Preliminary Phase 1 Safety and Antitumor Activity of XmAb819, a First-in-Class ENPP3 x CD3 Bispecific Antibody, in Patients with Advanced Clear Cell Renal Cell Carcinoma (ccRCC)

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BACKGROUND

XmAb819 Targets ENPP3, Highly Expressed in ccRCC

- Despite advances in the treatment of metastatic ccRCC, few patients are cured, and therapies exploiting novel targets are needed.
- Antigen screening identified ectonucleotide pyrophosphatase/phosphodiesterase family member 3 (ENPP3) as having consistently high expression in ccRCC and low expression in normal tissue.
- XmAb819 is a T-cell engaging bispecific antibody in development for patients with ccRCC.
- XmAb819 utilizes a multivalent 2+1 format with high-avidity bivalent binding to ENPP3 and low-affinity monovalent binding to CD3, a component of the T-cell receptor (TCR) complex.
- XmAb819 is engineered for preferential engagement of high ENPP3-expressing cancer cells to induce T-cell-mediated cytolysis.

Figure 1. ENPP3 Differential Expression

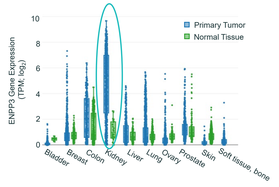
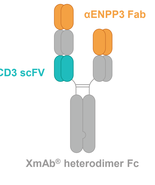


Figure 2. XmAb819: 2+1 ENPP3 x CD3



STUDY DESIGN

Study Objectives & Key Eligibility Criteria

XmAb819-01 is an ongoing Phase 1, multicenter, dose-escalation and expansion study in patients with advanced ccRCC. The study is planned to enroll globally.

Primary	Secondary
Safety and tolerability	Pharmacokinetics
Identify recommended doses	Anti-tumor activity by ORR, PFS, DOR, and OS per RECIST 1.1 criteria

Inclusion	Exclusion
≥ 18 years	Investigational anti-ENPP3/CD203c therapy
Subjects who have relapsed and refractory ccRCC and have undergone disease progression on standard-of-care therapies	Known active central nervous system metastases and/or carcinomatous meningitis
	Active known autoimmune disease
Subjects must have measurable disease by RECIST v1.1 as assessed by the local site investigator or radiology department	Diagnosis of immunodeficiency or receiving chronic systemic steroid therapy
	Inadequate organ function

Figure 3. Study Schema

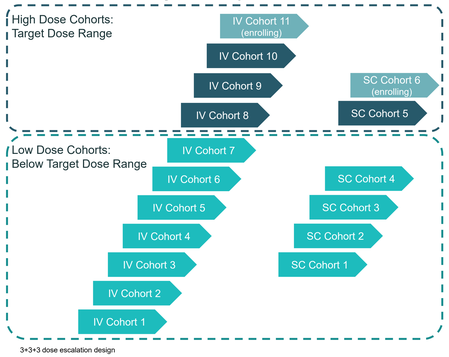
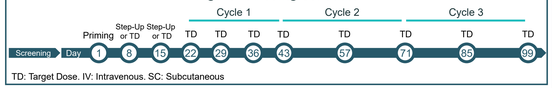


Figure 4. Dosing Schedule



TD: Target Dose. IV: Intravenous. SC: Subcutaneous

Scan the QR code to download an electronic version of the poster. The QR code is intended to provide scientific information for individual reference. The PDF should not be altered or reproduced in any way.

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Poster Support: Lauren Marek

SUBJECT DEMOGRAPHICS & DISPOSITION

Table 1. Demographics & Disease Characteristics

Baseline Characteristics	Overall N=69
Median Age, Years (Min, Max)	60 (34, 77)
Male, n (%)	55 (80)
Race, n (%)	
White	61 (88)
Other	8 (12)
Time Since Initial Disease Diagnosis, Months (Min, Max)	53.6 (8, 259)
IMDC Risk Score at Initial Diagnosis, n (%)	
Favorable	22 (32)
Intermediate	19 (28)
Poor	9 (13)
Not Available	19 (28)
Sarcomatoid Features, n (%)	7 (10)

Table 2. Prior Therapy

Prior Therapy	Overall N=69
# Prior Regimens, Median (Min, Max)	4.0 (1, 8)
1, n (%)	5 (7)
2	16 (23)
3	13 (19)
4	9 (13)
≥5	26 (38)
Prior Treatments, n (%)	
Checkpoint Inhibitor	69 (100)
VEGF TKI	69 (100)
2 or More TKI	42 (61)
HIF2α Inhibitor	25 (36)
Nephrectomy, n (%)	47 (68)

Table 3. Subject Disposition

	Overall N=69
Treatment Status, n (%)	
Ongoing	17 (25)
Discontinued	52 (75)
Reason for Treatment Discontinuation, n (%)	
Adverse Event*	3 (4)
Physician Decision	3 (4)
Subject Declines Further Treatment	2 (3)
Progressive Disease	38 (55)
Clinical Progression	6 (9)

