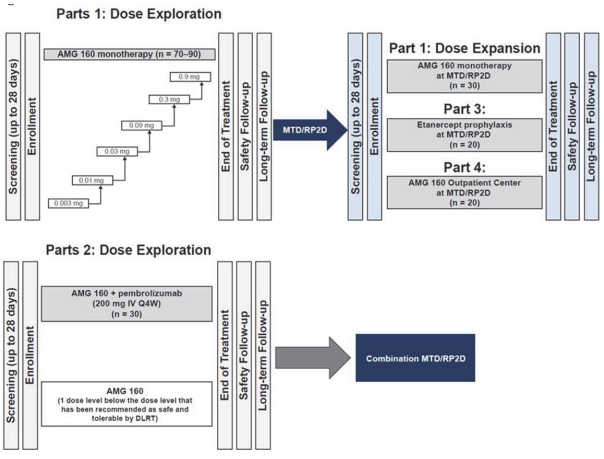
PSMA on cancer cells and CD3 on T cells, leading to T-cell activation, tumor-cell killing, and T-cell expansion. As the BiTE mode of action leads to an upregulation of immune checkpoints, combining AMG 160 with a PD-1 inhibitor may lead to sustained T cell–dependent killing of tumor cells. Cytokine release 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

341 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)

[1]Rahul Aggarwal*, [2]Dan Costin, [3]Jingsong Zhang, [4]Paul Monk, [5]Mark Linch, [6]Lawrence Karsh, [7]Diane Healey, [7]Stefani Corsi-Travali, [7]Sreenivas Adurthi, [7]Adedayo Adedoyin, [7]Vincent O'Neill. *[1]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [2]White Plains Hospital, Center for Cancer Care, White Plains, NY, USA; [3]H. Lee Moffitt Cancer Cneter and Research Institute, Tampa, FL, USA; [4]The Ohio State University Comprehensive, Columbus, OH, USA; [5]University College London Cancer Institu, London, UK; [6]The Urology Center of Colorado, Denver, CO, USA; [7]BioXcel Therapeutics, Madison, CT, USA*

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 cytotoxicchemotherapy for mCRPC, no prior anti-PD-1/PD-L1 or other T-cell directed anticancertherapy. Using a 3+3 design, pts received fixed-dose pembro (200 mgIV 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.

Acknowledgements All patients, their families, and caregivers who make this study possible; the participating investigators

and their staff; Cedric Burg PhD and J. MacDougall PhD of BioXcel Therapeutics, Valery Chatikhine MD of Iqvia Biotech and the Iqvia Biotech team for assisting in the conduct of the study.

Trial Registration NCT03910660EUDRACT 2018-003734-32

Ethics Approval This study was approved by Institution Review Boards or Ethics Committees affiliated with participating institutions.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0341

342 A PHASE 3 STUDY (COSMIC-313) OF CABOZANTINIB IN COMBINATION WITH NIVOLUMAB AND IPILIMUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED RENAL CELL CARCINOMA OF INTERMEDIATE OR POOR RISK

[1]Toni Choueiri*, [2]Laurence Albiges, [3]Thomas Powles, [4]Nehal Mohamed, [4]Fong Wang, [5]Robert Motzer. *[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Institute Gustave Roussy, Villejuif, Ile-de-France, France; [3]Barts Cancer Institute, London, UK; [4]Exelixis, Inc., Alameda, CA, USA; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA*

Background Cabozantinib (C) inhibits tyrosine kinases involved in tumor growth, angiogenesis, and immune regulation, including MET, VEGFR, and TAM kinases (Tyro3, AXL, MER), and may promote an immune-permissive tumor environment, resulting in enhanced response to immune checkpoint inhibitors. C has shown preliminary clinical activity and tolerability in combination with the PD-1 inhibitor nivolumab (N) and as part of a triplet combination with N and the CTLA-4 inhibitor ipilimumab (I) in patients (pts) with advanced renal cell carcinoma (aRCC) (Nadal *et al*. ASCO 2018). C is approved for pts with aRCC, and N+I is approved as a combination therapy in pts with previously untreated aRCC of intermediate or poor risk. We present the study design of a phase 3 trial of C+N+I vs N+I in previously untreated pts with aRCC of IMDC intermediate or poor risk (NCT03937219).

