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Title:

PHASE 1 STUDY OF AMG 160, A HALF-LIFE EXTENDED BITE® (BISPECIFIC T-CELL ENGAGER) THERAPY TARGETING PROSTATE-SPECIFIC MEMBRANE ANTIGEN, IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

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enzymes and other proteins involved in the adenosine axis (e. g., A2bR) revealed trends that could have predictive value, particularly in late-line subjects. Correlative trends were also observed between the infiltration of lymphocytes within baseline tumor samples and the extent of clinical benefit. Based on a preliminary and ongoing analysis of baseline biopsies, a number of molecular markers may correlate with better clinical outcomes, most relevantly in late-line mCRC subjects treated with AB928 + mFOLFOX-6. These data suggest the possibility that adenosine-related markers may be helpful in future studies for selection of patients to be treated with AB928 + mFOLFOX-6 therapy.

Conclusions N/A

Acknowledgements N/A

Trial Registration NCT03720678

Ethics Approval The study was approved by all the study site Institution's Ethics Boards, with Advarra IRB being the first, approval number SSU00070639 in USA.

Consent N/A

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PRELIMINARY SAFETY, TOLERABILITY AND EFFICACY RESULTS OF KN026 (A HER2-TARGETED BISPECIFIC ANTIBODY) IN COMBINATION WITH KN046 (AN ANTI-PD-L1/CTLA-4 BISPECIFIC ANTIBODY) IN PATIENTS (PTS) WITH HER2 ABERRATED SOLID TUMORS

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Background HER2 potently inhibits innate immunity through cGAS–STING signalling,¹ meanwhile HER2 antibody induced ADCP will also lead to macrophage mediated immune suppression. Preclinical and clinical studies suggested a coordination of engagement of innate and adaptive immunity with the combination of an anti-HER2 antibody and an immune checkpoint blockade. KN026 is a novel bispecific antibody that simultaneously binds to two distinct HER2 epitopes. KN046 is a novel bispecific antibody that blocks both PD-L1 interaction with PD-1 and CTLA-4 interaction with CD80/CD86. Here we reported the interim results from an ongoing phase Ib dose escalation and expansion study assessing the safety, tolerability and preliminary efficacy for KN026 in combination with KN046.

Methods This study enrolled pts with solid tumors who failed available standard of care, HER2 aberration status confirmed locally (HER2 mutation, HER2 amplification and/or HER2 overexpression). Eligible pts received combination of KN026 and KN046 at two dose levels until disease progression, unacceptable toxicity or withdrawal of informed consent (DL1: KN026 20 mg/kg Q2W + KN046 3 mg/kg Q2W; DL2: KN026 20 mg/kg Q2W with loading on Days 1, 8 of Cycle 1 + KN046 5 mg/kg Q3W). Tumor response was evaluated Q8W per RECIST 1.1. Primary endpoint was DLT and key secondary endpoints were efficacy parameters (ORR, DOR, PFS).

Results As of the Jul. 13, 2020, 21 pts were enrolled into DL1 (n = 18, 3 for dose escalation) and DL2 (n = 3)

(mGC/GEJ 12 pts; mCRC 7 pts; other solid tumors 2 pts). 11 pts remained on the study treatment and 10 pts discontinued treatment due to disease progression (n=5), death (n=2) and other reasons (n=3). 15 pts had HER2-positive status (11 of 15 failed previous trastuzumab therapy), 1 pts had HER2 mutation and 5 pts had HER2 low expression (without FISH amplification). No DLTs were observed. No pts experienced LVEF decreased or other clinically meaningful cardiac AEs. Treatment-related TEAEs occurred in 13 pts, of which 1 pts experienced grade 3 or above treatment-related TEAEs. 7 pts experienced irAEs, all of which were grade 1 or 2. The most common (≥ 10%) KN026 or KN046 related TEAEs were anaemia (n=5, 23.8%), AST increased (n=4, 19.0%), rash (n=4, 19.0%), diarrhea (n=4, 19.0%), blood bilirubin increased (n=3, 14.3%) and infusion related reaction (n=3, 14.3%). The objective response rate in pts with HER2-positive tumors (n = 7 efficacy evaluable pts) was 4/7 (57.1%, 95% CI 18.4~90.1%) and disease control rate 6/7 (85.7%, 95% CI 42.1~99.6%). 3 pts with HER2 mutation or low expression achieved SD including one patient with SD for more than 24 weeks. 2 death cases only received one cycle of KN026 plus KN046 due to COVID-19 restriction before died from clinical deterioration from underlying tumors.

Conclusions KN026 combined with KN046 is well tolerated and has demonstrated profound anti-tumor activity in HER2-positive solid tumors.

Trial Registration NCT04040699

Ethics Approval The study was approved by Beijing Cancer Hospital Institution's Ethics Board, approval number 2019YJZ37.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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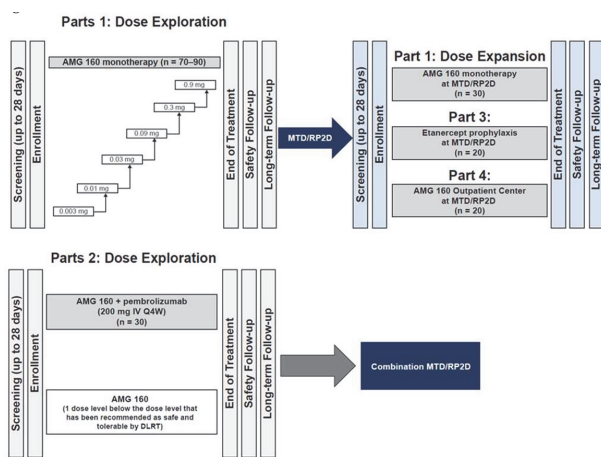
PHASE 1 STUDY OF AMG 160, A HALF-LIFE EXTENDED BITE® (BISPECIFIC T-CELL ENGAGER) THERAPY TARGETING PROSTATE-SPECIFIC MEMBRANE ANTIGEN, IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