* Elevated liver enzymes (n=1), non-fatal myocardial infarction in the presence of hypotension and CRS (n=1), AST/ ALT increased (n=1)

SAFETY (N=69)

Figure 5. Overall TEAE and Related TEAE by Maximum Severity Grade (N=69)

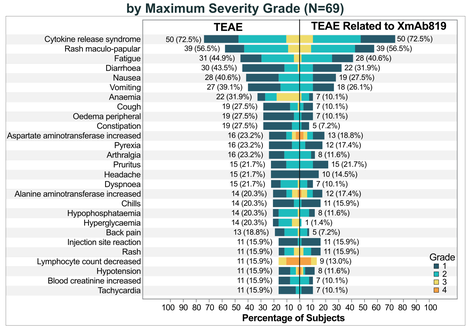
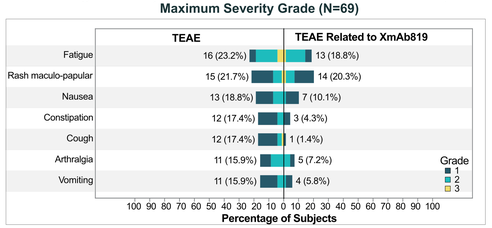


Table 4. Safety Summary

	Overall N= 69
TEAE, n (%)	68 (99)
Grade ≥ 3	48 (70)
Related Grade ≥ 3	31 (45)
Serious TEAE	35 (51)
Related Serious TEAE	28 (41)
Lead to Dose Reduction*	4 (6)
Did Not Reach Target Dose	6 (9)
Lead to Treatment Discontinuation	3 (4)
Lead to Death	0

* 3 dose reductions occurred during priming/step-up doses.

Figure 6. >Day 29 to End of Study TEAE and Related TEAE by Maximum Severity Grade (N=69)



- XmAb819 is well tolerated with low rates of discontinuation
  - >90% reach target dose
- Most common AEs are CRS and rash
  - Majority of CRS events are Grade 1/2 and occur during priming
  - Rash events are mostly Grade 1/2; responsive to antihistamines and steroids (topical/oral)
- Pharmacy errors diluting drug product during priming dose preparation led to higher drug exposure (3-8x) in some patients. Errors correlated to Grade 3 CRS and step-up dosing delays.
  - Overall, correct dose prep resulted in 4% Grade 3 CRS (2/51), whereas dose prep errors resulted in 28% Grade 3 CRS (5/18).
  - In the target dose range, correct dose prep resulted in 6% Grade 3 CRS (1/18), whereas dose prep errors resulted in 50% Grade 3 CRS (3/6).
- Mitigation via site retraining is complete; eliminating root cause of multiple dilution steps, with low concentration drug product rollout in 1H 2026.

PHARMACOKINETICS

Figure 7. Achieving Exposures in Target Dose Range

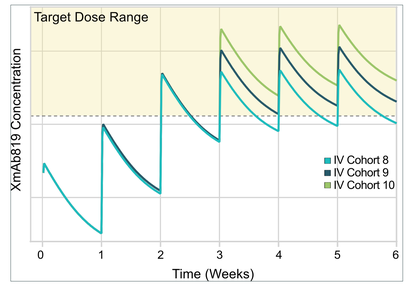


Table 5. PK Metrics

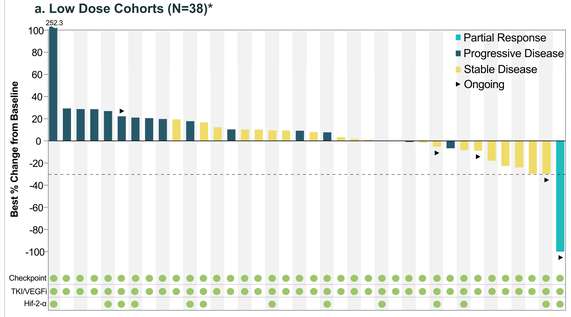
Parameter	Value
Half-life	8.7 Days
Subcutaneous Administration	
T_{max}	5.5 Days
Absolute Bioavailability	55-70%

- Steady state drug concentrations attained in Cohorts 9 and 10 fall within the PK target dose range expected to achieve anti-tumor activity.

