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Phase 1 results of XmAb819, a novel ENPP3 x CD3 bispecific, in advanced clear cell renal cell carcinoma (ccRCC)

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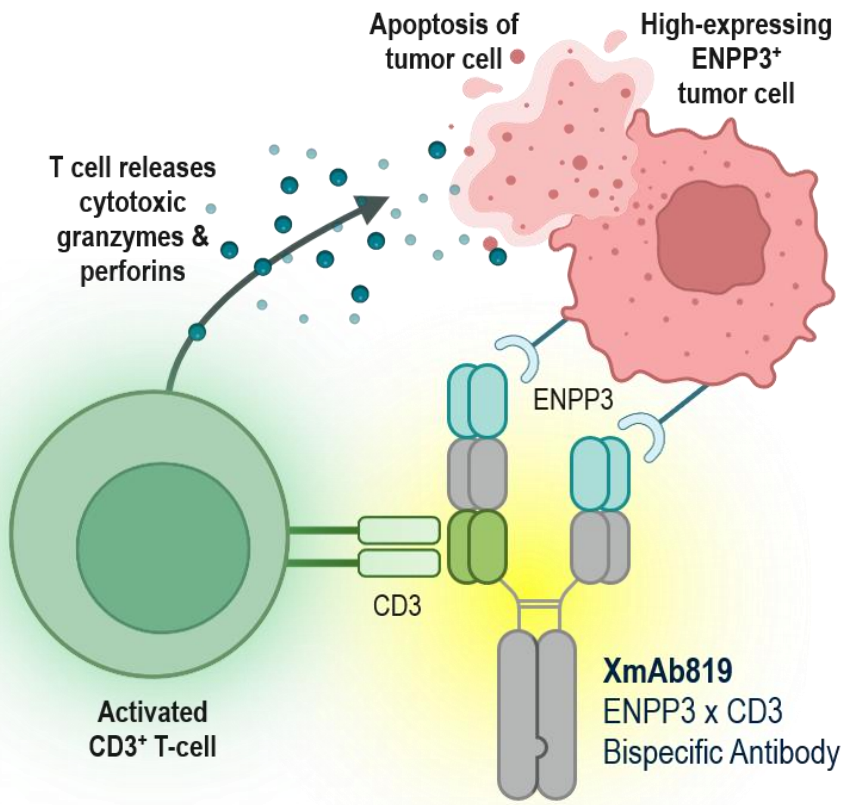
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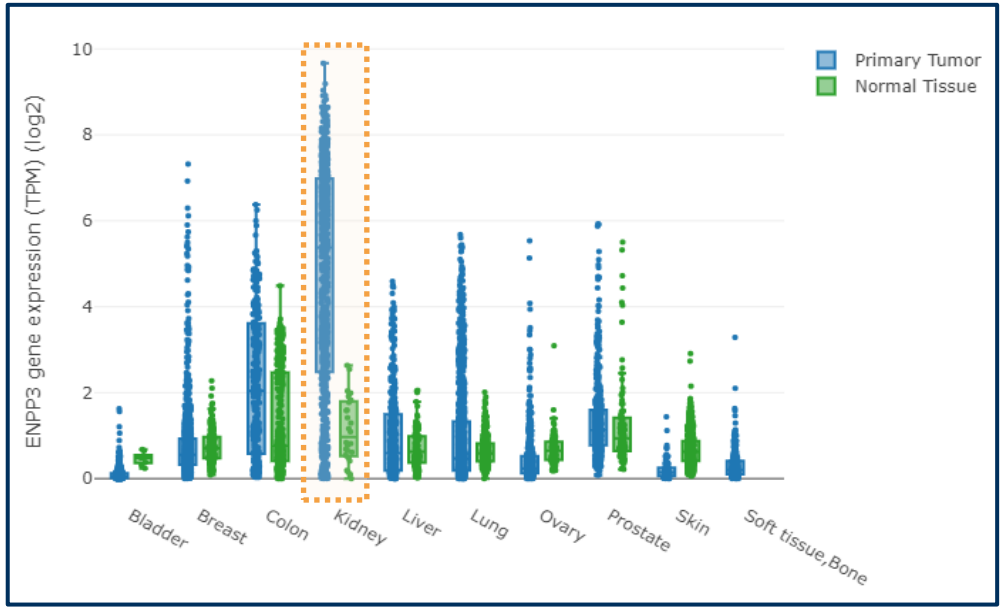
Abstract 2684

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XmAb819, ENPP3 x CD3 bispecific antibody in development for ccRCC



- ENPP3 is an extracellular nucleotide metabolizing enzyme with high expression in RCC and other solid tumors, and low expression in normal tissues[1]
- XmAb819 targets T cells for potent lysis of ENPP3+ tumor cells
- XmAb 2+1 format selectively binds and kills high density ENPP3 tumor cells, but spares low density normal tissue



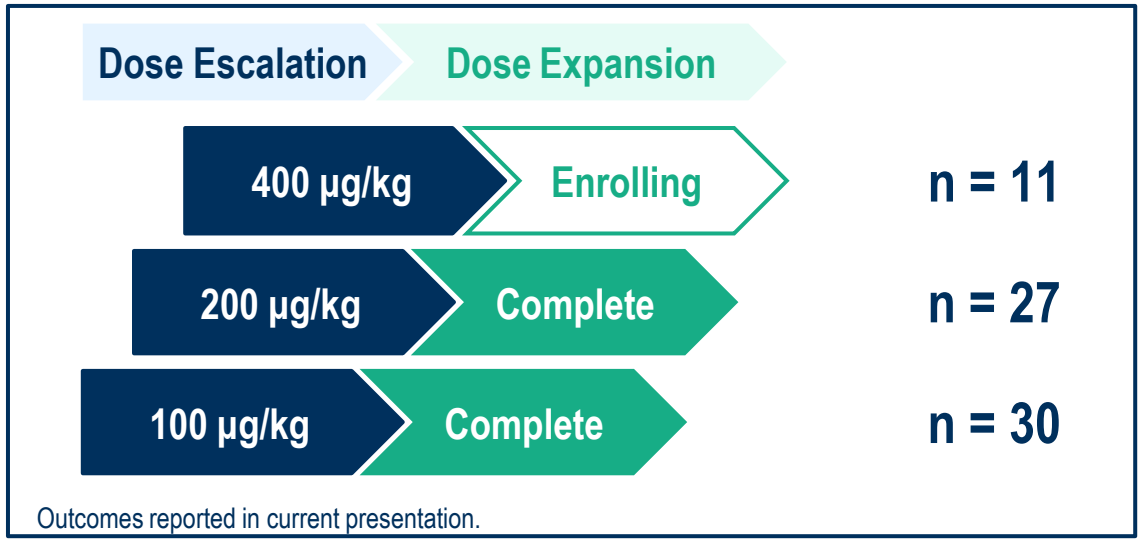
ENPP3 ectonucleotide pyrophosphatase / phosphodiesterase family member 3

[1]Doñate, Fernando, et al. Clinical Cancer Research 22.8 (2016)

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XmAb819-01: Phase 1 study design in advanced ccRCC

