TPS9601 **Poster Session**

The TIME trial: Phase II randomized controlled trial of time-of-day–specified immunotherapy for advanced melanoma.

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Background: Ipilimumab + nivolumab is standard of care for advanced melanoma patients based on data from the CheckMate 067 trial. The recent 10-year outcomes results were reported with a melanoma specific survival of 52%. While data are very encouraging, 50% of patients still succumb to their disease by 10-years. Preclinical data suggests that the circadian rhythm may influence the anatomic localization, function and activity of T cells, the target of immunotherapy. More T cells in the tumor or tumor-draining lymph node during initial immunotherapy administration may improve clinical responses and long-term outcomes. To investigate this idea, we performed a retrospective analysis, the MEMOIR study, finding that more evening infusions of immunotherapy were associated with significantly worse progression free and overall survival for metastatic melanoma patients. These findings have now been reproduced in other cancer types, in a large meta-analysis, and in pre-clinical mechanistic studies. In light of these data, we hypothesize that patients receiving morning or midday infusions of immunotherapy will have better outcomes than patients receiving infusions in the evening. **Methods:** The TIME trial is a three-arm phase II study of time-of-day specified administration of standard dose ipilimumab + nivolumab for metastatic melanoma. Newly diagnosed unresectable metastatic melanoma patients will be randomized to receive 4 cycles of ipilimumab + nivolumab every 3 weeks between either 8:00-11:00 (Arm A), 11:00-14:00 (Arm B), or 14:00-17:00 (Arm C). Following these 4 cycles, they will receive standard of care maintenance nivolumab in a time-of-day agnostic fashion. Eligible adult patients must have Stage III-IV unresectable cutaneous, acral or mucosal melanoma, no prior immunotherapy within 1 year, ECOG performance status of 0-1, and only asymptomatic brain metastases less than 2 cm. The primary objective is to determine whether progression free survival for Arm A or Arm B is superior to Arm C. Secondary objectives include assessments of adverse events, melanoma specific survival and overall survival. We also plan to evaluate the immune profiles of blood and tumor, when available, to assess the impact of time-of-day administered ipilimumab + nivolumab on the circulating immune responses and the tumor immune microenvironment. A sample size of 99 patients (33 in each arm) was selected for at least 80% power to detect a HR of 0.50 with a Type 1 error rate of 0.1 (2-sided) for a comparison of A vs. C and B vs. C. Research Sponsor: None.