A Phase 1 multiple-ascending dose study to evaluate the safety and tolerability of XmAb23104 (PD-1 x ICOS) in subjects with selected advanced solid tumors (DUET-3) (NCT03752398)

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Abstract 2604

Background

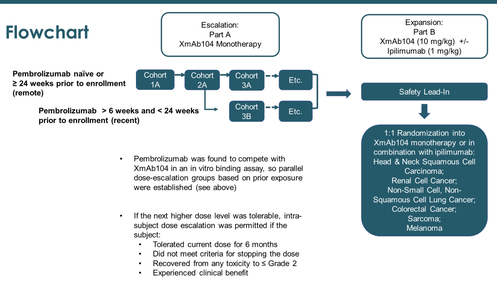
XmAb®23104 (XmAb104) is a bispecific antibody targeting T cells that simultaneously express PD-1, an immune checkpoint, and ICOS, a costimulatory molecule expressed after T cell activation. In an empirical screen for synergistic activity of checkpoint and costimulatory receptor targets, the PD-1 x ICOS bispecific demonstrated the most synergy.

DUET-3 is an ongoing, Phase 1, first-in-human, 3+3 dose-escalation and expansion study in subjects with advanced solid tumors designed to assess safety, tolerability and to identify the maximum tolerated dose (MTD) of XmAb104. Because CTLA4 blockade has been found to increase the frequency of ICOS-expressing T cells in prostate cancer, bladder cancer, and melanoma and may be applicable to other immunogenic tumor types,[1,2,3] XmAb104 +/- ipilimumab is being investigated in the expansion phase of the study.

We report preliminary data from the completed dose-escalation phase.

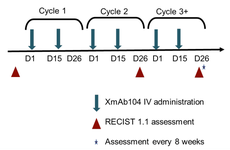
Methods

Study Flowchart



- Pembrolizumab was found to compete with XmAb104 in an in vitro binding assay, so parallel dose-escalation groups based on prior exposure were established (see above)
- If the next higher dose level was tolerable, intra-subject dose escalation was permitted if the subject:
  - Tolerated current dose for 6 months
  - Did not meet criteria for stopping the dose
  - Recovered from any toxicity to ≤ Grade 2
  - Experienced clinical benefit

Study Schema



Key Inclusion Criteria	Key Exclusion Criteria
• Histologically or cytologically confirmed advanced solid tumor • Measurable disease by RECIST 1.1 • Disease progression on standard of care therapy • ECOG 0 or 1	• Prior ICOS therapy • Grade 4-related adverse event from prior immunotherapy • Active CNS involvement • Active known or suspected autoimmune disease

Results

XmAb104 Exposure to Treatment by Starting Dose Level

Pembrolizumab naïve or received pembrolizumab for ≥ 24 weeks prior to enrollment (remote)			Pembrolizumab within > 6 weeks and < 24 weeks prior to enrollment (recent)		
Cohort	**Dose (mg/kg)**	**Subjects**	**Cohort**	**Dose (mg/kg)**	**Subjects**
1A	0.002	1			
2A	0.02	3			
3A	0.06	3	3B	0.06	3
4A	0.2	4	4B	0.2	4
5A	0.6	5	5B	0.6	7
6A	1.8	7	6B	1.8	3
7A	5.4	6	7B	5.4	3
8A	10	7	8B	10	3
9A	15	3			

No difference was observed between "remote" and "recent" cohorts, so data were pooled for safety analysis and presentation.

Subject Demographics

	0.002 mg/kg (N=1)	0.02 mg/kg (N=3)	0.06 mg/kg (N=6)	0.2 mg/kg (N=8)	0.6 mg/kg (N=12)	1.8 mg/kg (N=10)	5.4 mg/kg (N=9)	10 mg/kg (N=10)	15 mg/kg (N=3)	Overall (N=62)
Age, Median (range)	58.0 (58, 58)	57.0 (43, 59)	69.5 (56, 72)	55.0 (42, 80)	67.5 (35, 74)	59.0 (44, 84)	60.0 (28, 80)	63.0 (37, 83)	68.0 (64, 75)	63.0 (28, 84)
Male n(%)	1 (100.0)	2 (66.7)	1 (16.7)	6 (75.0)	7 (58.3)	5 (50.0)	6 (66.7)	5 (50.0)	2 (66.7)	35 (56.5)
Ethnicity, n(%)										
Not Hispanic or Latino	1 (100.0)	2 (66.7)	5 (83.3)	5 (62.5)	8 (66.7)	10 (100.0)	9 (100.0)	8 (80.0)	3 (100.0)	51 (82.3)
Hispanic or Latino	0	1 (33.3)	1 (16.7)	1 (12.5)	3 (25.0)	0	0	1 (10.0)	0	7 (11.3)
Missing	0	0	0	2 (25.0)	1 (8.3)	0	0	1 (10.0)	0	4 (6.5)
Primary Race, n(%)										
Black or African American	0	0	0	0	1 (8.3)	0	2 (22.2)	2 (20.0)	0	5 (8.1)
White	1 (100.0)	3 (100.0)	5 (83.3)	5 (62.5)	7 (58.3)	10 (100.0)	7 (77.8)	8 (80.0)	3 (100.0)	49 (79.0)
Multiple	0	0	0	0	1 (8.3)	0	0	0	0	1 (1.6)
Other	0	0	1 (16.7)	3 (37.5)	3 (25.0)	0	0	0	0	7 (11.3)