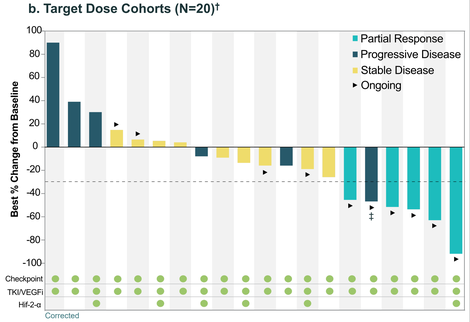
EFFICACY (N=69)

Figure 8. Best Percent Change from Baseline in Tumor Lesion (RECIST 1.1)

a. Low Dose Cohorts (N=38)*



b. Target Dose Cohorts (N=20)†

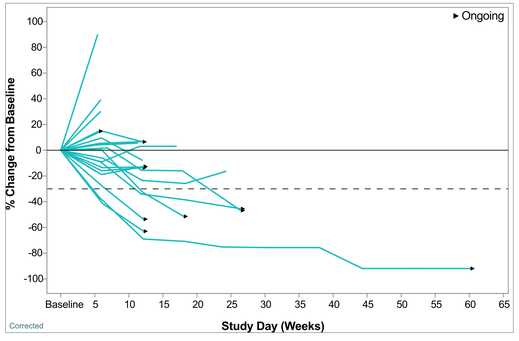


* Figure excludes four subjects without post-baseline scans and three subjects with non-evaluable post-baseline measurements.

† Figure excludes three subjects without post-baseline scans and one subject with non-evaluable post-baseline measurements.

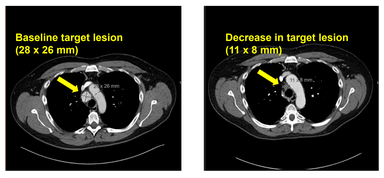
‡ PD at first scan (D48) prior to receiving target dose on D50. Continued treatment post-progression resulted in 47% tumor reduction. Continues on study at week 30.

Figure 9. Target Dose Range, Percent Change from Baseline (N=20)†



†Figure excludes three subjects without post baseline scans and one subject with non-evaluable post baseline measurements.

Figure 12. Representative CT Scans: 63% Reduction in Target Lesion



- 56-year-old male diagnosed ~10 years ago; metastatic disease less than 5 years ago
- Subject had 2 prior lines of therapy
  - Cabozantinib/nivolumab for 1 month
  - Lenvatinib/everolimus for 3 years
- Two target lesions: lymph node mediastinal
- Multiple non-target lesions: lung and pancreas
- Subject remains on treatment for >12 weeks

Figure 10. Target Dose Range Response

a. Summary of Best Overall Response

Best Overall Response	Efficacy Evaluable Target Dose Range N=20*
Objective Response Rate (ORR), % (95% CI)	25% (9, 49)
Complete Response (CR)	0
Unconfirmed Partial Response (uPR) / Confirmed Partial Response (cPR)†, n (%)	5 (25)
Stable Disease (SD), n (%)	9 (45)
Disease Control Rate (DCR), % (95% CI)	70% (46, 88)

* Excludes three subjects without post-baseline scans and one subject with non-evaluable post-baseline measurements.

† 4 cPR. 1 uPR subject deemed not evaluable after PR (54% reduction in target lesions at week 12) because of subsequent radiation to symptomatic non-target lesion with target lesion in field. The subject continues on treatment with stable scan at week 36.

b. Percent Change from Baseline, Responders (N=5)

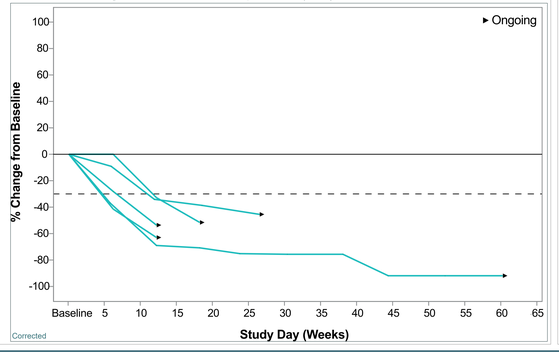
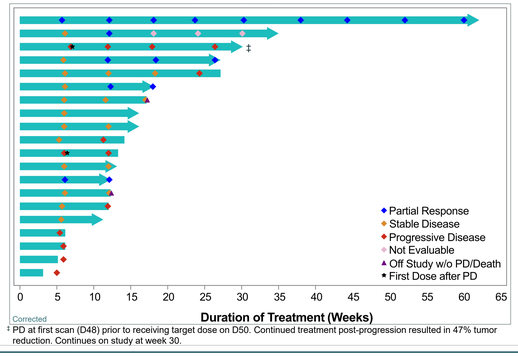


Figure 11. Efficacy Evaluable Target Dose Range (RECIST 1.1) Response by Subject (N=20)



‡ PD at first scan (D48) prior to receiving target dose on D50. Continued treatment post-progression resulted in 47% tumor reduction. Continues on study at week 30.

CONCLUSIONS

- XmAb819 is safe and well-tolerated at IV and SC doses in heavily pre-treated subjects with advanced ccRCC.
- CRS profile is primarily low grade and occurs primarily during early priming steps, with a 4% rate of Grade 3 CRS observed in patients without dose errors. No cases of ICANS have been reported.
- Treatment with XmAb819 has resulted in consistent anti-tumor activity within the predicted target dose range. RECIST responses have also been reported for patients that have progressed on prior treatment with belzutifan.
- IV Cohort 10 has been selected as the first expansion cohort, and dose escalation continues to identify dose for second expansion cohort.