PHASE IB/II STUDY OF XMAB23104 (PD1 X ICOS) AND XMAB22841 (CTLA-4 X LAG3) COMBINATION IN METASTATIC MELANOMA REFRACTORY TO PRIOR IMMUNE CHECKPOINT INHIBITOR THERAPY WITH AND WITHOUT CNS DISEASE

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Background For patients with metastatic melanoma, 5-year overall survival ranges from 26–52%. Immune checkpoint inhibitors (ICI) have greatly improved outcomes for these patients however despite these advances, ~50% of patients with metastatic melanoma do not respond to standard of care ICI. We strive to address this unmet clinical need through a Phase Ib/II, first-in-human, multi-center trial of two bispecific antibodies targeting four different immune checkpoints: XmAb23104 (PD1 X ICOS) and XmAb22841 (CTLA-4 X LAG3) in patients with melanoma refractory to ICI.1 This is the first trial of quadruple checkpoint inhibitor therapy. Furthermore, bispecific antibodies may allow simultaneous checkpoint blockade on the same cell and have been shown to heighten T cell activation in pre-clinical models. We postulate that treatment with XmAb23104 and XmAb22841 will enhance immune activation, overcome resistance, and improve disease control for patients refractory to traditional ICI.

Methods Eligible patients must have advanced/metastatic melanoma and progressed on prior PD1/PD-L1 inhibitor or PD1/CTLA4 dual inhibition. Patient with CNS metastasis are allowed if these are asymptomatic and stable on MRI imaging obtained within 4 weeks of enrollment. Patients with prior unresolved irAE or irAE ≥ grade 3 are not allowed. XmAb23104 and XmAb22841 will be given on D1 and D15 of a 28-day cycle for 4 cycles, after XmAb23104 (PD1 X ICOS) will be given alone for a total of 2 years.

The phase I portion will be a dose escalation using standard 3+3 design of XmAb22841 (CTLA-4 X LAG3) with three dose levels (0.3 mg/kg, 1 mg/kg and 3 mg/kg). The dose of XmAb23104 (PD1 X ICOS) will remain at 10 mg/kg. These doses were selected based on results of prior early phase trials23 where these agents were combined with PD1. Once the P2RD of XmAb22841 (CTLA-4 X LAG3) is established, we will move on to dose escalation using a Simon’s 2-stage design. This portion will include two arms: Arm A consisting of 17 patients without CNS disease and Arm B consisting of 17 patients with CNS disease (total 34). Primary endpoints include dose limiting toxicities (DLT)/irAE and Objective Response Rate (ORR) at the time of best response by RECIST 1.1. At the time of this abstract submission, Cohort 1 of dose escalation has begun with the first few patients still within the DLT observation window.

Trial Registration This is a registered trial: NCT05695898

REFERENCES
2. Xencor, Inc. ‘A Study of XmAb®23104 in Subjects With Selected Advanced Solid Tumors (DUET-3).’ Clinical trial registration. clinicaltrials.gov (accessed September 12, 2022).