Background Immune checkpoint inhibitors (ICI) are very effective in deficient DNA mismatch-repair system (dMMR)/microsatellite instable (MSI) metastatic colorectal cancer (mCRC). About 15% of MSS/pMMR CRCs are highly infiltrated by tumor infiltrating lymphocyte (TIL) with a good prognosis. Some immune scores based on CD3+ and/or CD8+ T-cells infiltration are validated and reproducible, especially TuLIS and ImmunoScore®. No data are available concerning efficacy of ICI in this subpopulation of mCRC. Pembrolizumab, an anti-PD1 (programmed death-1) monoclonal antibody has been recently reported very effective in patients with MSI/dMMR mCRC. Immunogenic cell death induced by chemotherapy, such as oxaliplatin, could increase the efficacy of ICI. We formulated the hypothesis that patients with a pMMR mCRC with a high immune infiltrate can be sensitive to ICI plus oxaliplatin-based chemotherapy.

Methods POCHI is a multicenter, open-label, single-arm phase II trial to evaluate efficacy of pembrolizumab in combination with chemotherapy as first-line treatment of pMMR mCRC with a high immune infiltrate. Primary objective is PFS at 10 months, i.e. number of patients alive and without radiological and/or clinical progression at 10 months evaluated by the investigator. Main secondary objectives are overall survival, secondary resection rate, depth of response and early tumour shrinkage. Main inclusion criteria are pMMR mCRC untreated for metastatic disease and with at least one measurable metastatic target according to RECIST v1.1 criteria. Patients must have resected primary tumor to evaluate two different immune scores (Immunoscore® and TuLIS) and patients are eligible if one score is ‘high’. Patients will receive combination of pembrolizumab (200 mg), bevacizumab (7.5 mg/kg), oxaliplatin (130 mg/m²) and capcitabine (2000 mg/m²/day, on day 1 to 14). Treatment will be repeated every 3 weeks until disease progression or unacceptable toxicity. The clinical hypotheses are to increase PFS at 10 months from 50% to 70%. With a one-sided type error of 5%, power of 85%, 10% rate of patients lost to follow-up or not evaluable, 55 patients have to be included. If 32 patients or more are alive and without progression at 10 months, the treatment will be considered as effective. Thus, with 15% ‘high’ immune score, about 400 patients must be tested in order to include 55 patients in POCHI trial. The ancillary study will consist to identify predictive biomarkers of response and included expression of PD-L1, circulating lymphocytes circulating tumour DNA, mutational load and gut microbiota. Inclusions will start in September 2020 and theoretical end of recruitment is 2023.
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 ANTIBODY) IN PATIENTS (PTS) WITH HER2 ABERGERED SOLID TUMORS

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 pt 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 AE. 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%), diarrhoea (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 Institute’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.

REFERENCE


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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