NSCLC: PD-1 Inhibitor Has Efficacy, But PD-L1 Found Not to be Reliable Biomarker

BY ROBERT H. CARLSON

PHILADELPHIA—Non-small cell lung cancer, not generally considered amenable to immunotherapy, responded favorably to the anti-PD-1 checkpoint inhibitor pembrolizumab in a Phase IIb trial reported here at the American Association for Cancer Research Annual Meeting (***Abstract CT104***) and published simultaneously in the *New England Journal of Medicine* (***DOI: 10.1056/NEJMoa1501824***).

The overall response rate for the 495 study patients in KEYNOTE-001 was 19.4 percent, with a median of 10.9 months follow-up. And patients with at least 50 percent of tumor cells staining for PD-L1 had a 45.2 percent response.

The trial, which was sponsored by Merck Sharp & Dohme, also attempted to validate PD-L1, the ligand to PD-1, as a biomarker for such patients, but those results were not as clear.

The 73 patients with positive PD-L1 staining in at least half the tumor cells also had a median progression-free survival of 6.3 months; median overall survival has not yet been reached.

"The benefit in this subgroup [with high PD-L1-expressing tumors] substantially exceeds that expected from cytotoxic chemotherapy," said the lead author, Edward B. Garon, MD, Associate Professor of Medicine at the David Geffen School of Medicine of UCLA. "However, the efficacy in patients with less tumor PD-L1 expression are also compelling."

Pembrolizumab treatment was associated with a manageable toxicity profile, emphasizing that there is a low incidence of immune-mediated adverse events, he said.

Assessing Biomarker Potential

Staining for the presence of PD-L1 in tumor cells was a key element of KEYNOTE-001, to assess the ligand as a potential biomarker for identifying patients likely to respond to anti-PD-1 therapy.

The results were ambiguous, however, because even though patients with high levels of PD-L1 expression in tumor cells responded to the drug, so did patients with low levels of PD-L1 expression, although not to the same degree.

Among the 495 patients who received one or more doses of pembrolizumab, 182 were assigned to a "training" group and 313 to an independent validation set.

In the validation group were 223 previously treated patients and 90 patients who had not received systemic therapy. Clinical outcomes after five months of follow-up were compared with immunohistochemistry evaluation using a prototype 22C3 antibody clone, an antibody that Merck has been using in its clinical trials to date, Garon said.

Former or current smokers fared better compared with never smokers, with a rate of response that was higher than has been seen in other trials, he noted.

Patients who had never smoked had far fewer responses than those who were former or current smokers—10.3 for never smokers versus 22.5 percent for former/current smokers. The researchers hypothesized that this was due to a higher mutational burden in these patients.

The median duration of response was 12.5 months for patients who did respond.

In general the drug was very well tolerated, he said; the most common adverse event considered related to pembrolizumab was fatigue, which was seen in less than 20 percent of the patients. Less than 10 percent of patients had a grade 3 or greater adverse event.

Staining by Category

In terms of staining, there were three categories:

- Patients whose cancer cells had an absence of staining for PD-L1;
- Patients who had staining for PD-L1 in 49 percent or less of their cancer cells; and
- Patients who had staining for PD-L1 in 50 percent or more of the tumor cells.

Garon said the study showed a correlation with the putative biomarker PD-L1 to predict which patients should be selected or prioritized for that therapy. He said the presence of PD-L1 in tumor cells or in inflammatory cells in the area of the tumor has been studied as a potential biomarker, particularly in metastatic NSCLC.

EDWARD B. GARON, MD: "Somewhat remarkably, in the treatment-naïve patients, not only is the median for overall survival not reached, but the lower boundary of 95 percent confidence interval is also not reached for the patients with stain in at least half their cells."

"Our study design is unique in that we actually amended the protocol to add a co-primary endpoint that was for the lung cancer cohort, to evaluate the role of pembrolizumab in patients who have high expression for PD-L1," Garon said.

