265 PHASE 1B STUDY OF AVELUMAB + M9241 (NHS-IL12) IN PATIENTS WITH ADVANCED SOLID TUMORS: INTERIM ANALYSIS RESULTS FROM A UROTHELIAL CARCINOMA (UC) DOSE-EXPANSION COHORT

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Background Avelumab is an anti–PD-L1 monoclonal antibody approved for the treatment of advanced UC after disease progression during or following platinum-based chemotherapy and as maintenance treatment in patients whose disease has not progressed with first-line platinum-based chemotherapy.[1–3] M9241 is an immunocytokine composed of 2 heterodimers of IL-12 fused to the heavy chains of a human antibody targeting DNA released from necrotic tumor cells.[4] During dose-escalation, avelumab + M9241 was well tolerated and showed promising antitumor activity in patients with advanced solid tumors, including 2 objective responses in patients with UC.[5] We report on an interim analysis of efficacy and safety from the dose-expansion part of JAVELIN IL-12 (NCT02994953).

Methods Eligible patients had locally advanced or metastatic UC that had progressed on first-line therapy, were aged =18 years, had an Eastern Cooperative Oncology Group performance status of 0/1, and were immune checkpoint inhibitor naive. Patients received the recommended phase 2 dose[5] of avelumab 800 mg intravenously once weekly (QW) in combination with M9241 16.8 µg/kg subcutaneously Q4W for the first 12 weeks, then continued the combination with avelumab Q2W. The primary endpoints were confirmed best overall response (BOR) per investigator assessment (RECIST 1.1) and safety. The expansion cohort followed a 2-stage design. During stage 1 (single-arm part of the study), 16 patients were enrolled and treated. A futility analysis based on BOR was planned to determine if stage 2 (randomized controlled part of the study) would be initiated.

Results At data cut-off (Jun 3, 2020), 16 patients had received avelumab + M9241 for a median duration of 8 weeks (range, 4.0–25.0 weeks). No complete or partial responses were observed; the study failed to meet the criterion (>2 responders) to initiate stage 2. Two patients (12.5%) had stable disease, 13 (81.3%) had progressive disease, and 1 (6.3%) was not evaluable. Any-grade treatment-related adverse events (TRAEs) occurred in 15 patients (93.8%); the most common (in =4 patients) were pyrexia (50.0%), nausea (37.5%), asthenia (31.3%), anemia (25.0%), and hyperthermia (25.0%); grade 4 gamma-glutamyltransferase increased occurred in 1 patient (6.3%). No TRAEs led to death. Pharmacodynamic effects on the peripheral immune system and results of pharmacokinetic and biomarker analyses will also be reported.

Conclusions The predefined efficacy criterion to proceed to stage 2 was not met. The combination was well tolerated; no new safety signals emerged and the profile was consistent with the dose-escalation part of the study.[5]

Trial Registration NCT02994953

Ethics Approval The study was approved by each site's independent ethics committee.

Consent N/A

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266 TUMOUR MUTATION BURDEN (TMB) AND EFFICACY OUTCOMES IN THE PHASE III DANUBE STUDY OF ADVANCED UROTHELIAL CARCINOMA (UC)

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Background The phase III DANUBE study assessed the efficacy of the PD-L1 inhibitor durvalumab (D), alone or in combination with the CTLA-4 inhibitor tremelimumab (T), versus standard of care chemotherapy (SoC) for the first-line treatment of unresectable, locally advanced or metastatic UC. The study did not meet its co-primary endpoints of improving overall survival (OS) for D monotherapy vs SoC in patients with high tumor PD-L1 expression or for D+T vs SoC in the intention-to-treat population.[1] TMB measurement in blood (bTMB) or tumour (tTMB) has been linked to improved efficacy with PD-1/PD-L1 inhibitors in UC and with D+T in non-small cell lung cancer[2] thus providing a rationale to explore TMB in the DANUBE trial.

Methods Baseline plasma samples from DANUBE were assessed for bTMB using the Guardant OMNI platform, while baseline tTMB was measured in formalin-fixed paraffin-embedded (FFPE) tumour samples using the FoundationOne CDx gene panel. Associations between progression-free survival (PFS) and median and landmark OS with bTMB and tTMB levels at various cutoffs were assessed as part of a pre-specified exploratory analysis. The data cutoff occurred on January 27, 2020.

Results Among 1032 patients randomised in DANUBE, 536 (51.9%) were evaluable for bTMB and 623 (60.4%) were evaluable for tTMB. For D vs SoC, bTMB and tTMB were not associated with OS or PFS at any cutoff. For D+T, stronger associations between bTMB and OS as well as PFS were observed with increasing bTMB cutoffs (table 1). At the bTMB cutoff ≥ 24 mut/Mb, 12-month OS rates were 76.7% for D+T and 54.3% for SoC, whereas for bTMB < 24 mut/Mb, 12-month OS rates were 53.4% for D+T and 51.2% for SoC. Similar trends for both OS and PFS were observed with tTMB (table 1).