Study Schema – IV Administration



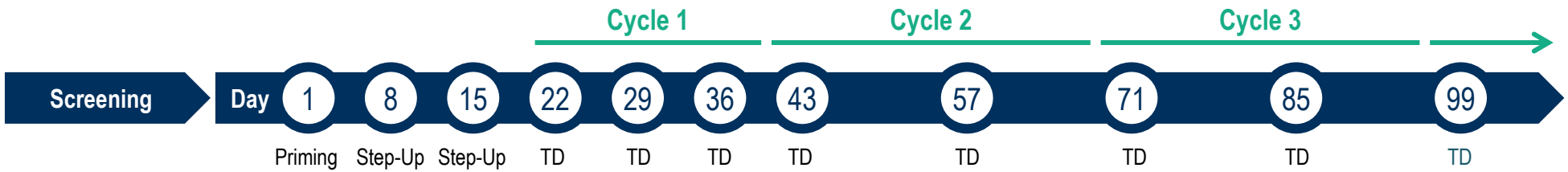
Key Eligibility Criteria

- R/R ccRCC – prior ICI & VEGFR-TKI
- Measurable disease by RECIST v1.1
- No prior anti-ENPP3 therapy

Endpoints

- Primary: Safety & Tolerability
- Secondary:
  - ORR, DOR, PFS per RECIST 1.1
  - Pharmacokinetics

NCT05433142. US & EU sites.



DOR, duration of response; **ICI**, immune checkpoint inhibitor; **IV,** intravenous; **ORR,** objective response rate; **PFS**, progression free survival; **R/R,** relapsed / refractory; **TD**, target dose; **TKI,** tyrosine kinase inhibitor; **VEGFR,** vascular endothelial growth factor receptor

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Patient characteristics

Baseline Characteristic	All IV Doses (n=119)	Expansion Doses (n=68)
Median Age, Years (range)	61 (34, 78)	62 (34, 78)
Male, n (%)	97 (81.5)	58 (85.3)
Race – White, n (%)	101 (84.9)	56 (82.4)
Time Since Disease Diagnosis, mo. (range)	52.5 (7, 287)	49.5 (7, 287)
IMDC Risk Score at Baseline[1], n (%)		
Favorable	8 (6.7)	4 (5.9)
Intermediate	81 (68.1)	46 (67.6)
Poor	30 (25.2)	18 (26.5)
Sarcomatoid Features, n (%)	16 (13.4)	13 (19.1)
≥3 Metastatic Sites, n (%)	84 (70.6)	46 (67.6)
Bone metastasis, n (%)	58 (48.7)	32 (47.1)
Liver metastasis, n (%)	48 (40.3)	27 (39.7)
Target Lesions SOD (mm), Median	90.0	90.5
ENPP3 Positive From Cases With Tissues[2] (%)	83/89 (93.3)	50/52 (96.2)

Prior Therapy	All IV Doses (n=119)	Expansion Doses (n=68)
# Prior Regimens, Median (Min, Max)	3 (1, 10)	3 (1, 10)
1, n (%)	7 (5.9)	4 (5.9)
2	35 (29.4)	22 (32.4)
3	30 (25.2)	18 (26.5)
≥4	47 (39.5)	24 (35.3)
Prior Treatments, n (%)		
Any Immune Checkpoint Inhibitor	119 (100)	68 (100)
Any VEGFR-TKI	119 (100)	68 (100)
2 or More VEGFR-TKIs	76 (63.9)	43 (63.2)
HIF2α Inhibitor	42 (35.3)	23 (33.8)
Nephrectomy, n (%)	81 (68.1)	46 (67.6)

Subjects who received ≥1 protocol-specified dose of XmAb819 were included in the baseline characteristics analysis. Data cut-off: **01 September 2026**. Excludes 1 participant who experienced approximately 10-fold higher exposure than intended at the first and only dose administered, and who subsequently developed Grade 4 CRS and discontinued treatment.

[1]IMDC risk derived at study baseline using central laboratory values; KPS <80% defined as ECOG ≥2.
[2]Tumor ENPP3 positivity was defined as a tumor proportion score (TPS) ≥1, regardless of expression intensity, by a clinical trial IHC assay (Roche Diagnostics).

HIF2α, hypoxia-inducible factor 2-alpha; **IMDC,** International Metastatic RCC Database Consortium; **IHC,** immunohistochemistry; **SOD,** sum of diameters; **TKI,** tyrosine kinase inhibitor; **VEGFR,** vascular endothelial growth factor receptor

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Adverse events

Summary of Adverse Events

Number of Subjects With, n (%)	All IV Doses (N=119)	Expansion Doses (n=68)
Grade ≥ 3	95 (79.8)	56 (82.4)
Related TEAE Grade ≥ 3	75 (63.0)	49 (72.1)
Serious TEAE	74 (62.2)	42 (61.8)
Related Serious TEAE	64 (53.8)	37 (54.4)
TEAE Leading to Dose Reduction	7 (5.9)	1 (1.5)
Did Not Reach Target Dose	9 (7.6)	3 (4.4)
TEAE Leading to Discontinuation	8 (6.7)	5 (7.4)
Related TEAE Leading to Discontinuation	7 (5.9)	4 (5.9)
Leading to Death	0	0

Subjects who received ≥1 protocol-specified dose of XmAb819 were included in the safety analysis. Data cut-off: **01 September 2026.** Excludes 1 participant who experienced approximately 10-fold higher exposure than intended at the first and only dose administered, and who subsequently developed Grade 4 CRS and discontinued treatment. Reported TEAEs were defined per MedDRA and CTCAE; CRS graded per ASTCT[2].

[1]Combined rash term includes 10 preferred terms: rash (unspecified, maculo-papular, erythematous, macular, morbilliform, pustular, pruritic, anal), erythema, dermatitis acneiform.

[2]Lee DW, et al. Biol Blood Marrow Transplant. 2019;25:625-638.

ALT, alanine aminotransferase; **ASTCT**, American Society for Transplantation and Cellular Therapy; **AST,** aspartate aminotransferase; **CTCAE,** Common Terminology Criteria for Adverse Events; **MedDRA,** Medical Dictionary for Regulatory Activities; **SAE,** serious adverse event; **TEAE,** treatment-emergent adverse event

- Low rate of dose reductions and treatment discontinuation due to TEAEs
- Events were predominately confined to the priming dose period
- Most common Grade ≥3 TEAEs were asymptomatic, transient transaminase increases