Methods This randomized, double-blind, controlled phase 3 study evaluates the efficacy and safety of C+N+I vs N+I in previously untreated pts with IMDC intermediate or poor risk aRCC. Eligible pts are randomized 1:1 to receive C+N+I or N+I in combination with placebo, stratified by IMDC prognostic score and geographic region. Pts receive C (40 mg oral QD) + N (3 mg/kg IV Q3W) x 4 doses + I (1 mg/kg IV Q3W) x 4 doses, followed by C (40 mg oral QD) + N (480 mg IV flat dose Q4W). Control pts receive C-matched placebo and the same treatment regimen for N+I as the experimental arm. N will be administered for a maximum of 2 years. Eligibility criteria include histologically confirmed metastatic or aRCC with a clear cell component, intermediate or poor risk RCC per IMDC criteria, measurable disease per RECIST 1.1, KPS $\geq$70%, adequate organ and marrow function and age $\geq$18 years. Exclusion criteria include prior systemic therapy for aRCC and uncontrolled significant illnesses. The primary endpoint is PFS per RECIST 1.1 by BICR; the secondary endpoint is OS. Additional endpoints include ORR, safety, correlation of biomarkers with outcomes, and pharmacokinetics of C in combination with N+I. The first patient was enrolled in June 2019 and enrollment is ongoing.

Results N/A

Conclusions N/A

Trial Registration ClinicalTrials.gov: NCT03937219

Ethics Approval This study is being conducted in compliance with Good Clinical Practice (GCP), including International Conference on Harmonisation (ICH) Guidelines, the most recent accepted version of the Declaration of Helsinki, and all applicable local laws and regulatory requirements. The appropriate Institutional Review Boards (IRBs) or Ethics Committees (ECs) of participating centers have approved approve the study protocol. All patients have provided written informed consent.

Consent All patients have provided written informed consent.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0342

343 PHASE 3 STUDY OF PEMBROLIZUMAB + DOCETAXEL AND PREDNISONE/PREDNISOLONE FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC) PRETREATED WITH NEXT-GENERATION HORMONAL AGENTS (NHAS) (KEYNOTE-921)

[1]Daniel Petrylak*, [2]Neal Shore, [3]Mostefa Bennamoun, [4]Raffaele Ratta, [5]Josep Piulats, [6]Ben Li, [6]Charles Schloss, [7]Karim Fizazi. *[1]Smilow Cancer Hospital, Yale New Haven Health, New Haven, CT, USA; [2]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [3]Institut Mutualiste Montsouris, Paris, France; [4]Hopital Foch, Suresnes, France; [5]Catalan Cancer Institute, Barcelona, Spain; [6]Merck and Co., Inc., Kenilworth, NJ, USA; [7]Gustave Roussy, Villejuif, France*

Background Cohort B of the phase 1b/2 KEYNOTE-365 study (NCT02861573) found that docetaxel + pembrolizumab + prednisone demonstrated activity in patients previously treated with abiraterone acetate or enzalutamide for mCRPC. The prostate-specific antigen (PSA) response rate was 28%; objective response rate (ORR) was 18% (7 partial responses); duration of response (DOR) was 6.7 months; progression-free survival (PFS) was 8.3 months; overall survival (OS) was 20.4 months; and the 12-month PFS and OS rates were 24.0% and 75.8%, respectively. The safety and tolerability profile of this combination was consistent with the profiles of each individual agent. The KEYNOTE-921 (NCT03834506) phase 3 trial will evaluate efficacy and safety of pembrolizumab + docetaxel + prednisone/prednisolone in patients with mCRPC after prior treatment with NHA.

Methods Eligible patients are adults with histologically or cytologically confirmed mCRPC who experience disease progression with androgen deprivation therapy (or after bilateral orchiectomy) within 6 months of screening and have Eastern Cooperative Oncology Group performance status 0/1. Other eligibility criteria are disease progression or intolerance to NHA in the metastatic hormone-sensitive prostate cancer setting or CRPC setting, no prior treatment with chemotherapy for mCRPC, and tissue available for biomarker analysis. Treatment stratification factors are prior treatment with abiraterone acetate (yes or no) and metastases location (bone only, liver, other). Approximately 1000 patients will be randomly assigned to receive docetaxel 75 mg/m2 IV Q3W + prednisone/prednisolone 5 mg orally BID and pembrolizumab 200 mg IV Q3W or docetaxel 75 mg/m2 IV Q3W + prednisone/prednisolone 5 mg PO BID + placebo IV Q3W (1:1 ratio). Response and progression will be determined using imaging (CT/MRI/bone) according to PCWG3–modified RECIST v1.1 by blinded independent central review (BICR) Q9W during the first year and Q12W thereafter. Treatment maximums are 10 cycles for docetaxel + prednisone/prednisolone and 35 cycles for pembrolizumab or placebo. Treatment discontinuation regardless of therapy received is mandated for disease progression, unacceptable toxicity, or consent withdrawal. The dual primary end points are radiographic PFS per PCWG3-modified