Updated Results From a Phase 1/2 Study of Epacadostat (INCB024360) in Combination With Ipilimumab in Patients With Metastatic Melanoma

Jeffrey S. Weber, MD, PhD, H. Lee Moffitt Cancer Center, Tampa, Florida

Indoleamine 2,3-dioxygenase 1 (IDO1), a tryptophan-catabolizing enzyme, is overexpressed in many cancers. Its effects on effector and regulatory T cells induce immune tolerance. In preclinical studies, the potent, selective IDO1 inhibitor epacadostat (INCB024360) showed antitumor activity and was generally well tolerated at doses of up to 700 mg twice daily in patients with advanced malignancies. In further preclinical research, epacadostat administered with an antibody antagonist to checkpoint receptors supported increased antitumor activity.

Presenting results from a phase 1/2 study (NCT01604889) of epacadostat in combination with ipilimumab among patients with unresectable or metastatic melanoma, Dr. Weber noted that preliminary data from the dose-escalation phase of the study showed a favorable objective response and disease control in immunotherapy-naïve patients. Additional patients (n = 25) were added, bringing the total to 42, with eight patients receiving 25 mg twice a day, 18 receiving 50 mg twice a day continuously, nine receiving 50 mg intermittently, and seven receiving 75 mg as a total daily dose. Thirty-two of the patients had not received prior immunotherapy for advanced or metastatic disease.

The overall response rate (ORR), including both complete responses (CRs) plus partial responses (PRs) by immune-related response criteria (irRC), was 31.3% in the immunotherapy-naïve population and 0% in those with prior immunotherapy. Disease control rates (CRs, PRs, and stable disease (SD)) were 62.5% and 30.0%, respectively. Median progression-free survival (PFS) by irRC was 8.3 months in the immunotherapy-naïve patients and 2.5 months among those with prior immunotherapy.

Pharmacodynamic analysis demonstrated dose-dependent inhibition of IDO1 at all doses, and a degree of inhibition shown to be sufficient for therapeutic effect in preclinical models was achieved at all doses.

“If you look at the totality of the data, it doesn’t look like there’s a huge difference between any dose, but you’re looking at some pretty small numbers,” Dr. Weber commented in an interview. “In terms of efficacy, we probably doubled the response rate. On a good day the ipilimumab response rate is 15% to 19%. On an average day it’s 10% to 15%. Here it’s 30%.” The disease control rate, even among heavily pretreated patients, was also 30%.

“These are very interesting and encouraging data,” Dr. Weber added. “Responses are prolonged, clearly better than ipilimumab alone, and at the end of the day, based on these analyses, I would think you’re going to see a nice-looking survival curve.”

Safety, Activity, and Response Durability Assessment of Single-Agent Rovaletuzumab Tesirine, a Delta-Like Protein 3 (DLL3)-Targeted Antibody Drug Conjugate (ADC), in Small-Cell Lung Cancer (SCLC)

M. Catherine Pietanza, MD, Memorial Sloan Kettering Cancer Center, New York, New York

In small-cell lung cancer (SCLC), resistance to chemotherapy and radiation therapy develops rapidly, leaving five-year survival rates “dismal” at 6%. Rovaletuzumab tesirine (Rova-T) is an antibody drug conjugate (ADC) made up of three components: an antibody, a linker, and the active chemotherapeutic, or cytotoxic payload. It is a delta-like protein (DLL3)-targeted ADC and a dominant inhibitor of notch signalling. DLL3 expression correlates with ASCL1, which is highly expressed in medullary thyroid cancer and SCLC. Rova-T cytotoxicity is DLL3-dependent and may mediate notch pathway inhibition downstream of ASCL1. The antibody recognizes cell surface receptors overexpressed in cancer cells, allowing direct delivery of chemotherapy to the tumor. The strategy, Dr. Pietanza said, maximizes efficacy and minimizes toxicity.

A phase 1b SCLC trial of Rova-T demonstrating an ORR of 44% and a clinical benefit rate of 78% in DLL3-positive patients confirmed its single-agent activity. The trial included 73 patients (45% with either primary refractory or resistant disease), among whom 45 had progressed after second-line therapy. Prior radiation was reported in 82% of patients. The first phase confirmed doses of 0.2 mg/kg every three weeks and 0.3 mg/kg every six weeks for the phase 1b expansion cohort. Fatigue, the most common adverse event (AE), occurred in 28% of patients (6% grade 3 or 4). AEs overall were manageable.

Best-response evaluation of 53 patients showed responses among all of the patients with high-DLL3 tumors. “Importantly, responses were similar in both second- and third-line therapy patients,” Dr. Pietanza said. She noted that responses were
durable, with mean overall survival (OS) of 236 days or more (range, 99 to 388 days). “This is very rare in SCLC patients receiving second- or third-line therapy,” she added.