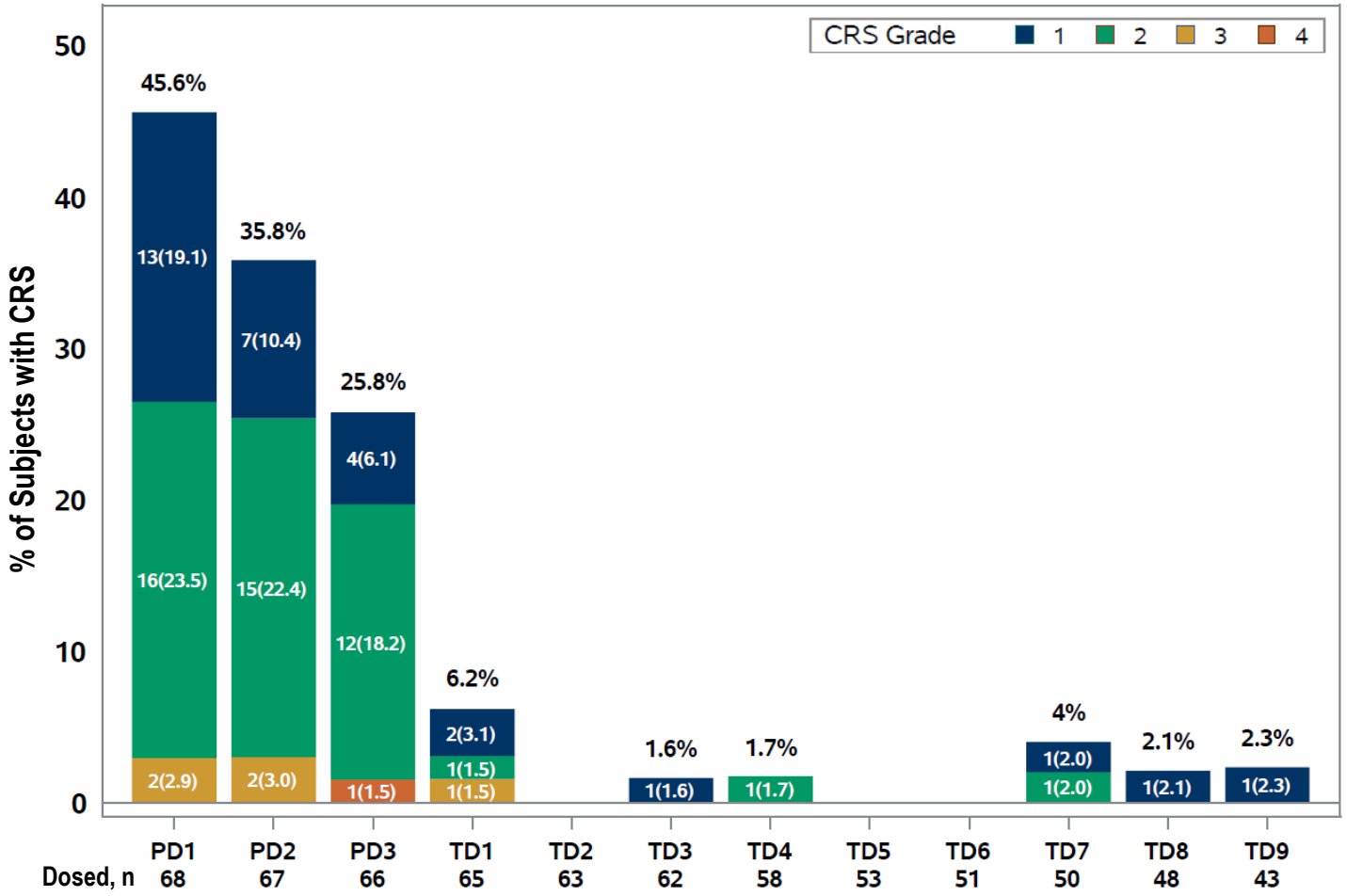
TEAEs reported in >25% Subjects by Maximum Severity Grade

Expansion Doses (n=68)	Any Incidence		>Day 29 Onset	
Preferred Term, n (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Rash (combined term)[1]	62 (91.2)	15 (22.1)	20 (29.4)	2 (2.9)
Cytokine release syndrome	46 (67.6)	4 (5.9)	12 (17.6)	1 (1.5)
ALT increased	36 (52.9)	23 (33.8)	12 (17.6)	7 (10.3)
Nausea	35 (51.5)	-	9 (13.2)	-
AST increased	33 (48.5)	24 (35.3)	10 (14.7)	6 (8.8)
Oedema peripheral	31 (45.6)	-	11 (16.2)	-
Vomiting	30 (44.1)	-	7 (10.3)	-
Diarrhoea	28 (41.2)	2 (2.9)	9 (13.2)	2 (2.9)
Fatigue	27 (39.7)	-	11 (16.2)	-
Headache	23 (33.8)	-	10 (14.7)	-
Hypophosphataemia	20 (29.4)	1 (1.5)	8 (11.8)	-
Hypotension	20 (29.4)	5 (7.4)	3 (4.4)	1 (1.5)
Pruritus	19 (27.9)	-	7 (10.3)	-
Chills	18 (26.5)	-	11 (16.2)	-
Cough	18 (26.5)	-	10 (14.7)	-

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Cytokine release syndrome (CRS)

CRS by Max Grade & Dose (n=68)



- CRS was predominately low-grade and occurred during priming
- No dose delays and one treatment discontinuation due to CRS
- Premedications for XmAb819:
  - Acetaminophen, diphenhydramine, and IV normal saline
  - Dexamethasone prior to priming doses
  - Tocilizumab prior to priming dose 1 (PD1)
- Graded per ASTCT consensus criteria; managed per institutional standards, or NCCN guidelines when local standards were absent

Subjects who received ≥1 protocol-specified dose of XmAb819 were included in the safety analysis. Data cut-off: **01 September 2026.** Excludes 1 participant who experienced approximately 10-fold higher exposure than intended at the first and only dose administered, and who subsequently developed Grade 4 CRS and discontinued treatment. Reported TEAEs were defined per MedDRA and CTCAE; CRS graded ASTCT[1]. Per-protocol PK samples were not collected for subject in plot (left) with reported Grade 4 CRS at priming dose 3; drug exposure could not be determined. Two subjects each experienced 2 events of Grade ≥3 CRS.

[1]Lee DW, et al. Biol Blood Marrow Transplant. 2019;25:625-638.

ASTCT, American Society for Transplantation and Cellular Therapy; **CRS,** cytokine release syndrome, **CTCAE,** Common Terminology Criteria for Adverse Events; **MedDRA,** Medical Dictionary for Regulatory Activities; **NCCN,** National Comprehensive Cancer Network; **PD**, priming dose, **TEAE,** treatment-emergent adverse event; **TD**, target dose