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Baseline Characteristics

	0.002 mg/kg (N=1)	0.02 mg/kg (N=3)	0.06 mg/kg (N=6)	0.2 mg/kg (N=8)	0.6 mg/kg (N=12)	1.8 mg/kg (N=10)	5.4 mg/kg (N=9)	10 mg/kg (N=10)	15 mg/kg (N=3)	Overall
Primary Disease, n(%)										
CRC	1 (100.0)	1 (33.3)	1 (16.7)	3 (37.5)	1 (8.3)	2 (20.0)	1 (11.1)	4 (40.0)	0	14 (22.6)
Other solid tumors	0	1 (33.3)	1 (16.7)	3 (37.5)	2 (16.7)	1 (10.0)	1 (11.1)	1 (10.0)	1 (33.3)	11 (17.7)
PDA	0	1 (33.3)	3 (50.0)	0	0	2 (20.0)	0	1 (10.0)	1 (33.3)	8 (12.9)
STS	0	0	0	1 (12.5)	3 (25.0)	1 (10.0)	2 (22.2)	1 (10.0)	0	8 (12.9)
Melanoma	0	0	0	0	1 (8.3)	1 (10.0)	1 (11.1)	2 (20.0)	1 (33.3)	6 (9.7)
HNSCC	0	0	0	0	3 (25.0)	2 (20.0)	0	0	0	5 (8.1)
RCC	0	0	0	0	2 (16.7)	0	1 (11.1)	1 (10.0)	0	4 (6.5)
EC	0	0	1 (16.7)	0	0	1 (10.0)	2 (22.2)	0	0	4 (6.5)
NSCLC	0	0	0	1 (12.5)	0	0	1 (11.1)	0	0	2 (3.2)
Tumor stage at screening, n(%)										
Stage II	0	0	1 (16.7)	1 (12.5)	0	0	0	0	0	2 (3.2)
Stage III	0	0	0	0	0	0	0	2 (20.0)	1 (33.3)	3 (4.8)
Stage IV	1 (100.0)	3 (100.0)	5 (83.3)	7 (87.5)	12 (100.0)	10 (100.0)	9 (100.0)	8 (80.0)	2 (66.7)	57 (91.9)
ECOG status, n(%)										
0	1 (100.0)	2 (66.7)	1 (16.7)	4 (50.0)	6 (50.0)	4 (40.0)	4 (44.4)	5 (50.0)	0	27 (43.5)
1	0	1 (33.3)	5 (83.3)	4 (50.0)	6 (50.0)	6 (60.0)	5 (55.6)	5 (50.0)	3 (100.0)	35 (56.5)
Lines of prior disease-specific therapies, median (range)	3 (3.3)	5 (3, 5)	3.5 (2, 10)	4 (0, 7)	3 (1, 8)	3 (1, 7)	2 (1, 8)	4 (1, 7)	3 (2, 4)	3 (0, 10)
Number of subjects with any prior immunotherapy, n (%)	0	2 (66.7)	3 (50.0)	5 (62.5)	9 (75.0)	6 (60.0)	5 (55.6)	8 (80.0)	1 (33.3)	39 (62.9)
Number of subjects with any prior checkpoint therapy, n (%)	0	2 (66.7)	3 (50.0)	5 (62.5)	9 (75.0)	6 (60.0)	5 (55.6)	8 (80.0)	1 (33.3)	39 (62.9)
Number of subjects with prior pembrolizumab, n (%)	0	0	3 (50.0)	3 (37.5)	7 (58.3)	5 (50.0)	4 (44.4)	3 (30.0)	0	25 (40.3)

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(CRC) colorectal cancer; (EC) endometrial cancer; (HNSCC) head and neck squamous cell carcinoma; (NSCLC) non-squamous non-small cell lung carcinoma; (PDA) pancreatic cancer; (RCC) renal cell carcinoma; (STS) soft tissue sarcoma. "Other" solid tumors were adrenocortical carcinoma, ampullary cancer, basal cell carcinoma, breast cancer, esophageal adenocarcinoma, gastric adenocarcinoma, thyroid cancer and urothelial carcinoma.

