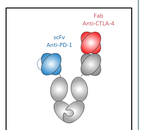
Preliminary Clinical Experience With XmAb20717, a PD-1 x CTLA-4 Bispecific Antibody, in Patients With Advanced Solid Tumors

Elaine Shum,[1] Matthew J Reilley,[2] Yana G Najjar,[3] Adil I Daud,[4] John A Thompson,[5] Joaquina C Baranda,[6] R Donald Harvey,[7] Anthony F Shields,[8] Ezra EW Cohen,[9] Shubham Pant,[10] Rom S Leidner,[11] Alain Mita,[12] Roger B Cohen,[13] Bartosz Chmielowski,[14] Mark N Stein,[15] Siwen Hu-Lieskovan,[16] Catherine A Fleener,[17] Ying Ding,[17] Lei Bao,[17] Sowmya Chollate,[17] Jolene S Shorr,[17] Raphael Clynes,[17] Barbara Hickingbottom[17]

[1]New York University; [2]University of Virginia; [3]University of Pittsburgh; [4]University of California, San Francisco; [5]University of Washington; [6]University of Kansas Cancer Center; [7]Emory University School of Medicine; [8]Karmanos Cancer Center; [9]University of California San Diego; [10]MD Anderson Cancer Center; [11]Providence Cancer Institute; [12]Cedars-Sinai Medical Center; [13]Perelman School of Medicine at the University of Pennsylvania; [14]University of California, Los Angeles; [15]Columbia University; [16]Huntsman Cancer Institute; [17]Xencor, Inc., Monrovia, California

BACKGROUND

- XmAb20717 (vudalimab) is a humanized bispecific monoclonal antibody that simultaneously targets PD-1 and CTLA-4, and binds preferentially to PD-1/CTLA-4 dual-positive cells
- DUET-2 (XmAb20717-01) is an ongoing, Phase 1, first-in-human, multicenter, dose-escalation and -expansion study in patients with selected advanced solid tumors
- A maximum tolerated dose was not reached in dose escalation
- 10 mg/kg XmAb20717 every 2 weeks (Q2W) was selected for tumor-specific expansion cohorts, based on
  - Consistent T-cell proliferation in peripheral blood indicative of dual PD-1/CTLA-4 checkpoint blockade
  - Response to treatment per RECIST 1.1[1]
- We report updated preliminary data on patients treated with XmAb20717 10 mg/kg Q2W, based on a 17 September 2021 data cut



Study Objectives

- Primary
  - To determine the safety and tolerability profile and the MTD or recommended dose of XmAb20717 for further evaluation
- Secondary
  - To characterize the PK and immunogenicity of XmAb20717
  - To assess antitumor activity, based on objective response and best overall response rates (RECIST 1.1), duration of response, and progression-free survival
- Key exploratory
  - To characterize the pharmacodynamics of XmAb20717, based on post-dosing changes in immune activity in peripheral blood and tumor
  - To evaluate the correlation between response to treatment and
    - Tumor mutational burden
    - Gene expression signatures

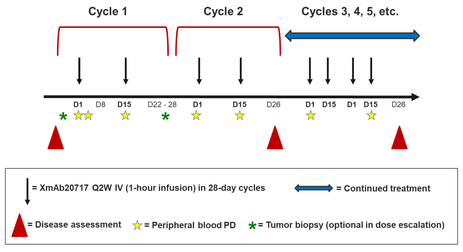
METHODS

Key Entry Criteria

Inclusion	Exclusion
• Histologically or cytologically confirmed eligible solid tumor – Dose escalation – tumor types with FDA-approved ICIs or published evidence of ICI antitumor activity – Dose expansion – melanoma, RCC, NSCLC, CRPC, and a basket of other solid tumors with published evidence of ICI antitumor activity, but no FDA-approved ICI • Cancer has progressed after treatment with all standard of care therapies or there are no standard treatment options • Measurable disease (except CRPC) • Evaluable disease per PCWG3 criteria (CRPC) • Adequate tumor biopsy tissue • ECOG 0 or 1	• Ongoing anticancer therapy (luteinizing hormone-releasing hormone analogue therapy permitted for CRPC patients) • Anti-CTLA-4 antibodies within 6 weeks or anti-PD-1 or anti-PD-L1/PD-L2 antibodies within 4 weeks prior to initiation of XmAb20717 • Grade 4 immune-mediated adverse event related to prior immunotherapy • Active known or suspected autoimmune disease* • Known active CNS metastases or carcinomatous meningitis • Estimated creatinine clearance < 30 mL/minute

