406 CDX527–01, A PHASE 1 DOSE-ESCALATION AND EXPANSION STUDY OF THE PD-L1XCD27 BISPECIFIC ANTIBODY CDX-527 IN PATIENTS WITH ADVANCED MALIGNANCIES

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Background CD27 ligation and PD-1 blockade elicit complementary signals mediating T cell activation and effector function. CD27 is constitutively expressed on most mature T cells and the interaction with its ligand, CD70, plays key roles in T cell costimulation leading to activation, proliferation, enhanced survival, maturation of effector capacity, and memory. The PD-1/PD-L1 pathway plays key roles in inhibiting T cell responses. Pre-clinical studies demonstrate synergy in T cell activation and anti-tumor activity when combining a CD27 agonist antibody with PD-(L)1 blockade, and clinical studies have confirmed the feasibility of this combination by demonstrating safety and biological and clinical activity. CDX-527 is a novel human bispecific antibody containing a neutralizing, high affinity IgG1k PD-L1 mAb (9H9) and the single chain Fv fragment (scFv) of an agonist anti-CD27 mAb (2B3) genetically attached to the C-terminus of each heavy chain, thereby making CDX-527 bivalent for each target. Pre-clinical studies have demonstrated enhanced T cell activation by CDX-527 and anti-tumor activity of a surrogate bispecific compared to individual mAb combinations, and together with the IND-enabling studies support the advancement of CDX-527 into the clinic.

Methods A Phase 1 first-in-human, open-label, non-randomized, multi-center, dose-escalation and expansion study evaluating safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of CDX-527 is ongoing. Eligible patients have advanced solid tumor malignancies and have progressed on standard-of-care therapy. Patients must have no more than one prior anti-PD-1/L1 for tumor types which have anti-PD-1/L1 approved for that indication and no prior anti-PD-1/L1 for tumor types that do not have anti-PD-1/L1 approved for that indication. CDX-527 is administered intravenously once every two weeks with doses ranging from 0.03 mg/kg up to 10.0 mg/kg or until the maximum tolerated dose. The dose-escalation phase initiates with a single patient enrolled in cohort 1. In the absence of a dose limiting toxicity or any $\geq$ grade 2 treatment related AE, cohort 2 will enroll in a similar manner as cohort 1. Subsequent dose-escalation cohorts will be conducted in 3+3 manner. In the tumor-specific expansion phase, up to 4 individual expansion cohort(s) of patients with specific solid tumors of interest may be enrolled to further characterize the safety, PK, PD, and efficacy of CDX 527. Tumor assessments will be performed every 8-weeks by the investigator in accordance with iRECIST. Biomarker assessments will include characterizing the effects on peripheral blood immune cells and cytokines, and for the expansion cohorts, the impact of CDX-527 on the tumor microenvironment.

Results N/A

Conclusions N/A

Trial Registration NCT04440943

Ethics Approval The study was approved by WIRB for Northside Hospital, approval number 20201542

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407 PRELIMINARY SAFETY, PHARMACOKINETICS/PHARMACODYNAMICS, AND ANTITUMOR ACTIVITY OF XMAB20717, A PD-1 X CTLA-4 BISPECIFIC ANTIBODY, IN PATIENTS WITH ADVANCED SOLID TUMORS

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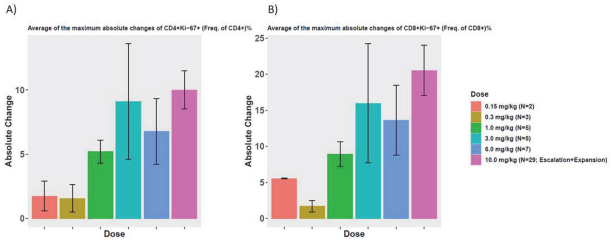
Background XmAb20717 is a humanized bispecific monoclonal antibody that simultaneously targets PD-1 and CTLA-4. We report preliminary data from an ongoing, multicenter, Phase 1 study investigating the safety/tolerability, pharmacokinetics/pharmacodynamics, and clinical activity (RECIST 1.1) of XmAb20717 in patients with selected advanced solid tumors.

Methods A 3+3 dose-escalation design was used to establish a maximum tolerated (MTD)/recommended dose for evaluation in parallel expansion cohorts, including melanoma, renal cell carcinoma, non-small cell lung cancer (NSCLC), prostate cancer, and a basket of tumor types without an FDA-approved checkpoint inhibitor (CI; n≤20 each). XmAb20717 was administered as an infusion on Days 1 and 15 of each 28-day cycle.

Results As of 08Jul2020, 109 patients had been treated (table 1), and 30 were continuing treatment. In escalation, 6 dose levels (0.15–10.0 mg/kg) were evaluated (n=34); an MTD was not established. Expansion cohorts were initiated at 10 mg/kg (n=72), and a 15 mg/kg escalation cohort was added (n=3). T-cell proliferation was noted in peripheral blood at doses as low as 3 mg/kg and was highest at 10 mg/kg. At this dose, consistent proliferation of CD8+ and CD4+ T cells was observed, indicative of dual PD-1 and CTLA-4 checkpoint blockade (figure 1). Paired pre- and post-dosing biopsies showed increased intratumoral T-cell infiltration and IFN-response signatures following treatment. Grade 3/4 treatment-related adverse events (TRAEs) reported for ≥3 patients included rash (13%), transaminase elevations (7%), lipase increased (4% [2% with amylase increased]), and acute kidney injury (3%), all considered immune-related. There were 2 Grade 5 TRAEs: immune-mediated pancreatitis (in the pres-

