Phase 1b dose-finding study of avelumab (anti-PD-L1) + axitinib in treatment-naïve patients with advanced renal cell carcinoma


1Department of Medical Oncology, Royal Marsden Hospital, London, UK, 2Department of Hematology and Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA, 3Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, UK, 4Department of Medical Oncology, University of Manchester, The Christie NHS Foundation Trust, Manchester, UK, 5Division of Arizona Center for Cancer Care, Pinnacle Oncology Hematology, Scottsdale, AZ, USA, 6Immuno-Oncology, Pfizer Inc., Milan, Italy, 7Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute/Brigham and Women’s Hospital, Boston, MA, USA

Background: Axitinib, a tyrosine kinase inhibitor (TKI) selective for VEGFRs, is approved in 2nd-line advanced renal cell carcinoma (aRCC). Combining a TKI with a checkpoint inhibitor has the potential to improve patient (pt) outcomes. Avelumab* (MSB0010718C) is a fully human IgG1 antibody that inhibits PD-L1. This ongoing phase 1b study (NCT02493751) evaluates safety and tolerability of avelumab + axitinib in treatment-naïve pts with aRCC to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D).

Methods: Eligible pts have histologically confirmed aRCC with a clear-cell component, primary tumour resection, ≥1 measurable lesion, available tumour specimen, ECOG PS ≤1, and no prior systemic therapy for aRCC. MTD was estimated using the modified toxicity probability interval method, which determines the dose for future cohorts using all pts treated in prior and current cohorts. Adverse events (AEs) were graded by NCI CTCAE v4. Objective response rate (ORR; RECIST v1.1) was evaluated.

Results: The starting dose was avelumab 10 mg/kg (1h IV infusion) Q2W + axitinib 5 mg PO BID. By 5 Apr 2016, 6 pts (median 59.5 yrs [range 45-73]) were treated with avelumab for a median of 17.0 wks (range 11.9-21.7) and axitinib for 16.3 wks (range 12.7-22.7). One DLT of grade 3 proteinuria occurred. The most common treatment-related adverse events (TRAEs) of any grade were dysphonia and hypertension (n = 4 pts each) and fatigue and headache (n = 3 each). Grade 3-4 TRAEs occurred in 4 pts: hypertension (n = 2), palmar-plantar erythrodysesthesia syndrome (n = 1), lipase increased (n = 1), and proteinuria (n = 1). No pt discontinued due to a TRAE. Confirmed PR was observed in 5 pts (ORR 83.3%, 95% CI: 35.9, 99.6) and stable disease in 1 pt with tumour shrinkage not meeting PR.

Conclusions: The combination of avelumab 10 mg/kg Q2W + axitinib 5 mg BID met MTD criteria and RP2D. Clinical benefit was observed in all 6 pts studied, with PR in 5 pts. Enrolment is ongoing in the expansion cohort. These results provide a rationale to investigate efficacy and safety of avelumab + axitinib vs current monotherapies for aRCC, including a pivotal, randomised phase 3 trial vs sunitinib that began in Mar 2016. *Proposed INN

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