PRELIMINARY RESULTS FROM KEYNOTE-A36, A STUDY OF GB1275, A FIRST-IN-CLASS ORAL CD11B MODULATOR, ALONE AND WITH PEMBROLIZUMAB OR CHEMOTHERAPY IN SPECIFIED ADVANCED SOLID TUMORS

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Background GB1275 is a first-in-class CD11b modulator that reduced myeloid-derived suppressor cells (MDSCs) and tumor associated macrophages (TAMs), repolarized M2 immunosuppressive TAMs to an M1 phenotype, and increased tumor infiltration of activated CD8+ T cells in preclinical models. Preclinical anti-tumor activity was observed with single-agent therapy and in combination with chemotherapy or immunotherapy. We report results from the dose escalation portion of an ongoing, first-in-human study of GB1275 monotherapy and combined with pembrolizumab in patients with specific advanced solid tumors. (NCT04060342)

Methods This study comprises phase 1 dose escalation followed by phase 2 expansion in specific tumor types. In phase 1, cohorts of 3 to 6 patients with histologically confirmed, locally advanced/metastatic pancreatic, esophageal, gastric, MSS colorectal, metastatic castrate-resistant prostate cancer, or triple negative breast cancer are sequentially assigned to one of the ascending dose levels of GB1275 orally twice daily (BID) in 1 of 3 regimens: A (GB1275 monotherapy); B (GB1275 + pembrolizumab) commenced after completion of two cohorts of A; and C (GB1275 + nab-paclitaxel + gemcitabine) will be initiated after A. Patients in Regimens A and B had previously exhausted standard of care treatment options. Dose escalation was based on safety, including dose-limiting toxicity (DLT). Serial blood samples were collected for pharmacokinetic (PK) and biomarker analyses; tumor tissue was also collected for biomarker analysis.

Results As of July 28, 2020, 36 patients were treated, 23 in Regimen A (GB1275 100 mg to 1200 mg BID) and 13 in Regimen B (GB1275 100 mg to 800 mg BID + pembrolizumab). No DLIs or adverse events requiring steroid treatment were reported. GB1275-related adverse events were reported in 19 (52.8%) patients; most were Grade 1 and most frequent events (>10%) were dysesthesia (13.9%) and photosensitivity reaction (11.1%). Stable disease was reported in 4 (17%) patients in Regimen A and 6 (46%) in Regimen B with a median (range) exposure of 84 days (35–172). A dose-dependent increase in GB1275 exposure was observed. An increase in tumor infiltrating lymphocyte (TIL) counts was noted in both Regimens A and B. Other biomarker analyses in serial blood and tumor tissue are ongoing.

Conclusions Dose escalation of GB1275, up to 1200 mg and 800 mg BID in Regimens A and B, respectively, demonstrated tolerability as monotherapy and combined with pembrolizumab. The maximum tolerated dose has not been reached. Preliminary observation of an increase in TILs after treatment is encouraging.

Ethics Approval This ongoing study is being conducted in accordance with the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines. The study was approved by the Ethics Boards of the University of Colorado Hospital, Washington University School of Medicine - Siteman Cancer Center, Memorial Sloan Kettering Cancer Center, The Sarah Cannon Research Institute/Tennessee Oncology, South Texas Accelerated Research Therapeutics, and The Royal Marsden NHS Foundation Trust.

REFERENCE

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COMBINING TRANSCRIPTOMIC- AND TISSUE-BASED IMMUNE BIOMARKERS TO EVALUATE GB1275, A CD11B MODULATOR, AS A SINGLE AGENT OR WITH PEMBROLIZUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background GB1275 is a first-in-class CD11b modulator in development as monotherapy and in combination with pembrolizumab or chemotherapy for the treatment of advanced solid tumors. Nonclinical data show that GB1275 reduced influx of tumor-associated myeloid-derived suppressor cells (MDSCs) and macrophages (TAMs), and repolarized M2 immuno-suppressive TAMs towards an M1 phenotype. We hypothesize that GB1275 administration can alleviate myeloid cell-mediated immunosuppressive effects and improve cancer treatment outcomes. A phase 1 trial evaluating GB1275 as monotherapy and in combination with pembrolizumab in specified advanced tumors in ongoing (NCT04060342).

Methods Blood gene expression variations as well as core tissue biopsies pre- and post-treatment were assessed following GB1275 monotherapy and combination with pembrolizumab. After obtaining informed consent, peripheral blood for MDSCs was collected from 21 patients pre- and two weeks post-treatment; core tissue biopsies were collected from 13 patients pre- and post-treatment. The frequency of MDSCs in whole blood was measured using the Serametrix MDSC FACS assay. Gene expression transcriptome profiles were generated using NovaSeq platform. CD8 staining was performed at Neo-genomics, and tumor infiltrating lymphocyte (TIL) quantification was performed by an independent pathologist.

Results Preliminary statistical analysis of MDSC immunophenotyping pre- and post-treatment is consistent with the proposed mechanism of GB1275, showing modulation of peripheral blood MDSCs in some patients. Preliminary gene expression analysis in the blood showed dose-dependent clusters following treatment with GB1275 alone. Moreover, the transcriptomic analysis revealed two unique expression patterns for patients treated with GB1275 monotherapy or in combination with pembrolizumab. Gene Set Enrichment Analysis showed that the CD11b pathway is downregulated in patients