% CI: 0.61–1.00). The FDA is expected to issue their recommendations by May 2019.

Q. How can the accuracy of the PD-L1 biomarker assay be improved in selecting NSCLC patients for PD-1/PD-L1 immunotherapy?

The utility of PD-L1 as a predictive biomarker for immunotherapy could be improved upon through two steps:

A) Taking into consideration the role played by oncogenic signaling pathways in upregulating PD-L1, effectively generating PD-L1 positive tumors that would not respond to PD-1-directed therapy.[21] This point has been confirmed through a meta-analysis of three large randomized trials comparing anti-PD-1/PD-L1 to docetaxel,[22] as well as a prospective first-line trial of pembrolizumab in previously untreated EGFR-mutated NSCLC.[23] As a corollary of this, oncologists ought to ensure that patients

with newly diagnosed stage IV adeno-NSCLC will undergo proper comprehensive genomic profiling using next-generation sequencing in order to identify actionable driver mutation that could benefit from targeted therapy. The use of anti-PD-1 in patients with oncogene-driven NSCLC ought to be approached with caution given the recently reported increased incidence in interstitial lung disease/pneumonitis.[24]

B) Incorporation of several predictive biomarkers into the decision-making process, instead of just one, in order to gain a better understanding of the tumor biology as well as help select the most appropriate first line regimen. In this context, several new biomarkers are currently being evaluated, including TMB, gene-expression profile,[25,26] and DNA methylation profile.[27] ❑

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