*Exceptions include vitiligo, type 1 diabetes mellitus or residual hypothyroidism due to autoimmune condition treatable with hormone replacement therapy only; autoimmune skin conditions managed without systemic therapy; arthritis managed without systemic therapy beyond oral acetaminophen and NSAIDS.
CRPC = castration-resistant prostate cancer; ICI = immune checkpoint inhibitor; NSCLC = non-small cell lung cancer; PCWG3 = Prostate Cancer Working Group 3; RCC = renal cell carcinoma

Study Schema



References

1. Shum E, et al., JITC 2020.
2. Yuen et al., Nat Med 2020.
3. Schalper et al., Nat Med 2020.

Acknowledgements

With gratitude to the patients, their families and caregivers, and the XmAb20717-01 investigational study teams for support in the conduct of this research.

RESULTS

Patient Disposition

	Cohort 1 Melanoma	Cohort 2 RCC	Cohort 3 NSCLC	Cohort 4 CRPC	Cohort 5 Basket*	Total at 10 mg/kg†
Safety population, n‡	20	21	20	21	21	110
Efficacy evaluable population, n (%)§	20 (100)	21 (100)	20 (100)	21 (100)	21 (100)	110 (100)
Treatment ongoing, n (%)	0	4 (19.0)	0	0	0	4 (3.6)
Discontinued treatment, n (%)	20 (100)	16 (76.2)	20 (100)	21 (100)	21 (100)	105 (95.5)
Reason for discontinuation, n (%)						
Progressive disease	10 (50.0)	5 (23.8)	14 (70.0)	6 (28.6)	10 (47.6)	46 (41.8)
Adverse event	5 (25.0)	9 (42.9)	4 (20.0)	10 (47.6)	7 (33.3)	39 (35.5)
Withdrawal by subject	2 (10.0)	1 (4.8)	1 (5.0)	3 (14.3)	2 (9.5)	9 (8.2)
Other¶	3 (15.0)	1 (4.8)	1 (5.0)	1 (4.8)	1 (4.8)	8 (7.3)
Physician decision	0	0	0	1 (4.8)	1 (4.8)	3 (2.7)

* Tumor types include ovarian/fallopian tube cancer (n = 8), cervical cancer (n = 3); high-grade neuroendocrine tumor (n = 2); and cholangiocarcinoma, chondrosarcoma, gastric cancer, head and neck small cell carcinoma, Leydig tumor, malignant adrenal neoplasm, parotid adenocarcinoma, and squamous cell carcinoma of anus (n = 1 each).
† Includes 2 patients treated with 10 mg/kg in the dose-escalation phase (melanoma [n = 3], cervical cancer [n = 1], and NSCLC, TNBC, and gastric cancer [n = 1 each]), and all patients treated in the dose-expansion phase.
‡ Patients who receive any amount of XmAb20717.
§ Patients who receive any amount of XmAb20717 and have been followed for ≥ 2 cycles prior to data cut-off for analysis.
¶ Death due to disease progression (n = 3) and clinical progression, complete response, management of concomitant medical condition, patient decision, and to start other anticancer therapy (n = 1 each).