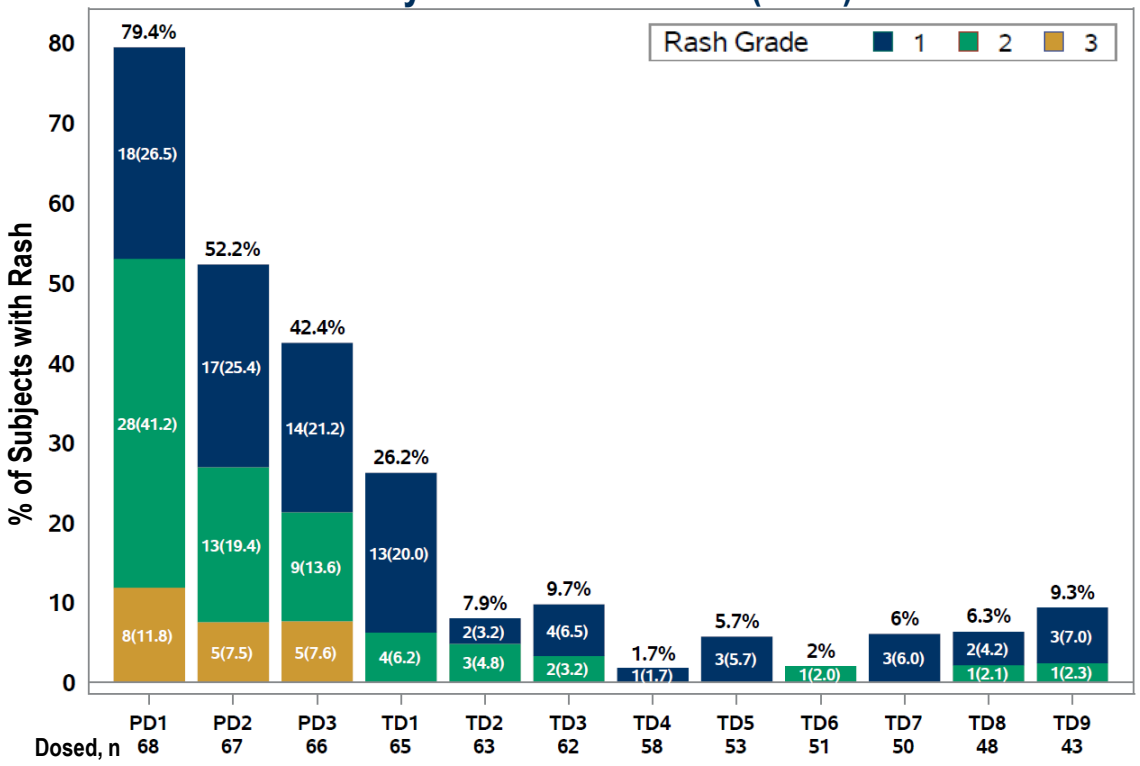
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Cytokine-driven adverse events

- Rash, an on-target effect due to ENPP3 expression on basophils and mast cells, is well managed with daily antihistamine (oral) and steroids (topical & oral).
- Dose delays due to rash occurred in 4.4% of subjects, with no treatment discontinuations.

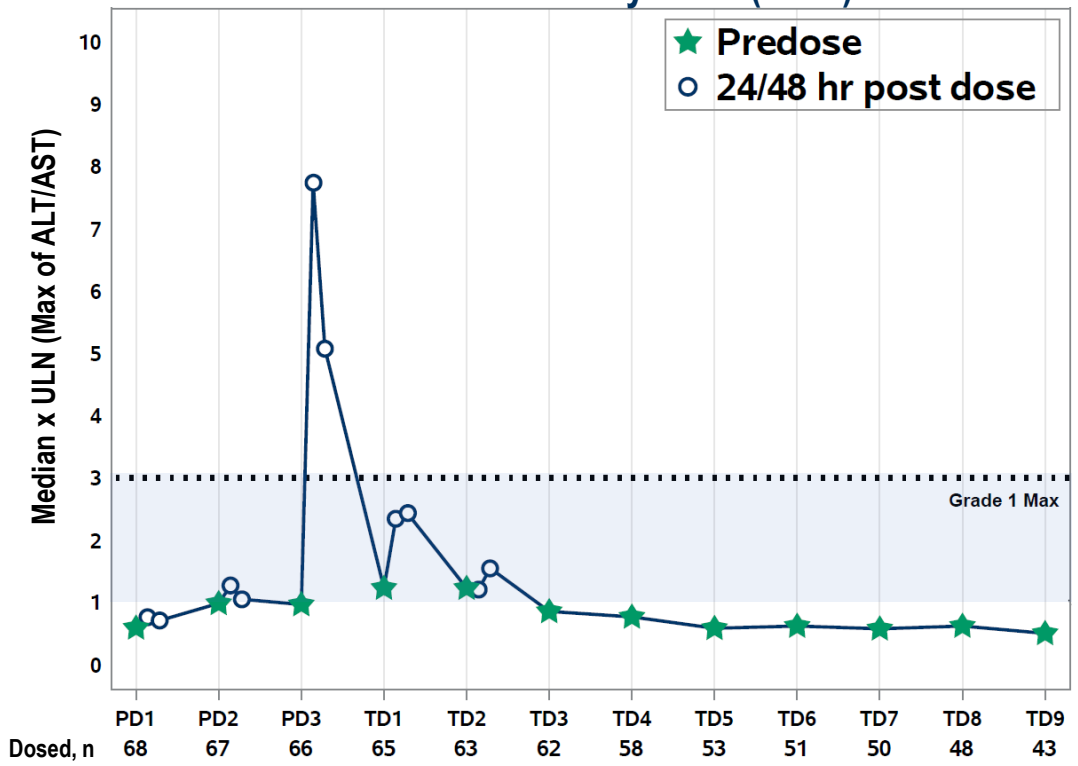
- Transaminase elevations were asymptomatic, transient, and self-limited, with a median time to resolution of 7 days and no clinical sequelae.
- Dose delays due to transaminase elevations occurred in 14.7% of subjects, with no treatment discontinuations.

Rash by Max Grade & Dose (n=68)



Combined rash terms (10 PTs): rash (unspecified, maculo-papular, erythematous, macular, morbilliform, pustular, pruritic, anal), erythema, dermatitis acneiform. Reported TEAEs were defined per MedDRA and CTCAE. Data cut-off: **01 September 2026.**

Transaminase kinetics by Dose (n=68)