Subject Disposition

Subject Disposition	0.002 mg/kg	0.02 mg/kg	0.06 mg/kg	0.2 mg/kg	0.6 mg/kg	1.8 mg/kg	5.4 mg/kg	10 mg/kg	15 mg/kg	Overall
Safety population [a]	1	3	6	8	12	10	9	10	3	62
Number of treatment cycles completed, n (%) [b]										
0	0	0	0	0	2 (16.7)	1 (10.0)	0	0	0	3 (4.8)
1	0	1 (33.3)	0	1 (12.5)	6 (50.0)	2 (20.0)	1 (11.1)	4 (40.0)	0	15 (24.2)
2	0	2 (66.7)	4 (66.7)	3 (37.5)	2 (16.7)	2 (20.0)	6 (66.7)	1 (10.0)	1 (33.3)	21 (33.9)
>2	1 (100.0)	0	2 (33.3)	4 (50.0)	2 (16.7)	5 (50.0)	2 (22.2)	5 (50.0)	2 (66.7)	23 (37.1)
Number of subjects on treatment, n(%)	0	0	0	1 (12.5)	0	1 (10.0)	0	2 (20.0)	0	4 (6.5)
Reason for treatment discontinuation, n(%)	1 (100.0)	3 (100.0)	6 (100.0)	7 (87.5)	12 (100.0)	9 (90.0)	9 (100.0)	8 (80.0)	3 (100.0)	58 (93.5)
Progressive Disease	1 (100.0)	2 (66.7)	5 (83.3)	6 (75.0)	8 (66.7)	6 (60.0)	8 (88.9)	7 (70.0)	2 (66.7)	45 (72.6)
Adverse Event	0	0	0	0	1 (8.3)	2 (20.0)	0	0	1 (33.3)	4 (6.5)
Withdrawal by Subject	0	0	0	0	2 (16.7)	0	1 (11.1)	1 (10.0)	0	4 (6.5)
Physician Decision	0	0	0	1 (12.5)	1 (8.3)	0	0	0	0	2 (3.2)
Other [c]	0	1 (33.3)	1 (16.7)	0	0	0	0	0	0	2 (3.2)
Protocol Deviation	0	0	0	0	0	1 (10.0)	0	0	0	1 (1.6)

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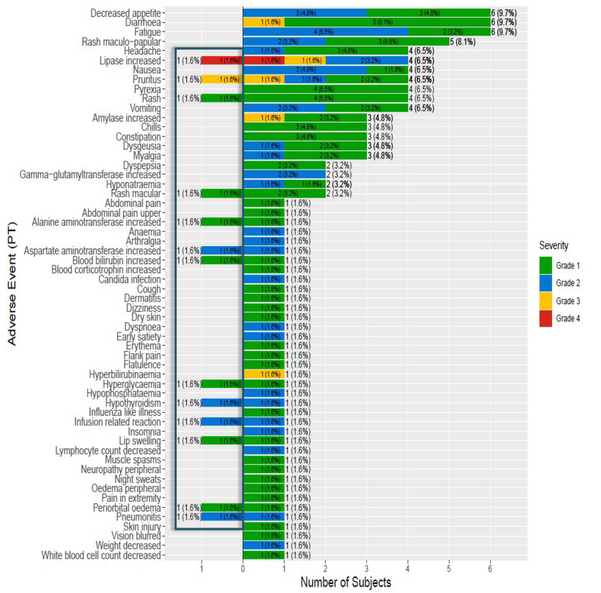
a. The safety population is defined as all subjects who received at least 1 infusion of XmAb104.
b. The subject's last dose is the same as or beyond the last scheduled dose of the cycle.
c. Reasons for "other" end of treatment: clinical progression, subject entering hospice

Treatment-Related Adverse Events (TRAEs; on the right) and the Subset of Immunotherapy-Related Adverse Events (irAEs; on the left) by Preferred Term in Safety Population