Demographics and Baseline Characteristics

	Cohort 1 Melanoma (n = 20)	Cohort 2 RCC (n = 21)	Cohort 3 NSCLC (n = 20)	Cohort 4 CRPC (n = 21)	Cohort 5 Basket* (n = 21)	Total at 10 mg/kg† (n = 110)
Age, median (range)	67 (45-82)	61 (46-85)	71.5 (49-81)	69 (56-89)	61 (39-78)	65 (39-89)
Male, %	60.0	76.2	75.0	100	33.3	66.4
Primary race, n (%)						
White	17 (85.0)	17 (81.0)	16 (80.0)	18 (85.7)	17 (81.0)	91 (82.7)
Black or African American	1 (5.0)	1 (4.8)	2 (10.0)	2 (9.5)	2 (9.5)	9 (8.2)
Asian	2 (10.0)	2 (9.5)	2 (10.0)	1 (4.8)	0	7 (6.4)
Other	0	1 (4.8)	0	0	2 (9.5)	3 (2.7)
ECOG 1, %	50.0	71.4	75.0	76.2	57.1	65.5
Months since initial diagnosis, median (range)	57.7 (6.1-510.7)	77.0 (30.1-248.6)	37.4 (8.0-112.7)	105.5 (15.2-228.5)	36.5 (6.0-164.6)	55.3 (6.0-510.7)
Lines of prior systemic therapy, median (range)	2.5 (0-9)	4 (2-10)	3 (1-9)	5 (3-11)	5 (1-8)	4 (0-11)
Prior treatment with checkpoint inhibitor regimen, n (%)	17 (85.0)	20 (95.2)	19 (95.0)	1 (4.8)	9 (42.9)	71 (64.5)
≥ 2 prior checkpoint inhibitor regimens, n (%)	11 (55.0)	7 (33.3)	8 (40.0)	0	0	27 (24.5)
Best overall response to last ICI, n (%)‡						
Number of patients with known response	10	15	14	0	5	48
PR	0	0	2 (14.3)	NA	0	2 (4.2)
SD	1 (10.0)	6 (40.0)	7 (50.0)	NA	2 (40.0)	17 (35.4)
PD	9 (90.0)	9 (60.0)	5 (35.7)	NA	3 (60.0)	29 (60.4)

* Tumor types include ovarian/fallopian tube cancer (n = 8); cervical cancer (n = 3); high-grade neuroendocrine tumor (n = 2); and cholangiocarcinoma, chondrosarcoma, gastric cancer, head and neck small cell carcinoma, Leydig tumor, malignant adrenal neoplasm, parotid adenocarcinoma, and squamous cell carcinoma of anus (n = 1 each).
† Includes 2 patients treated with 10 mg/kg in the dose-escalation phase (melanoma [n = 3], cervical cancer [n = 1], and NSCLC, TNBC, and gastric cancer [n = 1 each]), and all patients treated in the dose-expansion phase.
‡ Denominator is patients for whom response to last prior checkpoint inhibitor therapy was known.

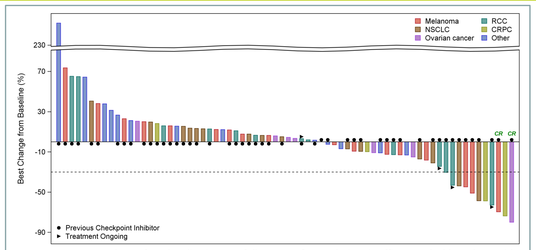
Best Overall Response (Investigator Assessment) – Efficacy Evaluable Patients With Follow-Up RECIST 1.1 Assessments

	Cohort 1 Melanoma (n = 15)	Cohort 2 RCC (n = 13)	Cohort 3 NSCLC (n = 14)	Cohort 4 CRPC (n = 12)	Cohort 5 Basket (n = 18)	Total at 10 mg/kg* (n = 78)
Objective response rate	13.3%	23.1%	14.3%	16.7%	5.6%	14.1%
Duration of response (days), K-M median (95% CI)	119.0 (NE, NE)	NE	59.0 (NE, NE)	NE	NE	NE
Best overall response, n (%)						
CR	0	0	0	0	1 (5.6)	2 (2.6)†
PR	2 (13.3)	3 (23.1)	2 (14.3)	2 (16.7)	0	9 (11.5)†
SD	7 (46.7)	6 (46.2)	5 (35.7)	0	6 (33.3)	27 (34.6)
Non-CR/non-PD	0	0	0	6 (50.0)	0	6 (7.7)
PD	5 (33.3)	3 (23.1)	7 (50.0)	3 (25.0)	10 (55.6)	29 (37.2)
Not evaluable	1 (6.7)	1 (7.7)	0	1 (8.3)	1 (5.6)	5 (6.4)
Disease control rate	60.0%	69.2%	50.0%	16.7%	38.9%	48.7%