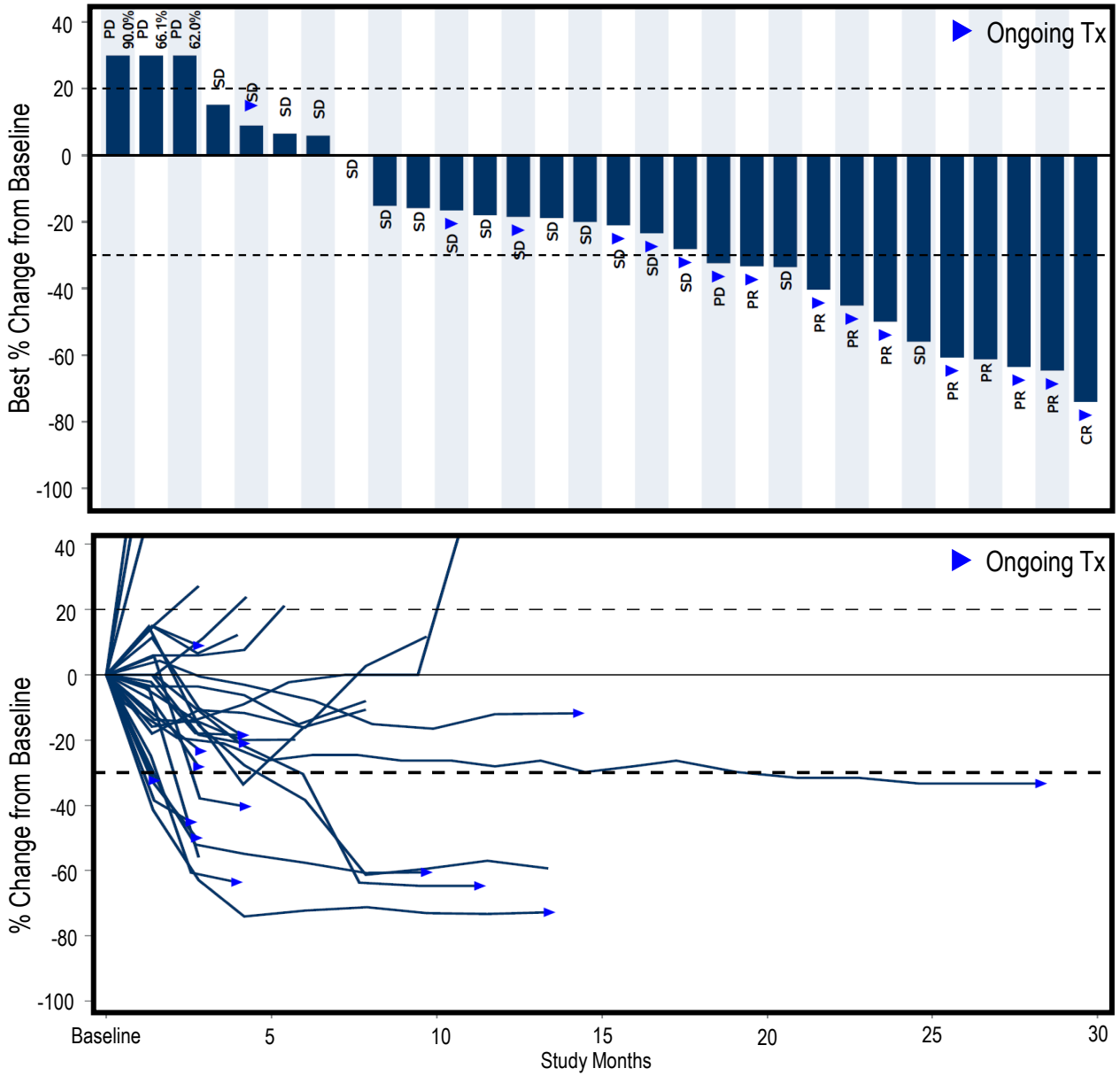


Median of the per-subject maximum of ALT and AST (central laboratory), expressed as ×ULN, among subjects with an available result at each timepoint. Data cut-off: **01 September 2026.**

PD, priming dose; **TD**, target dose

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Antitumor activity at target dose of 100 µg/kg



Efficacy Evaluable	100 µg/kg (n = 30)
Confirmed ORR, % (95% CI)	**30.0 (14.7, 49.4)**
BOR, n (%)	
CR	1 (3.3)
PR	8 (26.7)
SD	17 (56.7)
PD	4 (13.3)
DCR, % (95% CI)	86.7 (69.3, 96.2)
Median follow-up, months (range)	4.1 (1.1, 28.3)

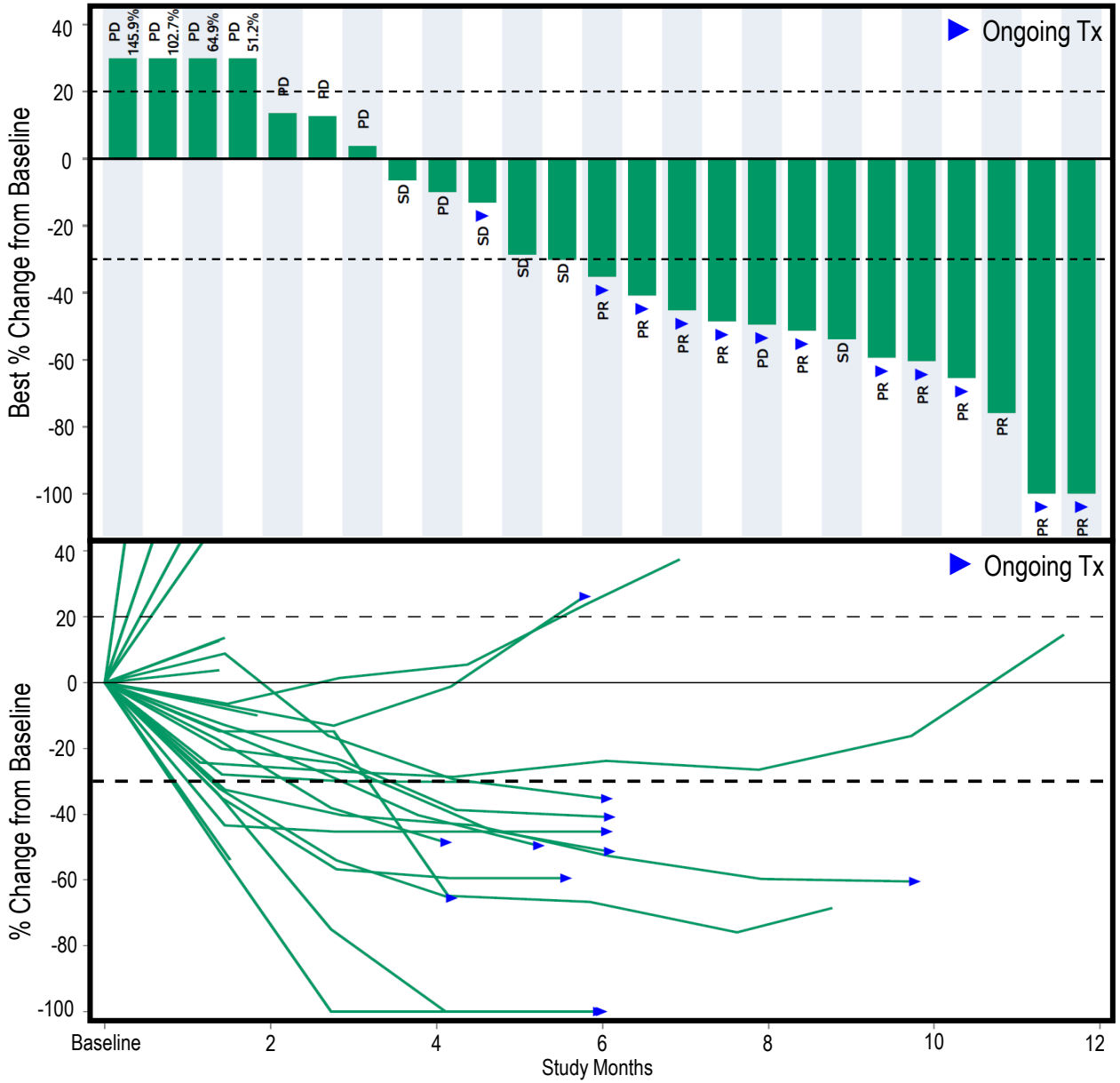
Efficacy analysis includes subjects with ≥1 protocol-specified dose of XmAb819 and ≥1 post-baseline tumor assessment. Confirmed responses per investigator assessment, RECIST v1.1. Data cut-off: **01 September 2026.** CR subject has two resolved lymph node target lesions with residual mass <10 mm.