The ORR among all patients sensitive to chemotherapy was 28%; it was 64% in DLL3-positive patients. Among patients refractory or resistant to chemotherapy, the ORR was 16% overall and 23% among DLL3-positive patients.

Dr. Pietanza concluded that Rova-T has single-agent activity in SCLC. “DLL3 is the first predictive biomarker associated with drug efficacy in SCLC,” she observed.

**An Open-Label, Randomized, Phase 2 Study Of Nivolumab Given Sequentially With Ipilimumab in Patients With Advanced Melanoma (CheckMate 064)**

- F. Stephen Hodi, MD, Associate Professor of Medicine, Harvard Medical School, Assistant Professor of Medicine, Dana-Farber Cancer Institute, Boston, Massachusetts

An examination of the impact of treatment sequence with nivolumab and ipilimumab in Checkmate 064 showed consistent efficacy advantages for nivolumab followed by ipilimumab compared with ipilimumab followed by nivolumab in patients with advanced melanoma.

Dr. Hodi noted that nivolumab, which targets the programmed death-1 (PD-1) receptor, demonstrated improved long-term OS and PFS in the phase 3 CheckMate 066 trial (with an ORR of 40% in treatment-naïve/BRAF wild-type melanoma). Ipilimumab, which targets cytotoxic T-lymphocyte-associated protein 4 (CTLA4), has demonstrated 10-year survival in approximately 20% of advanced melanoma patients. Furthermore, a phase 3 study of combined nivolumab plus ipilimumab in untreated melanoma showed longer PFS for the combination (11.5 months) than for nivolumab alone (6.9 months) or ipilimumab alone (2.9 months). The ORR for nivolumab plus ipilimumab was 58% compared with 44% and 19% for the respective monotherapies. Grade 3 or 4 treatment-related AEs were reported, however, in 55% for the combination.

Dr. Hodi’s open-label, randomized, phase 2 trial had treatment-related grade 3 or 4 AEs during the induction period as the primary endpoint and confirmed ORR at week 25 and progression at weeks 13 and 25 as secondary endpoints. It included 68 patients in the nivolumab-to-ipilimumab group and 70 in the ipilimumab-to-nivolumab group (mean age, 60 years; 67% male).

In the induction periods, treatment-related grade 3 or 4 AE rates were 50% (95% confidence interval [CI], 37.6%–62.4%) for nivolumab to ipilimumab and 43% (95% CI, 31.1%–55.3%) for ipilimumab to nivolumab. The most common AEs, rash and pruritus, were similar (3% and 2% for nivolumab to ipilimumab; 3% and 0% for ipilimumab to nivolumab), while hepatic events (elevated alanine transaminase/aspartate aminotransferase) were more common in the nivolumab-first group (15% versus 4%).

Analysis revealed that treatment was discontinued because of disease progression in 27% of patients receiving nivolumab first and in 56% of patients receiving ipilimumab first. Toxicity caused discontinuation more often in the nivolumab-to-ipilimumab group (31% versus 14%). No drug-related deaths were reported.

Confirmed ORRs at week 25 were 41.2% for nivolumab to ipilimumab and 20.0% for ipilimumab to nivolumab. Progression rates were 38.2% and 60.0%, respectively. Median tumor burden changes at week 25 were −50% and −17% for the nivolumab-first and ipilimumab-first cohorts, respectively.

Dr. Hodi concluded, “The data from this study, including planned correlative biomarker analyses that are under way, may help inform the choice of initial treatment approaches in advanced melanoma.”

Caroline Robert, MD, PhD, of Institute Gustave Roussy in Villejuif, France, the discussant for the session, acknowledged the superiority of nivolumab to ipilimumab. However, she added that in light of the safety profile, “I don’t see a clear benefit for this sequence design as compared with nivolumab monotherapy.”

**First-Line Monotherapy With Nivolumab in Advanced Non–Small-Cell Lung Cancer (NSCLC): Safety, Efficacy, and Biomarker Analyses**

- Scott N. Gettinger, MD, Yale Comprehensive Cancer Center, New Haven, Connecticut

Survival was encouraging and responses were durable with first-line nivolumab monotherapy in patients with advanced non–small-cell lung cancer (NSCLC) in the Checkmate 012 study. While platinum-based doublet chemotherapy is standard in this population, one- and two-year OS rates are in the ranges of 30% to 40% and 10% to 15%, respectively. These rates are improved modestly (51% for one-year OS and 23% for two-year OS) with the addition of bevacizumab in patients with nonsquamous NSCLC. Other options include small-molecule tyrosine kinase inhibitors, but their activity is limited to the 15% to 20% of NSCLC patients harboring EGFR mutations or ALK rearrangements. The fully human immunoglobulin G4 (IgG4) PD-1 immune checkpoint inhibitor antibody nivolumab has improved survival versus docetaxel in previously treated patients with advanced NSCLC in two phase 3 trials.