The response rate was 45.2 percent for patients in the validation set who had staining for PD-L1 in half or more of their cells, compared with 16.5 percent for patients who had staining in less than half. The response rate for those in whom staining was absent was 10.7 percent.

There were no clear differences between previously treated and treatment-naïve patients, he said.

For all 492 patients in the combined validation and training sets, the response rate for those with prior therapy was 18.0 percent, versus 24.8 percent for treatment-naive patients.

Patients with squamous cell carcinoma had more responses than those with non-squamous cell histology—23.5 versus 18.7 percent. And the overall response by dosage—10 mg every two weeks versus 10 mg every three weeks—was virtually identical, at 19.2 and 19.3 percent, respectively.

PFS Doubled

Longer progression-free survival was seen in patients with higher levels of PD-L1 and in those previously untreated. Analysis of all 492 patients showed that patients with staining in

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The response is considered notable because non-small cell lung cancer has not been considered amenable to immunotherapy.

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"The importance of a good predictive assay in this field is so great that it is impossible to ascribe any true differences in efficacy between drugs separate from the degree of enrichment that their associated assays produce."

at least half of their cells had a progression-free survival time of 6.3 months versus 3.3 months for those with less than half of cells staining for PD-L1, and 2.3 months for those with no staining.

In previously treated patients, progression-free survival was 6.1 months for those with staining in at least half of their cells, versus 2.3 months for those with staining in less than half, and 2.2 months for those with no staining.

For treatment-naïve patients, progression-free survivals were 12.5, 4.3, and 3.5 months, respectively.

For overall survival, 10.9 months median follow-up, in the group of patients with staining in at least half of their cells, the median overall survival is not reached. This compared with 8.8 months in the other treatment groups.

In the previously treated patients, overall survival again has not been reached in the patients with staining in more than half of their cells, versus 7.3 months for less than half and 8.6 months for patients with none.

"Somewhat remarkably, in the treatment-naïve patients, not only is the median for overall survival not reached, but the lower boundary of 95 percent confidence interval is also not reached for the patients with stain in at least half their cells," he said. This is compared with 16.2 and 10.4 for less than half the cells staining and for no staining.

Tumors Evade Immune Response

A hallmark of cancer is immune evasion, in which the immune system does not mount an effective antitumor response, Garon explained. PD-1 is a negative co-stimulatory receptor expressed primarily on the surface of activated T cells. The binding of PD-1 to one of its ligands, PD-L1 or PD-L2, can inhibit a cytotoxic T-cell response.

SUZANNE L. TOPALIAN, MD: "These new results are especially impressive in this particular treatment setting of a very difficult to treat population in advanced non-small cell lung cancer, with more than three-quarters of patients having had previous systemic treatment for cancer with progressive disease after that."

Tumors can co-opt this pathway to escape T-cell–induced antitumor activity.

Pembrolizumab, a highly selective, humanized monoclonal IgG4 kappa isotype antibody against PD-1, can disrupt the engagement of PD-1 with its ligands and impede inhibitory signals in T cells, which results in tumor recognition by cytotoxic T cells.

"Seeing responses in patients regardless of the degree of PD-L1 expression is one of the exciting outcomes with this class of drug," Garon said.

In general, the side effect profile was favorable, he said. The most common treatment-related adverse events were fatigue, pruritus, and decreased appetite. There was one drug-related death, resulting from pneumonitis. Pneumonitis was seen in 3.6 percent of all patients but half of those cases were grade 1 or 2.

Other immune-related adverse events occurring in at least two percent of the patients were infusion reactions and hypothyroidism.

Even though patients with high levels of PD-L1 expression in tumor cells responded to the drug, so did patients with low levels, although not to the same degree

Garon mentioned two other ongoing pembrolizumab studies:

- KEYNOTE-024, which is randomly assigning patients with PD-L1 staining in at least half of their cells to receive standard chemotherapy or pembrolizumab; and
- KEYNOTE-10, testing a lower dosage of 2 mg/kg every three weeks, as there was no clear difference in safety or efficacy in KEYNOTE-001 between the 10 mg/kg every two weeks versus every three weeks.