BOR, best overall response; **CR**, complete response; **DCR,** disease control rate; **ORR,** objective response rate; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease; **Tx**, treatment

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Antitumor activity at target dose of 200 µg/kg



Efficacy Evaluable[1]	200 µg/kg (n = 25)
Confirmed ORR, % (95% CI)	**44.0 (24.4, 65.1)**
BOR, n (%)	
CR	-
PR	11 (44.0)
SD	5 (20.0)
PD	9 (36.0)
DCR, % (95% CI)	64.0 (42.5, 82.0)
Median follow-up, months (range)	4.5 (0.8, 11.6)

Efficacy analysis includes subjects with ≥1 protocol-specified dose of XmAb819 and ≥1 post-baseline tumor assessment. Confirmed responses per investigator assessment, RECIST v1.1. Data cut-off: **01 September 2026.**

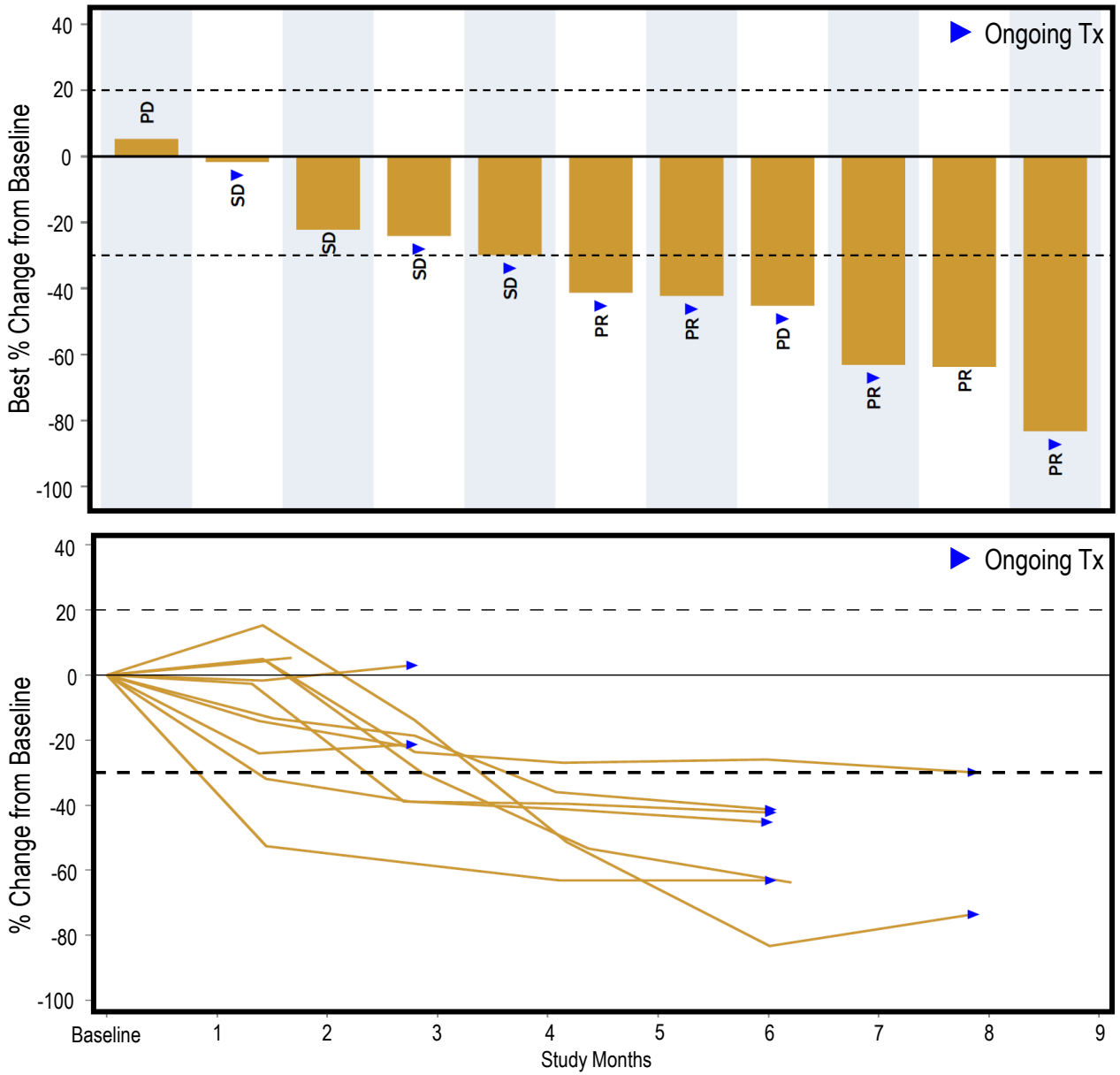
[1]Two subjects at 200 µg/kg discontinued treatment without a post-baseline response assessment and without documented progression.

BOR, best overall response; **CR**, complete response; **DCR,** disease control rate; **ORR,** objective response rate; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease; **Tx**, treatment

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Antitumor activity at target dose of 400 µg/kg



Efficacy Evaluable	400 µg/kg (n = 11)
Confirmed ORR, % (95% CI)	**45.5 (16.8, 76.6)**
BOR, n (%)	
CR	-
PR	5 (45.5)
SD	4 (36.4)
PD	2 (18.2)
DCR, % (95% CI)	81.8 (48.2, 97.7)
Median follow-up, months (range)	6.0 (1.4, 7.9)

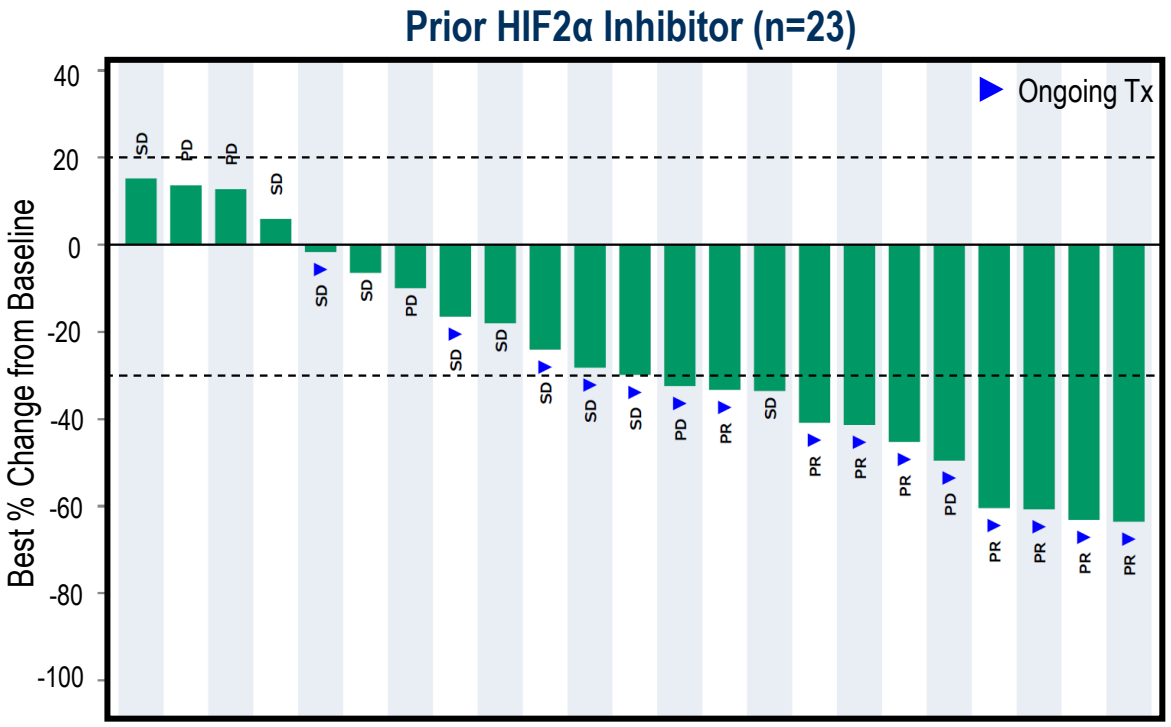
Efficacy analysis includes subjects with ≥1 protocol-specified dose of XmAb819 and ≥1 post-baseline tumor assessment. Confirmed responses per investigator assessment, RECIST v1.1. Data cut-off: **01 September 2026.**