Dr. Gettinger reported on CheckMate 012, which enrolled 52 stage IIIIB/IV NSCLC patients (nonsquamous, n = 39, or squamous, n = 13) who had not had prior chemotherapy. They received nivolumab 3 mg/kg (intravenous every two weeks) until disease progression or unacceptable toxicity. The primary objectives were safety and tolerability. ORR per RECIST version 1.1 and PFS at 24 weeks were secondary endpoints. Thirty-seven percent of patients enrolled had prior systemic therapy; EGFR mutations were present in 15% and KRAS mutations in 17%.

The confirmed ORR was 23% (26% in nonsquamous), and the disease control rate was 50% (62% in squamous, 46% in nonsquamous). PFS at 24 weeks was 41% (31% in squamous, 45% in nonsquamous). One-year OS was 74% (76% in squamous, 74% in nonsquamous).

Dr. Gettinger noted that clinical activity was observed regardless of programmed death ligand 1 (PD-L1) expression, with higher ORRs in patients whose tumors expressed PD-L1 across all prespecified expression levels (at least 1% to at least 50%). Also, among patients with nonsquamous histology, responses were noted regardless of EGFR or KRAS mutation status.
Median PFS was longer in current smokers than in former or never smokers (10.5 months versus 3.7 and 3.2 months, respectively).

Consistent with prior studies, nivolumab monotherapy was associated with a tolerable safety profile. Most treatment-related AEs were low-grade (any grade, 71%; grade 3 or 4, 19%). Those with a potential immunological etiology requiring more frequent monitoring or intervention included rash (19%), diarrhea (12%), pruritus (12%), hypothyroidism (6%), and pneumonitis (6%). Five patients discontinued therapy because of treatment-related AEs.

Dr. Gettinger noted that a phase 3 trial (CheckMate 026, NCT02041533) is evaluating nivolumab versus the investigator’s choice of chemotherapy as first-line therapy for stage IV or recurrent PD-L1-positive NSCLC.

Efficacy and Safety of Nivolumab in Patients With Metastatic Renal Cell Carcinoma Who Were Treated Beyond Progression in a Randomized Phase 2 Dose-Ranging Trial (CheckMate 010)

Saby George, MD, Assistant Professor of Oncology, Roswell Park Cancer Institute, Buffalo, New York

Most approved targeted therapies for metastatic renal cell carcinoma (mRCC) were approved based on favorable PFS. However, OS is limited among previously treated patients. The phase 3 CheckMate 025 trial of nivolumab2 demonstrated a significant survival advantage over everolimus in patients who had previously received anti-angiogenic treatment (median OS, 18.2 to 25.5 months).

Dr. George noted that tumor flare, the growth of existing lesions or the appearance of new lesions, may precede anti-tumor effects, possibly leading to premature discontinuation of therapy. Infiltration of T cells to the tumor site, he said, may make tumors look larger, fulfilling criteria for RECIST-defined progression. The objective of his trial was to assess the benefit of continuing nivolumab treatment beyond the first RECIST-defined progression in patients with clear-cell mRCC. Dose response by PFS was the primary endpoint.

Patients received nivolumab at doses (1:1:1) of 0.3, 2, or 10 mg/kg every three weeks until progression or toxicity. Enrollment criteria included prior treatment with one or more agents targeting the vascular endothelial growth factor pathway and three or fewer systemic therapies. Treatment with nivolumab beyond first progression as defined by RECIST (version 1.1) was permitted in patients who tolerated nivolumab and had investigator-assessed clinical benefit at the time of progression.

Thirty-six patients were treated with nivolumab beyond progression, and 92 who progressed were not treated. The majority of patients in both groups (approximately 69%) had received one prior anti-angiogenic regimen in the metastatic setting. Dr. George observed that prior to first progression, the time to objective response was somewhat longer in the group treated beyond progression (4.2 months versus 2.6 months), and that group also had better median PFS (4.2 months versus 2.3 months).

The median number of doses received was 5.0 and 3.0 in patients treated and not treated beyond progression. Median OS in the 36 patients treated beyond progression was 30.5 months (95% CI, 18.1–41.1); in those not treated beyond progression (n = 92), OS was 15.2 months.

The majority of the 36 patients treated beyond progression achieved a tumor-burden reduction, Dr. George observed. “Nearly a third achieved significant tumor shrinkage that was maintained for a long time.” However, he added, “I would exercise a little bit of caution in interpreting this because the two groups were not balanced or controlled.”

After adjusting for drug exposure, patients treated beyond progression experienced a lower incidence of AEs (incident rate per 100 patient years: 322.9 versus 518.7 for those treated and not treated beyond progression).

Dr. George concluded that mRCC patients treated with nivolumab beyond progression were able to safely continue treatment with nivolumab. Some patients experienced subsequent tumor shrinkage and extended survival. Further analysis of phase 3 trials will help validate this clinical benefit.

REFERENCES