'Exciting Development'

Suzanne L. Topalian, MD, Professor of Surgery and Oncology and Director of the Melanoma Program at the Johns Hopkins Kimmel Cancer Center, served as moderator at a news conference at the meeting that highlighted noteworthy immunotherapy studies.

Topalian, who has led several major trials of PD-1 inhibition in solid tumors including lung cancer, said the most exciting moment for her personally in the development of anti-PD-1 drugs was the realization that lung cancer could respond to this form of immunotherapy.

D. ROSS CAMIDGE, MD, PHD: "An imperfect enrichment strategy can be highly useful if we don't think about drug treatments as all-or-nothing, but rather as treatments with different chances of benefit in different situations. And at each decision point we prioritize the therapy with the greatest chance of success."

"In the past we had tried many forms of immunotherapy that had not had any impact on lung cancer," she said. "These new results are especially impressive in this particular treatment setting of a very difficult to treat population in advanced non-small cell lung cancer, with more than three-quarters of patients having had previous systemic treatment for cancer with progressive disease after that.

"It's a patient population where the impact of second- and third-line agents is limited and generally not expected to prolong survival."

Discussant's Remarks

The Discussant for the paper was D. Ross Camidge, MD, PhD, Director of the Thoracic Oncology Clinical Program at the University of Colorado Cancer Center, who titled his speech "PD-1 Access Inhibition: An Imperfect Panacea?"

He began with a slightly fanciful characterization of the immune system: "It's important to realize that the T cell is a painfully insecure cell because of the fear of autoimmunity. It requires multiple pro-stimulatory signals to occur and the absence of multiple inhibitory signals on separate time points in order to mount an immune response.

"Lack of engagement of the PD-1 access is just one such shout of encouragement for the T cell," he said.

Access blockade to stimulate anticancer immunity is being approached through two main approaches, with antibodies directed either against the ligand, or as with pembrolizumab, against the receptor.

The pros and cons of each are theoretical and as yet clinically unproven, he said, but there is no doubt that PD-1 access blockade has been a major breakthrough in the therapy of solid tumors, with a significant number of tumor types already showing dramatic responses to therapy.

FDA Gives Fast Track Designations to Drugs for AML, Pancreatic Cancer, and NSCLC, and Prevention of Oral Mucositis

The Food and Drug Administration has granted several new Fast-Track designations:

The Fast Track designation, established under the FDA Modernization Act of 1997, is designed to facilitate frequent interactions with the FDA review team to expedite clinical development and submission of a New Drug Application for medicines with the potential to treat serious or life-threatening conditions and address unmet medical needs. The designation permits the drug developer the opportunity to submit sections of an NDA on a rolling basis as data become available, allowing the FDA to review those materials on a rolling basis as well.

The following are the new agents given the designation:

- **AG-120** for the treatment of patients with acute myelogenous leukemia with an isocitrate dehydrogenase-1 (IDH1) mutation. AD-120 is a first-in-class, oral, selective, potent inhibitor of the mutated IDH1 protein. The drug is currently being evaluated in a Phase I clinical trial for this indication and results are expected to be presented at the European Hematology Association Annual Congress this month, according to a news release from Agios Pharmaceuticals, the drug's manufacturer. In addition, a Phase III study to evaluate the drug for this indication is being planned to begin in 2016.
- **Evofosfamide** (previously named TH-302) for use in combination with gemcitabine for the treatment of patients with previously untreated metastatic or locally advanced resectable pancreatic cancer. Evofosfamide is an investigational hypoxia-activated prodrug thought to be activated under the severe tumor hypoxic conditions typical of many solid tumors. The drug is currently in Phase III trials for this indication. The drug, being developed by Merck in collaboration with Threshold Pharmaceuticals, Inc., has also previously received Fast Track designation for use in combination with doxorubicin for the treatment of advanced soft tissue sarcoma.
- **Sacituzumab govitecan** for the treatment of patients with metastatic non-small cell lung cancer that has failed to respond to two prior lines of therapy, including targeting therapies such as ALK inhibitors, EFGR inhibitors, and PD-1 inhibitors. Sacituzumab govitecan is an antibody-drug conjugate that works by conjugating SN-38, the active metabolite of irinotecan. Updated results of the current clinical trial for the drug were expected to have been reported at the American Society of Clinical Oncology Annual Meeting, according to a news release from the drug's manufacturer, Immunomedics, Inc. Sacituzumab had previously received Fast-Track status for the treatment of patients with triple-negative breast cancer or small-cell lung cancer; and the drug has also received Orphan Drug designation for the treatment of patients with small-cell lung or pancreatic cancers (***OT 2/10/15 issue***).
- **Cobiprostone** for the prevention of oral mucositis in patients with head and neck cancer receiving concurrent radiation and chemotherapy. Cobiprostone is a locally acting chloride channel activator that works to stimulate and protect the mucosal barrier function. A proof-of-concept, Phase II study of cobiprostone for this indication is planned to be initiated by the end of the quarter, according to a news release from the manufacturer, Sucampo Pharmaceuticals, Inc., and the drug is also being developed for the treatment of the gastroesophageal reflux disease subtype of non-erosive reflux disease.