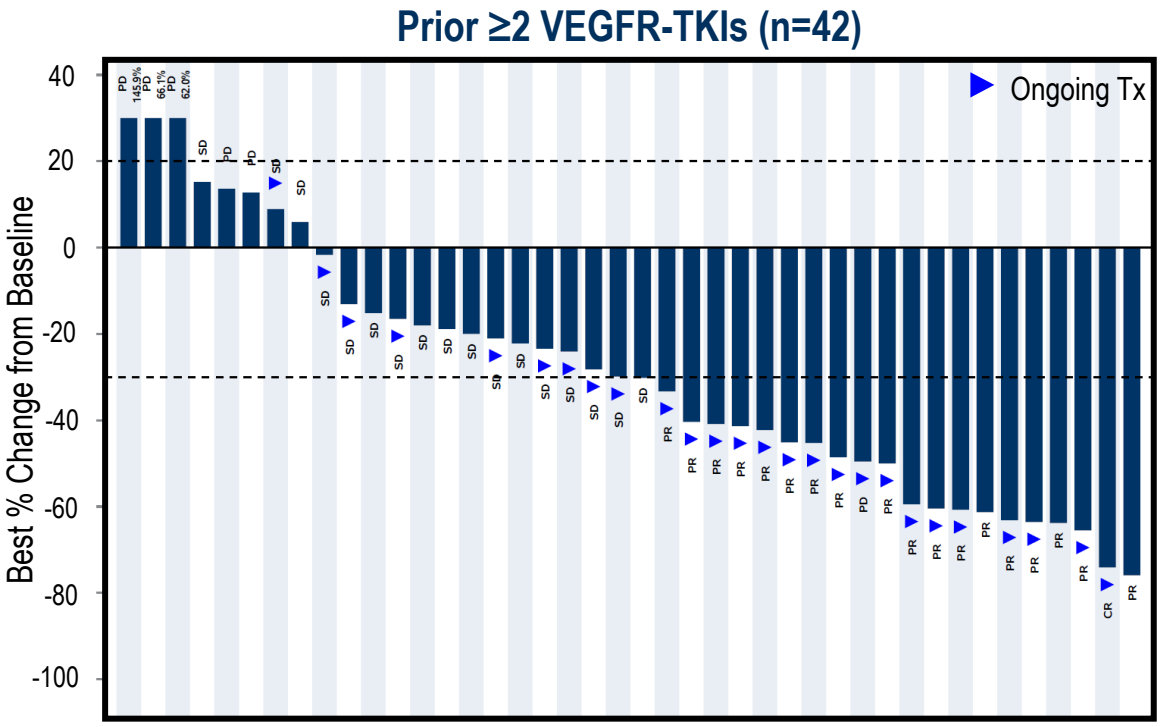
BOR, best overall response; **CR**, complete response; **DCR,** disease control rate; **ORR,** objective response rate; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease; **Tx**, treatment

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Antitumor activity of 100-400 µg/kg doses in prior therapy subgroups





Expanded Doses	Prior HIF2α (n = 23)	≥2 VEGFR-TKIs (n=42)
Confirmed ORR, % (95% CI)	**34.8 (16.4, 57.3)**	**45.2 (29.9, 61.3)**
DCR, % (95% CI)	78.3 (56.3, 92.5)	85.7 (71.5, 94.6)

Efficacy analysis includes subjects with ≥1 protocol-specified dose of XmAb819 and ≥1 post-baseline tumor assessment. Confirmed responses per investigator assessment, RECIST v1.1. Data cut-off: **01 September 2026.** CR subject has two resolved lymph node target lesions with residual mass <10 mm.

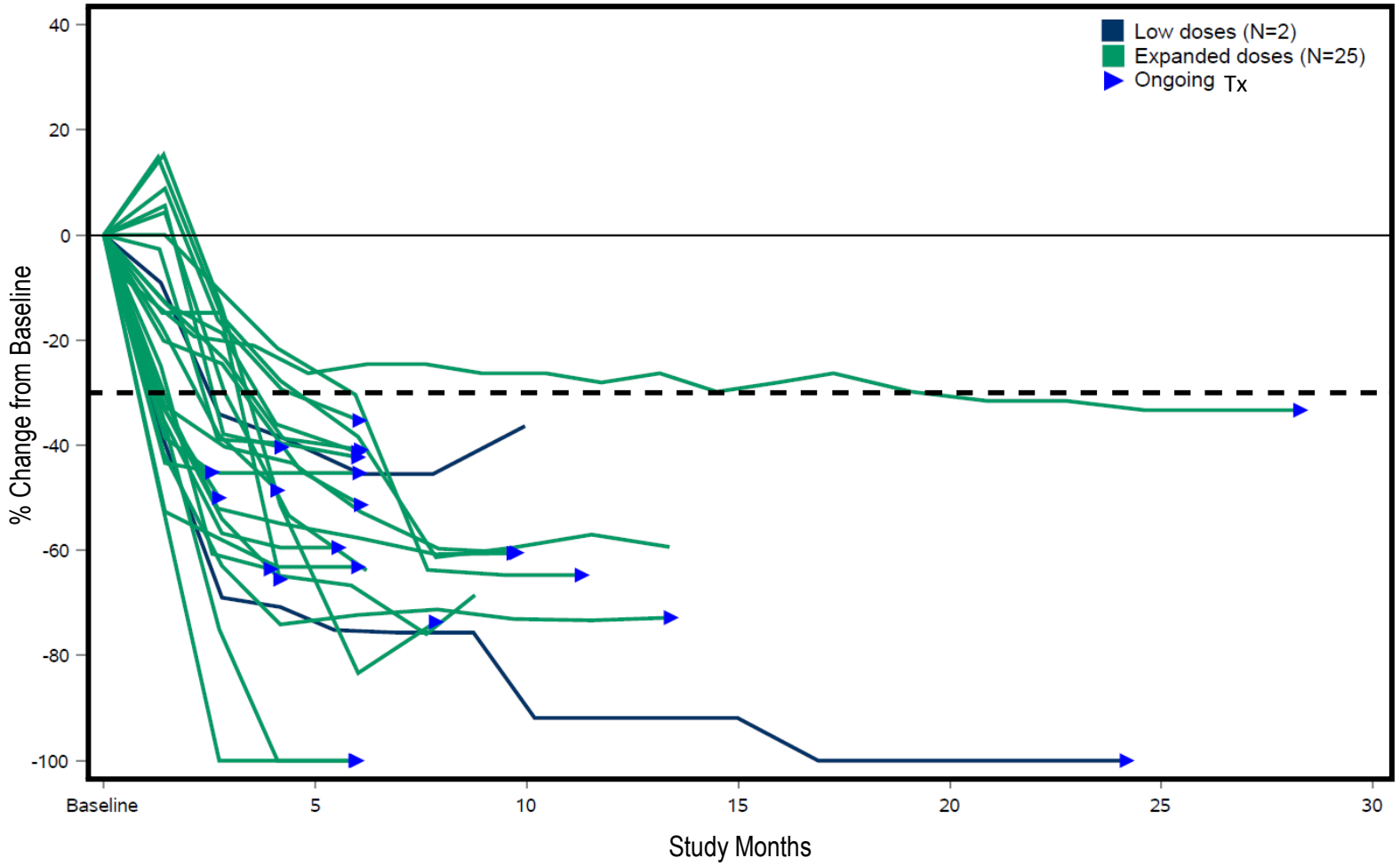
DCR, disease control rate; **HIF2α,** hypoxia-inducible factor 2-alpha; **ORR,** objective response rate; **TKI,** tyrosine kinase inhibitor; **Tx**, treatment; **VEGFR,** vascular endothelial growth factor receptor