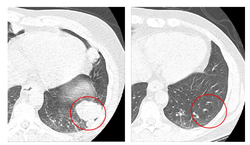


- No dose-limiting toxicities (DLTs) were observed, and the MTD was not reached.
- TRAEs were mostly mild. A single Grade 4 asymptomatic lipase increase was reported as an irAE.
- 10 mg/kg was determined to be the recommended dose based on feasibility of administration at higher dose levels and review of safety data across dose levels with investigators.
- Nineteen subjects (30.6%) experienced serious adverse events (SAEs)
  - SAEs reported for more than one subject were acute kidney injury and small intestinal obstruction (n=2 each)
- Two subjects (3.2%) experienced treatment-related SAEs: a Grade 3 hyperbilirubinemia and the Grade 4 asymptomatic increased lipase. Both events resolved with prednisone.

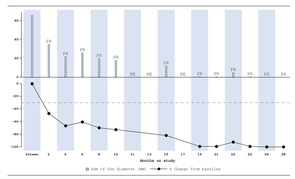
Clinical Activity

Confirmed Partial Response:

Subject 10403, a patient who is immunotherapy naïve with undifferentiated pleomorphic sarcoma, enrolled into the 0.2 mg/kg cohort and dose escalated to 0.6 mg/kg. Two target lesions were identified in the lung and subpleural lingular nodule, which completely resolved, and a single non-target lesion in the lung remained.



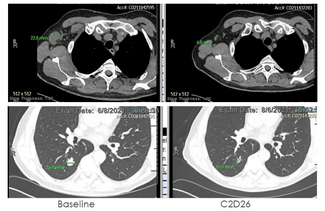
Baseline C4D26



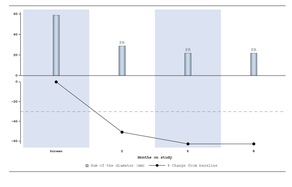
Clinical Activity

Confirmed Partial Response:

Subject 10853 is a patient with renal cell carcinoma, clear cell histology who enrolled into the 10 mg/kg recent pembrolizumab cohort. The only prior therapy was pembrolizumab/axitinib with stable disease as best overall response. Two target lesions in the ribs, one target lesion in the right axillary lymph node, and a non-target lesion in bone were identified. A partial response was observed at the end of Cycle 2, and the patient remained in response at the time of datacut.



Baseline C2D26



Unconfirmed Partial Response:

Subject 10652 is a patient with head and neck squamous cell carcinoma who was enrolled into the 1.8 mg/kg recent pembrolizumab cohort. Prior therapies included neo-adjuvant nivolumab, cisplatin, nivolumab, GAL-3 inhibitor and recent (2 months) pembrolizumab. The subject experienced disease progression on all prior therapies. Two target lesions in the lung were identified and had a partial response at the end of Cycle 2. A new lesion was identified at the next time point, and the subject was taken off study.

Durable Stable Disease:

Two subjects have had stable disease for > 20 months.

- A subject with MSI high* CRC was treated at an initial dose of 1.8 mg/kg and dose escalated to 5.4 and 10 mg/kg. Local laboratory results showed a decrease in tumor marker CEA over time. The subject experienced a Grade 3 small bowel obstruction and other mild adverse events, reported as unrelated to study drug.
- A subject with MSI high CRC was treated at the 10 mg/kg dose, was in Cycle 22 at the time of datacut, and had no related AEs > Grade 1.

*This subject was misidentified as MSS in the e-poster, but has been verified as MSI-high.

Conclusions

Preliminary data on subjects with advanced solid tumors treated with XmAb104 in the dose-escalation phase of this study show:

- XmAb104 was well tolerated at doses from 0.002 to 15 mg/kg
  - No DLTs were observed
  - MTD was not reached
  - 10 mg/kg was determined to be the recommended dose based on feasibility of administration at higher dose levels and review of safety data across dose levels with investigators
  - irAEs were reported for a limited percentage of subjects, were predominantly Grades 1 and 2, and showed no relationship to dose
- Partial responses to therapy were observed at doses as low as 0.2 mg/kg and in different tumor types
- PK was linear, and exposure was not affected by recent prior pembrolizumab

Safety and PK data support development of XmAb104 in advanced solid tumor types including HNSCC, NSCLC, CRC, sarcoma, melanoma, and ccRCC. The dose-expansion phase of the study, in which 10 mg/kg XmAb104 in combination with ipilimumab is being investigated, is ongoing.

References

1) Chen H, PNAS, 2009;106(8):2729-34; 2) Liakou CI, PNAS, 2008;105(39):14987-92; 3) Wei SC, Cell, 2017;170(6):112033

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