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Camidge said Garon's presentation has now shed more light on a search for who is deriving the most benefit from monotherapy with these agents, at least in non-small cell lung cancer.

"Early clues suggest that while histology may play a small role, smoking status produced a far greater enrichment for responders, the assumption being that the presence of neo-antigens induced by mutagens such as cigarettes drive the initial immunogenic state of the tumor."

Camidge said this is supported by recent data showing that the mutational burden measured by whole exome sequencing strongly correlates with the progression-free survival with pembrolizumab.

The other aspect of determining the effect of PD-1 access effect is to show engagement of the pathway with PD-L1, he continued. PD-L1 levels have been extensively explored, either because PD-L1 expression may be additional evidence of an immunogenic state, or evidence that that immunologic state has utilized the PD-1 axis as its means to "discourage the nervous T cell."

"The problem with measuring PD-L1 levels is that it represents a continuous variable," Camidge said. "PD-L1 is present on different cells, is inducible rather than hard-wired—that is, it changes over time—and, at least for the PD-1 antagonists, PD-L1 is associated with but is not itself the direct target of the drug."

Nevertheless, PD-L1 immunohistochemistry continues to hint at its contribution to an elusive PD-1 access sensitivity signature, he said.

"Each company developing a drug has looked slightly differently, including Merck, with different antibodies, different target cells, use of archival versus fresh tissue, and different cut points, for sensitivity and for positivity.

> "Seeing responses in patients regardless of the degree of PD-L1 expression is one of the exciting outcomes with this class of drug."

"It is vital to realize that, to date, the importance of a good predictive assay in this field is so great that it is impossible to ascribe any true differences in efficacy between drugs separate from the degree of enrichment that their associated assays produce. A higher cut point [of staining for PD-L1 positivity] is associated with a higher response rate, and yet responses still occur in those who manifest lower degrees of positivity."

PD-L1 not a perfect biomarker by any means, Camidge said. In all of the groups in KEYNOTE-001, including the high PD-L1 group, approximately 30 to 40 percent of patients are still rapid progressives on therapy.

Camidge considered the interesting idea that prior cytotoxic chemotherapy or its associated medications such as corticosteroids may either have a long-term effect in blunting immune responses, or conceivably, immunogenic pruning of sub-populations of cells by the cytotoxic therapy.

Either PD-L1 expression itself is a good prognostic factor, or alternatively, the biomarker may be predicting the ongoing benefit after the initial immunotherapy is finished, including potentially modifying outcomes from subsequent lines of therapy, he said.

"When we don't 100 percent know who a drug works in, this does not mean either that we shouldn't give it to anyone until we do or that we should give it to everybody. An imperfect enrichment strategy can be highly useful if we don't think about drug treatments as all-or-nothing, but rather as treatments with different chances of benefit in different situations. And at each decision point we prioritize the therapy with the greatest chance of success."