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These data will be presented at an AACR press briefing at 7:30 a.m. PT in room 15B of the San Diego Convention Center. Reporters who cannot attend in person can dial in using either 866-297-6395 (U.S./Canada) or 847-944-7317 (International). Confirmation code: 36855817

# Biomarker Identifies Melanoma Patients Who May Respond to Immunotherapy MK-3475

SAN DIEGO — Among melanoma patients treated with the PD-1 inhibitor MK-3475, those whose tumors had the protein PD-L1 had better immune responses and higher survival rates, according to results presented here at the AACR Annual Meeting 2014, April 5-9.

When the protein PD-L1, which is present on some melanoma tumors, binds to PD-1, a protein present on T cells, "brakes" are applied on these T cells, preventing them from attacking the cancer cells. The immunotherapy MK-3475 blocks PD-1, releasing the brakes on T cells and enabling them to attack the cancer cells.

This study found that among melanoma patients who received MK-3475, those whose tumors had PD-L1 had an overall response rate of 46 percent, while those whose tumors did not have PD-L1 had an overall response rate of 17 percent. At six months, 64 percent of the patients whose tumors were PD-L1-positive had no disease progression, compared with 34 percent of those whose tumors were PD-L1-negative. Similarly, 86 percent of the patients whose tumors were PD-L1-positive were alive after one year, compared with 72 percent of those whose tumors were PD-L1-negative.

"We found a major difference in the response rates between patients with PD-L1-positive and PD-L1-negative tumors treated with MK-3475," said Adil I. Daud, M.D., co-director of the UCSF Melanoma Center, and director of melanoma clinical research at the UCSF Helen Diller Family Comprehensive Cancer Center. "This is the largest data set yet, to my knowledge, looking at PD-L1 expression in tumors from melanoma patients treated with PD-1 inhibitors.

"Data from this study identifies PD-L1 as a robust marker in determining which melanoma patients may be well served when treated with MK-3475. However, we are studying more samples from randomized trials of PD-1 inhibitor versus ipilimumab or chemotherapy to establish the validity of this marker," added Daud.

To evaluate the relationship between tumor PD-L1 expression and clinical outcome, Daud and colleagues studied tumor samples collected from 195 patients recruited to a phase I clinical trial

testing MK-3475 at three different doses. All patients had late-stage melanoma, and some of them had received prior treatment with another immunotherapy drug called ipilimumab.

The investigators measured the amounts of PD-L1 in the tumor samples and considered them PD-L1-positive if at least one cell per 100 tumor cells had the protein. They found that, of the 125 evaluable tumor samples, 89 were PD-L1-positive and 36 were PD-L1-negative.

Patients with PD-L1-positive tumors had disease that did not progress for about 50 weeks, while disease progressed at about 12 weeks for those with PD-L1-negative tumors.

The investigators also found that among patients whose tumors were PD-L1-positive, overall response rates between those who had and had not received prior therapy with ipilimumab (44 percent versus 47 percent) were not significantly different. Similarly, among patients whose tumors were PD-L1-negative, overall response rates between those who had and had not received prior therapy with ipilimumab (14 percent versus 17 percent) were not significantly different.

"This suggests that prior treatment with the anti-CTLA-4 antibody ipilimumab does not impact the ability of these tumors to respond to MK-3475, nor does it affect the viability of PD-L1 as a marker of response to MK-3475," said Daud.

The investigators found a 24 percent and 17.5 percent increase in two types of activated T cells, CD8-positive and CD4-positive T cells, in the blood of patients treated at three different doses of MK-3475 for six weeks, leading them to suggest that the treatment improved the immune response in these patients at all doses tested.

This study was funded by Merck. Daud has served on the advisory boards of Merck and GlaxoSmithKline PLC.

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**Abstract Number:** CT104

**Presenter:** Adil I. Daud, M.D.

**Title:** Antitumor activity of the anti-PD-1 monoclonal antibody MK-3475 in melanoma (MEL): Correlation of tumor PD-L1 expression with outcome

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**Background:** Previous data on the relationship between PD-L1 expression and activity of anti-PD-1 and anti-PD-L1 antibodies have been conflicting. MK-3475, a humanized monoclonal IgG4 antibody against PD-1, has demonstrated durable antitumor activity in MEL and NSCLC. We evaluated tumor PD-L1 expression and its relationship with outcomes in a phase I clinical trial of MK-3475. We also evaluated T cell activation as a pharmacodynamic marker of MK-3475 activity.

**Methods:** 135 MEL pts received MK-3475 10 mg/kg Q2W, 10 mg/kg Q3W, or 2 mg/kg Q3W. Tumor response was assessed by RECIST 1.1 per independent central review, including requirement for a confirmatory CT scan. Pretreatment biopsy was required. Serial blood samples were collected before infusion at the start of cycles 1-5 (Q2W dosing) or 1-4 (Q3W dosing). Tumor PD-L1 expression was assessed by IHC. A preliminary cutoff of 1% of stained cells was used to define PD-L1positivity. Absolute $CD4^+$ and $CD8^+$ T cell counts and the percentage of activated (HLA-DR as marker) $CD4^+$ and $CD8^+$ T cells in peripheral blood were assessed by multiplex flow cytometry (n = 101).

**Results:** Median PFS was 36 weeks, 6-month overall survival (OS) rate was 89%, and 12-month OS rate was 81%. Median duration of response and OS were not reached. In the 116 pts with measurable disease, ORR was 41%. PFS and response rate were significantly associated with tumor PD-L1 expression (Table). At week 6, a statistically significant percent increase from baseline in the percentage of activated ($HLA\text{-}DR^+$) $CD4^+$ and $CD8^+$ T cells was observed at all doses (pooled mean percent change [SE], +24.0% [4.7%] for $HLA\text{-}DR^+/CD8^+$, +17.5% [2.7%] for $HLA\text{-}DR^+/CD4^+$).

**Conclusions:** Tumor PD-L1 expression levels were associated with tumor response and PFS in MEL pts treated with MK-3475; activity was also observed in pts with low PD-L1 expression. As assessed by HLA-DR expression, post-treatment T cell activation in the circulating pool was increased at all doses tested.

| | **Patients With Measurable Disease and Interpretable PD-L1 IHC Results** | | **Patients With Interpretable PD-L1 IHC Results and PFS and OS Data** | | | | |
|---|---|---|---|---|---|---|---|
| **PD-L1 Tumor Expression** | N | ORR, n (%) | N | PFS at 6 months, % (95% CI) | Median PFS | OS at 6 months, % (95% CI) | Median OS |
| Positive (membrane staining in ≥1% of cells) | 55 | 29 (53) | 60 | 58 (47-72) | 10.6 mo | 93 (87-100) | Not reached |
| Negative (membrane staining in <1% of cells) | 16 | 1* (6) | 22 | 32 (16-64) | 2.9 mo | 75 (58-97) | Not reached |
| HR (95% CI) for PD-L1-positive vs negative | – | – | – | – | 0.54 (0.28-1.05) | – | 0.67 (0.25-1.83) |
| One-sided *P* value (PD-L1 association test) | – | <0.004 (logistic regression) | – | – | 0.034 (Cox regression) | – | 0.220 (Cox regression) |

*IPI-pretreated patient who received MK-3475 10 mg/kg Q2W.