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Background Prostate-specific membrane antigen (PSMA) is a clinically validated target for metastatic castration-resistant prostate cancer (mCRPC). AMG 160 BiTE® immuno-oncology therapy redirects T cells to cancer cells by binding to

PSMA on cancer cells and CD3 on T cells, leading to T-cell activation, tumor-cell killing, and T-cell expansion. As the BiTE mode of action leads to an upregulation of immune checkpoints, combining AMG 160 with a PD-1 inhibitor may lead to sustained T cell-dependent killing of tumor cells. Cytokine release syndrome (CRS) is a first-dose effect induced by BiTE molecule-mediated T-cell activation. An approach to mitigate CRS is prophylaxis with an anti-inflammatory agent.

Methods The phase 1 study (NCT03792841) has four parts: AMG 160 monotherapy; AMG 160 in combination with pembrolizumab; AMG 160 monotherapy with etanercept prophylaxis; and AMG 160 monotherapy administered in outpatient centers with 24-hour monitoring. Included in the study are men with histologically/cytologically confirmed mCRPC who are refractory to novel androgen receptor signaling inhibitors: abiraterone, enzalutamide, darolutamide, and/or apalutamide and have failed, refused, or are unsuitable for taxanes; and who have ongoing castration with evidence of progressive disease. Patients who received prior PSMA radionuclide therapy are eligible. Patients with CNS metastases, leptomeningeal disease, spinal cord compression, or active autoimmune disease are excluded. Primary objectives are to evaluate safety and tolerability and determine the MTD or RP2D of AMG 160 monotherapy or in combination with pembrolizumab. Secondary objectives are to characterize pharmacokinetics and preliminary antitumor activity. Evaluation of preliminary antitumor activity will be based on RECIST 1.1 with Prostate Cancer Working Group 3 modifications, PSA response, CTC response, progression-free survival (radiographic and PSA), and overall survival. PSMA PET/CT and FDG PET/CT imaging will be used for evaluation of exploratory objectives (figure 1). The study opened in February 2019 and is currently recruiting patients.



Abstract 340 Figure 1 Study schema

Results N/A

Conclusions N/A

Trial Registration NCT03792841

Ethics Approval The study was approved by all institutional ethics boards.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0340>

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PHASE 1B/2 STUDY OF BXCL701, AN ORAL ACTIVATOR OF THE SYSTEMIC INNATE IMMUNITY PATHWAY, COMBINED WITH PEMBROLIZUMAB (PEMBRO), IN MEN WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)

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Background BXCL701 (talabostat) is an oral small molecule inhibitor of dipeptidyl peptidases (DPP) primarily DPP8 and DPP9, which triggers inflammasome mediated pyroptosis in macrophages leading to induction of IL-18 and IL-1beta, bridging between innate and adaptive immunity. PD-L1 expression correlates with amplification of DPP8 and DPP9. In syngeneic animal models, significant tumor growth inhibition was observed with BXCL701 plus checkpoint inhibition. In a prior clinical study, single-agent BXCL701 resulted in objective responses in patients (pts) with Stage IV melanoma (unpublished).

Methods In Phase 1b portion of this multicenter study, eligible pts had progressing mCRPC (PCWG3), at least 1 prior systemic therapy, ≤ 2 lines of cytotoxic chemotherapy for mCRPC, no prior anti-PD-1/PD-L1 or other T-cell directed anticancer therapy. Using a 3+3 design, pts received fixed-dose pembro (200 mg IV q21-days) with escalating doses of BXCL701 on days 1-14. The primary endpoint was determination of the recommended Phase 2 dose (RP2D). Response (RECIST 1.1, PSA, CTC), plasma drug concentration and change in relevant immune effector cytokines were also evaluated.

Results 13 pts were treated in 3 cohorts of BXCL701: 0.4 mg qd (n = 3); 0.6 mg qd (n = 3) and 0.6 mg split dose (n=7). 7 pts had adenocarcinoma, 6 had small cell/neuroendocrine prostate cancer features. Prior treatment included ADT (n = 10), 2nd-generation androgen signaling inhibitors (n = 9), chemotherapy (n = 11), RT (n = 11). On-target AEs consistent with cytokine activation were seen at the highest dose levels. In the 0.6 mg qd cohort, all pts had events consistent with cytokine release: 3/3 had hypotension (including 1 grade 3 syncope (DLT)) and 2pts each had dizziness and LE edema. Splitting the 0.6 mg dose improved the tolerability while maintaining the TDD previously associated with objective response; 3/7 pts had fatigue, and 1pt each had low grade hypotension, dyspnea, chills, myalgia. Preliminary anti-tumor activity was seen with 1 pt achieving a PSA response and 3 pts with RECIST1.1 stable disease. BXCL701 was quantifiable in plasma. Consistent dose and time dependent increases in serum IL-18 levels were observed with 0.6 mg split dose.

Conclusions BXCL701 0.3 mg BID (0.6 mg TDD) administered on days 1-14 was identified as the RP2D when administered with pembro 200 mg every 21 days. Splitting the TDD was associated with improved tolerability as evidenced by no reported DLTs and lower rates of other adverse events of interest such as hypotension and peripheral edema. The Phase 2 portion of the study is enrolling.

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