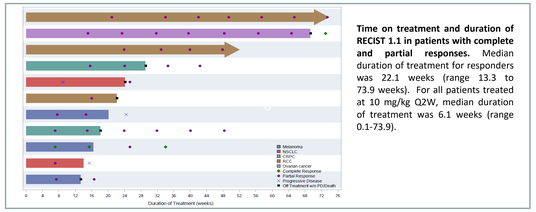
* Includes 7 patients treated with 10 mg/kg in the dose-escalation phase (melanoma [n = 3], cervical cancer [n = 1], and NSCLC, TNBC, and gastric cancer [n = 1 each]), and all patients treated in the dose-expansion phase.
† CR – 1 confirmed (melanoma [patient treated in dose-escalation phase]), 1 unconfirmed (ovarian cancer); PRs – 6 confirmed (2 each melanoma, RCC, and CRPC), 3 unconfirmed (1 RCC, 2 NSCLC).
Efficacy-evaluable patients are those who receive any amount of XmAb20717 and have been followed for ≥ 2 cycles prior to data cut-off for analysis.

Response to XmAb20717 Treatment

- Complete responses were observed for 2 patients. Both patients were alive and remained in response as of the data cut-off date.
  - Patient 1 – a 60-year-old male with melanoma refractory to prior treatment with pembrolizumab in the metastatic setting. The patient received a total of 4 doses of XmAb20717 over a 16-week period and had a complete response of inguinal lymph node tumor and non-target disease.
  - Patient 2 – a 66-year-old, BRCA1-mutation positive female with high-grade serous ovarian cancer who had received multiple prior treatments, including olaparib and nivolumab in the metastatic setting. Following 4 cycles of XmAb20717, she had a partial response of 4 target and 2 non-target lesions in the abdomen and lung. By Cycle 12, all target lesions had resolved, except a 30 mm lesion in the abdominal wall, and non-target disease was stable. The patient and physician discontinued treatment after a single dose in Cycle 18, when imaging showed the abdominal lesion was stable and no non-target lesions were seen. A biopsy of the abdominal wall lesion performed 2 weeks later showed no cancer cells.
- The CRPC responders (2 of 4 patients with measurable disease and follow-up RECIST assessments) had visceral and nodal (pelvic and/or extrapelvic) metastases, response durations of 41.3 and 27.0 weeks, were without progression on bone scans, and had confirmed PSA decreases ≥ 50% from baseline
  - 2 additional patients had decreases in PSA ≥ 50% out of a total of 12 with baseline and follow-up assessments
- Other than those with CRPC, all responders had prior anti-PD-1 and/or anti-CTLA-4 therapy (except 1 patient who received experimental ICI therapy), including more than half in the metastatic setting
- Note, the disease control rate in CRPC cohort is due to the proportion of patients without measurable disease (and thus in whom SD cannot be determined), as reflected by a best overall response assessment of non-CR/non-PD for half of the efficacy evaluable patients in this cohort



Best percent change from baseline in sum of diameters of target lesions in efficacy evaluable patients with measurable disease and follow-up RECIST assessments (n = 70). "Other" includes cervical cancer, cholangiocarcinoma, chondrosarcoma, gastric cancer, Leydig tumor, high-grade neuroendocrine tumor, parotid adenocarcinoma, squamous cell carcinoma of anus, and TNBC.

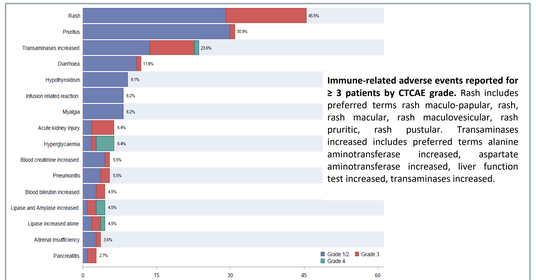


Time on treatment and duration of RECIST 1.1 in patients with complete and partial responses. Median duration of treatment for responders was 22.1 weeks (range 13.3 to 73.9 weeks). For all patients treated at 10 mg/kg Q2W, median duration of treatment was 6.1 weeks (range 0.1-73.9).