Abstract 407 Table 1 Demographics and baseline characteristics

Characteristic	Escalation (n = 37)	Expansion Cohorts				
		Melanoma (n = 20)	RCC (n = 8)	NSCLC (n = 20)	Prostate (n = 7)	Basket (n = 17)
Age, median (range)	56 (32-81)	67 (45-82)	64 (55-85)	72 (49-81)	69 (63-74)	61 (41-78)
Male	60%	60%	75%	75%	100%	24%
Months since initial diagnosis, median (range)	43 (3-313)	58 (6-511)	74 (52-249)	38 (8-113)	85 (1-110)	30 (1-165)
Lines of prior systemic therapy, median (range)	4 (0-9)	3 (0-9)	4 (0-6)	3 (0-9)	0 (0-11)	5 (0-8)
Prior checkpoint inhibitor therapy	76%	80%	63%	70%	14%	35%



Abstract 407 Figure 1 Mean change from baseline in percentage of Ki67+ T–cell expression in peripheral blood during first two cycles of XmAb20717

ence of pancreatic metastases) and immune-mediated myocarditis (Grade 4) that contributed to respiratory failure. A complete response was reported as the best overall response for 1 patient (melanoma); partial responses were reported for 5 patients (2 melanoma, 2 NSCLC, 1 ovarian). The objective response rate was 13% overall and 21% at 10 mg/kg (6/46 and 6/29 evaluable patients, respectively). All responders had prior CI exposure. Responses were observed only at 10 mg/kg and, within the 10 mg/kg group, appeared to correlate with higher peak serum concentration and area under the curve.

Conclusions XmAb20717 induced T-cell proliferation in peripheral blood consistent with dual-checkpoint blockade. Preliminary data indicate XmAb20717 was generally well-tolerated and associated with evidence of antitumor activity in CI-pretreated patients with various types of advanced solid tumors.

Trial Registration NCT03517488

Ethics Approval The study was approved by each institution's IRB.

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408 PHASE I, FIRST-IN-HUMAN TRIAL EVALUATING BI 1387446 (STIMULATOR OF INTERFERON GENES [STING] AGONIST) ALONE AND COMBINED WITH BI 754091 (ANTI-PROGRAMMED CELL DEATH [PD]-1) IN SOLID TUMORS

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Background Activation of the STING pathway in intratumoral immune cells leads to increased type I interferon production, promoting recruitment and priming of T-cells against tumor antigens, and providing anti-tumor activity.[1] Intratumoral administration of STING agonists has resulted in notable therapeutic activity in animal models.[1] STING agonists have also shown clinical activity in patients, which was more pronounced when combined with an anti-PD-1 antibody.[2,3] BI 1387446 potently and highly selectively activates the STING pathway; BI 754091 is a humanized IgG4 anti-PD-1 monoclonal antibody. Intratumoral administration of BI 1387446 resulted in tumor regression, and enhanced the activity of anti-PD-1 therapy in syngeneic tumor models.[4]

Methods NCT04147234 is a first-in-human, Phase I, open-label, multicenter trial of BI 1387446 in patients aged ≥18 years with advanced, unresectable and/or metastatic malignant solid tumors. Patients (up to ~122) will be enrolled from ~six sites across Europe and the USA. The main objectives are to characterize safety and determine the maximum tolerated dose (MTD) for BI 1387446 ± BI 754091. BI 1387446 will be administered intratumorally at increasing doses as monotherapy in Arm A, and in combination with BI 754091 (240 mg every three weeks, intravenously) in Arm B. In both arms, BI 1387446 will be administered in superficial lesions. In a potential third arm, Arm C, BI 1387446 will be administered in deep/visceral lesions in combination with intravenous BI 754091. Dose escalation will be guided by a Bayesian Logistic Regression Model with overdose control.For trial eligibility, patients must have exhausted standard treatment options, have ≥1 tumor lesion suitable for injection, ≥1 additional tumor lesion amenable to biopsy, and ECOG performance status of 0/1. Treatment will continue until progressive disease, unacceptable toxicity, other withdrawal criteria, or a maximum treatment duration of 34 cycles (for cycle 19 and onwards, administration of BI 1387446 is applicable for patients with a partial response), whichever occurs first. Primary endpoints are the MTD based on number of dose-limiting toxicities (DLTs), and number of patients with DLTs in the MTD evaluation period. Secondary endpoints are objective response based on RECIST 1.1, and best percentage change from baseline in size of target and injected lesions. Paired pre- and post-treatment biopsies of injected- and non-injected lesions and peripheral blood will be collected to assess pharmacodynamic changes associated with treatment. The trial is currently open for recruitment.

Results N/A

Conclusions N/A

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Trial Registration NCT04147234

Ethics Approval Not applicable.

Consent Not applicable.

REFERENCES

1. Corrales L, *et al*. *J Clin Invest* 2016;**126**:2404–2411.
2. Meric-Bernstam F, *et al*. 33rd Ann Mtg and Pre-Conf Programs of the Society for Immunotherapy of Cancer (SITC), Washington, November 7–11 Nov 2018 (Poster #P309). 2018.
3. Harrington K, *et al*. 43rd Ann Cong of the European Society for Medical Oncology (ESMO), Munich, 19–23 Oct 2018 (Poster #5475). 2018.
4. Gremel G, *et al*. American Association for Cancer Research (AACR), Virtual Meeting, 22–24 Jun 2020 (Poster #4522). 2020.

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409 A PHASE I TRIAL OF TALIMOGENE LAHERPAREPVEC FOR THE TREATMENT OF PERITONEAL SURFACE MALIGNANCIES (TEMPO)

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