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Depth and duration of responses

Spider Plot of Confirmed Responders Across All IV Doses (n = 27)



Responders	Expansion Doses (n=25)
Ongoing Responses, n (%)	19 (76.0)
Median TTR, months (range)	2.7 (1.3, 20.9)
Median time on treatment, months (range)	7.0 (3.4, 28.3)

Efficacy analysis includes subjects with ≥1 protocol-specified dose of XmAb819 and ≥1 post-baseline tumor assessment. Confirmed responses per investigator assessment, RECIST v1.1. Data cut-off: **01 September 2026.**

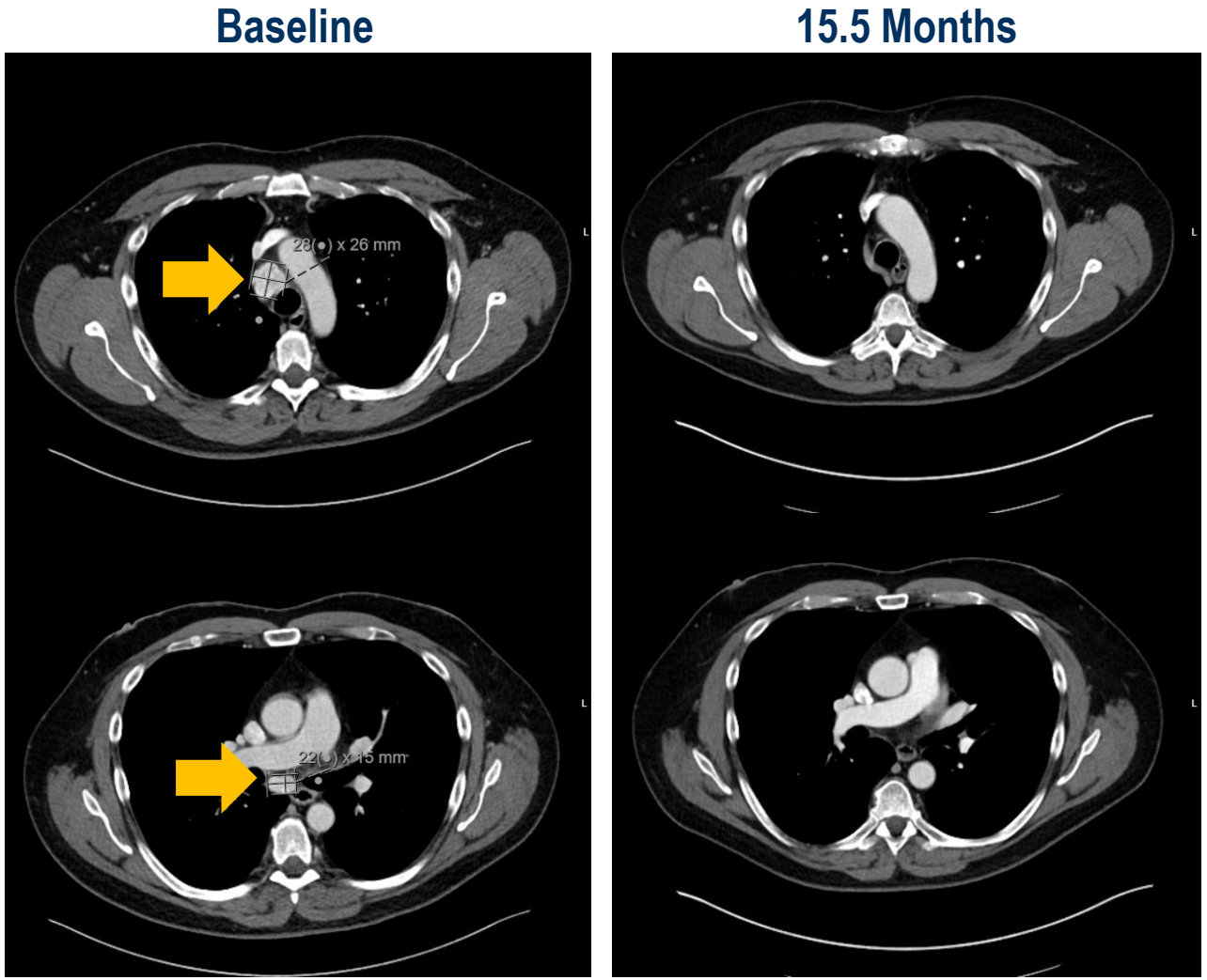
TTR, time to response; **Tx**, treatment

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Patient case study: Deepening of response over time

- **Background:** Male, 57 years old, RCC diagnosed 10 years ago, metastatic disease ~5 years ago
- **Prior therapy:** 2 prior therapy lines
  cabozantinib + nivolumab (1 mo) → progression
  & lenvatinib + everolimus (3 yrs) → progression
- **Baseline:** Two enlarged mediastinal lymph nodes
  both > 2 cm longest diameter
  multiple small lung and pancreas lesions
  membrane ENPP3+ <25% tumor cells
- **Response:** PR week 6, deepened to CR week 42
  normalization of lymph nodes
  disappearance of lung and pancreas lesions
- **Treatment and response ongoing at month 16**



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Conclusions

- XmAb819 (ENPP3 x CD3) showed meaningful antitumor activity in patients with advanced ccRCC.
- Antitumor activity was observed in a dose-dependent manner, with a cORR of 30% at 100 µg/kg, 44% at 200 µg/kg, and 45% at 400 µg/kg, and a majority of responses ongoing at data cut.
- Consistent activity in subgroups with prior exposure to HIF2α inhibitors (cORR 35%) and ≥2 VEGFR-TKIs (cORR 45%).
- These data support continued development of XmAb819 as a monotherapy for advanced clear cell RCC and evaluation of rational combination strategies in earlier lines of treatment.

cORR, confirmed objective response rate; **HIF2α,** hypoxia-inducible factor 2-alpha; **TKI,** tyrosine kinase inhibitor; **VEGF,** vascular endothelial growth factor receptor

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- The patients and their families and caregivers who made this study possible
- The investigators of the XmAb819-01 trial
- The clinical study teams
- This study is sponsored by Xencor, Inc.

Evaluation of XmAb819 in papillary RCC, colorectal cancer, and NSCLC expansion cohorts is now ongoing - NCT05433142

Contact: 819-01info@xencor.com

Clinicaltrials.gov
NCT05433142

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