Progression-Free and Overall Survival – Efficacy Evaluable Patients

	Cohort 1 Melanoma (n = 20)	Cohort 2 RCC (n = 21)	Cohort 3 NSCLC (n = 20)	Cohort 4 CRPC (n = 21)	Cohort 5 Basket (n = 21)	Total at 10 mg/kg* (n = 110)
Progression-Free Survival						
Subjects with events, n (%)	12 (60)	9 (42.9)	16 (80.0)	9 (42.9)†	13 (61.9)	61 (55.5)†
K-M median (95% CI) PFS, months	3.55 (1.71, 5.52)	3.15 (1.74, NE)	1.95 (1.71, 2.14)	6.7 (2.20, NE)	1.81 (1.41, 5.75)	2.37 (1.87, 3.68)
PFS at 3 months	55.9	55.6	18.8	64.6	35.0	47.6
PFS at 6 months	0	39.7	NE	56.5	14.0	27.5
PFS at 12 months	0	26.5	NE	NE	14.0	18.3
Overall Survival						
Subjects with events, n (%)	5 (25.0)	3 (14.3)	7 (35.0)	5 (23.8)	4 (19.0)	26 (23.6)
K-M median (95% CI) OS, months	NE (3.38, NE)	NE	5.45 (3.32, NE)	NE (10.78, NE)	NE (7.95, NE)	NE (14.13, NE)
OS at 3 months	83.5	88.4	78.9	83.2	89.3	85.6
OS at 6 months	62.6	81.1	49.6	77.3	81.2	73.6
OS at 12 months	62.6	81.1	49.6	66.2	54.1	64.6

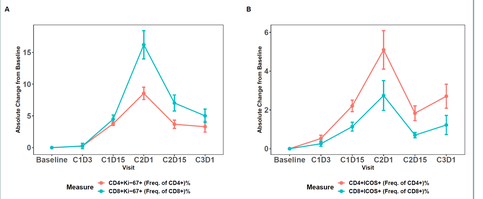
* Includes 7 patients treated with 10 mg/kg in the dose-escalation phase (melanoma [n = 3], cervical cancer [n = 1], and NSCLC, TNBC, and gastric cancer [n = 1 each]), and all patients treated in the dose-expansion phase.
† Radiographic progression for CRPC patients includes assessments based on both soft tissue and bone progression, per PCWG3 guidelines.
Efficacy-evaluable patients are those who receive any amount of XmAb20717 and have been followed for ≥ 2 cycles prior to data cut-off for analysis.



Immune-related adverse events reported for ≥ 3 patients by CTCAE grade. Rash includes preferred terms rash maculo-papular, rash, rash macular, rash maculovesicular, rash pruritic, rash pustular. Transaminases increased includes preferred terms alanine aminotransferase increased, aspartate aminotransferase increased, liver function test increased, transaminases increased.

XmAb20717 was generally well-tolerated. The most common treatment-related adverse events tended to be immune-related adverse events (irAEs). Immune-related colitis (preferred terms colitis [n = 2] and enterocolitis [n = 1]) was reported for 3 patients (2 Grade 3). Neurological irAEs were restricted to Grade 1 peripheral neuropathy (n = 2). There were 2 Grade 5 irAEs: immune-mediated pancreatitis (patient with RCC who had pancreatic metastases at baseline that progressed on study) and myocarditis (patient with NSCLC who had a history of atrial fibrillation and a pacemaker).

XmAb20717 Induces Peripheral T-Cell Activation and Proliferation Consistent With Dual PD-1/CTLA-4 Blockade

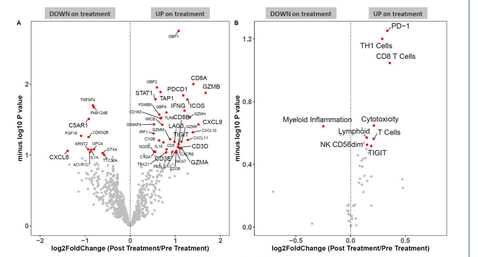


Peripheral flow cytometry demonstrates expected dual PD-1/CTLA-4 blockade pharmacodynamic activity, peaking at Cycle 2 Day 1.

A. Proliferation (%Ki-67) is robustly observed in both CD4+ and CD8+ T cells
B. ICOS upregulation was also observed on both CD4+ and CD8+ T cells

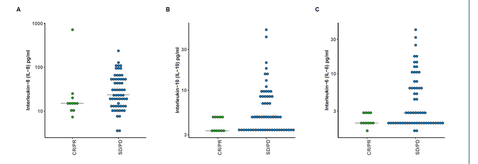
Values represent the absolute change in the frequency (%) of ki67 or ICOS+ T cells from baseline.

