AMADEUS TRIAL: TUMOR AGNOSTIC PRE- AND ON- TREATMENT BIOMARKERS OF RESPONSE TO NIVOLUMAB PLUS IPILIMUMAB CORRELATE WITH ON- TREATMENT TUMORAL T CELL INFILTRATION

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Background Although immune checkpoint inhibitors (ICI) are efficacious in some patients with cancer, many do not benefit. Identifying pre- and on-treatment biomarkers correlating with clinical outcomes is essential for better treatment strategies. High pre- and on-treatment recruitment of CD8+ T cells into the tumor are associated with improved outcomes following ICI therapy. We report orthogonal biomarker results from the AMADEUS study, an all-comer solid tumors trial, in which patients were treated with nivolumab (NIVO) with or without ipilimumab (IPI) based on the proportion of pretreatment tumoral CD8+ T cells.

Methods AMADEUS is a prospective, non-randomized, multi-center study that enrolled 79 patients with various metastatic solid tumors. The frequency of pretreatment tumoral CD8+ T cells was measured by a CLIA-certified immunohistochemistry (IHC) assay. Patients with ≥15% tumoral CD8 received NIVO monotherapy (CD8 high) and those with <15% tumoral CD8 received NIVO+IPI (CD8 low). Pre- and on-treatment tumor and blood samples were collected for longitudinal multi-omic biomarker analysis. Bulk RNA/DNA sequencing and high dimensional imaging technologies were used to analyze the tumor biopsies. Peripheral blood analyses included mass cytometry time of flight (CyTOF) for broad immune profiling, and a high parameter flow cytometry panel for T cell specific phenotypic evaluation.

Results In the CD8 low arm, on-treatment conversion from CD8 low to high (≥15%) was associated with a trend towards improved clinical benefit (p = 0.0582), whereas pretreatment tumoral CD8 T cell frequency was not correlated with clinical benefit. Analysis of tumor bulk mRNA sequencing yielded pan-tumor gene signatures of response and resistance to NIVO +IPI. Responders had elevated expression of genes relating to IFNg and JAK/STAT signaling, whereas glycolysis pathway genes and MYC targets dominated in the non-responders. Analysis of pretreatment peripheral blood immune cell populations demonstrated a significantly higher frequency of T cells with a stem cell progenitor-like phenotype (TCF1+) (p = 0.0179) in the non-responders compared to the responders. On-treatment, elevated frequencies of circulating gdT cells, NK cells, as well as enhanced activation and proliferation of effector and central memory conventional T cells were associated with response to ICI therapy.

Conclusions In this study, increased tumoral infiltration of CD8+ T cells on-treatment (≥15%) was associated with a trend towards improved clinical benefit (p = 0.0582). Using multi-omic analysis of pre- and on-treatment tissue and blood samples, we identified additional composite tumor agnostic biomarkers correlating with response. These biomarkers warrant further investigation for patient stratification and identification of novel drug targets to overcome ICI resistance.

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Trial Registration ClinicalTrials.gov (NCT03651271)

Ethics Approval The study was approved by MD Anderson Cancer Center IRB, Approval Number: 2017-0446

Consent All participants provided written informed consent before enrollment