XmAb20717 Induces Intratumoral T-Cell Inflammatory Responses Differentially Expressed Genes and IO360 Gene Signatures Pre-Treatment vs Post-Treatment



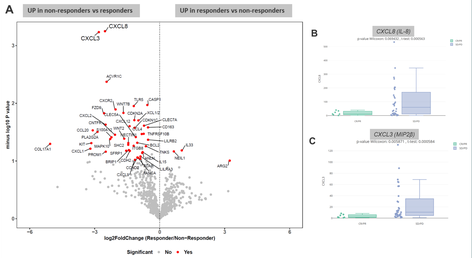
mRNA profiling of FFPE tumor biopsies was performed using the nCounter® PanCancer IO 360™ Panel. IO360 individual genes (A) and IO360 gene scores (B) were analyzed in 23 paired biopsies. XmAb20717 PD effects included induction of genes associated with increased T cells (*CD3D, CD8A*), T-cell activation markers (*GZMB, PDCD1, ICOS),* increased IFNg response/Ag presentation *(STAT1, TAP1, CXCL9, IFNG*) and decreased myeloid inflammation (IO360 gene score and *CXCL8, C5aR*).

Lower Baseline Serum Levels of Immunosuppressive Factors are Associated With XmAb20717 Clinical Response



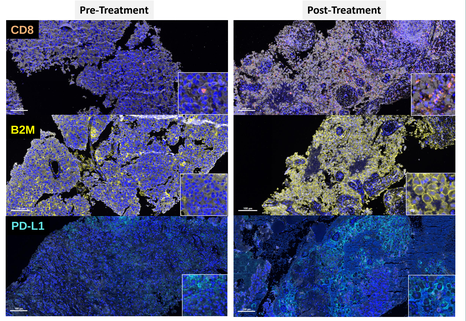
Baseline serum levels of IL-8 (A), IL-10 (B), and IL-6 (C) trended lower in patients who achieved CR/PR on study. Serum analytes were measured using the human MAP immunoassay platform (Myriad RBM). Elevated IL-8, IL-6, and IL-10 have previously been associated with myeloid-derived suppressor cells and for IL-8, diminished responses to checkpoint blockade.[2,3]

Low Baseline Tumor Expression of Myeloid Recruitment Genes was Associated With Response



Baseline gene expression from the IO360 panel (A) was evaluated in CR/PR vs SD/PD patients. Low *CXCL8* and *CXCL3* was associated with clinical benefit. Increases in intratumoral IL-8 (B) and CXCL3 (C) are recruitment factors for inhibitory myeloid-derived cells (TAM, MDSCs, neutrophils) and are associated with diminished checkpoint response.[2]

Potent Anti-Tumor Immune Response in CRPC Patient With Partial Response



Multiplex immunofluorescence staining of paired pre-treatment and post-treatment biopsies from a CRPC responder demonstrates increases in cellular immunity (CD8+ T cells), marked induction of MHC I antigen presenting machinery (B2M), and IFN pathway response (upregulation of PD-L1).

CONCLUSIONS

Updated, preliminary data on patients with selected advanced solid tumors treated with 10 mg/kg XmAb20717 Q2W in this Phase 1 study show

- XmAb20717 was associated with complete and partial responses in heavily pretreated patients with tumor types known to be responsive to single-agent checkpoint inhibition (melanoma, RCC, NSCLC), as well as those for which single-agent therapy has generally not been successful (CRPC, ovarian cancer)
  - Responding patients included those who progressed on prior anti-PD-1 and/or anti-CTLA-4 therapy in the metastatic setting
  - Responders included CRPC patients with visceral and lymph node metastases, which are associated with poor prognosis relative to disease only in the bone
- Treatment has been generally well tolerated, with rash, pruritus, and increased transaminases being the most frequently reported irAEs
- XmAb20717 induced intratumoral and peripheral T-cell activation, consistent with effective dual-checkpoint PD-1/CTLA-4 blockade
- Increased myeloid suppressor cell recruitment factors at baseline in tumor and serum were associated with unfavorable clinical response

These data support further development of XmAb20717 in advanced solid tumors, including those not generally associated with response to single-agent checkpoint inhibitor therapy, such as metastatic prostate cancer and ovarian cancer. Initiation of studies including these populations is in progress.