CX-2029, a PROBODY Drug Conjugate Targeting CD71 (Transferrin Receptor): Results From a First-in-Human study (PROCLAIM-CX-2029) in Patients With Advanced Cancer

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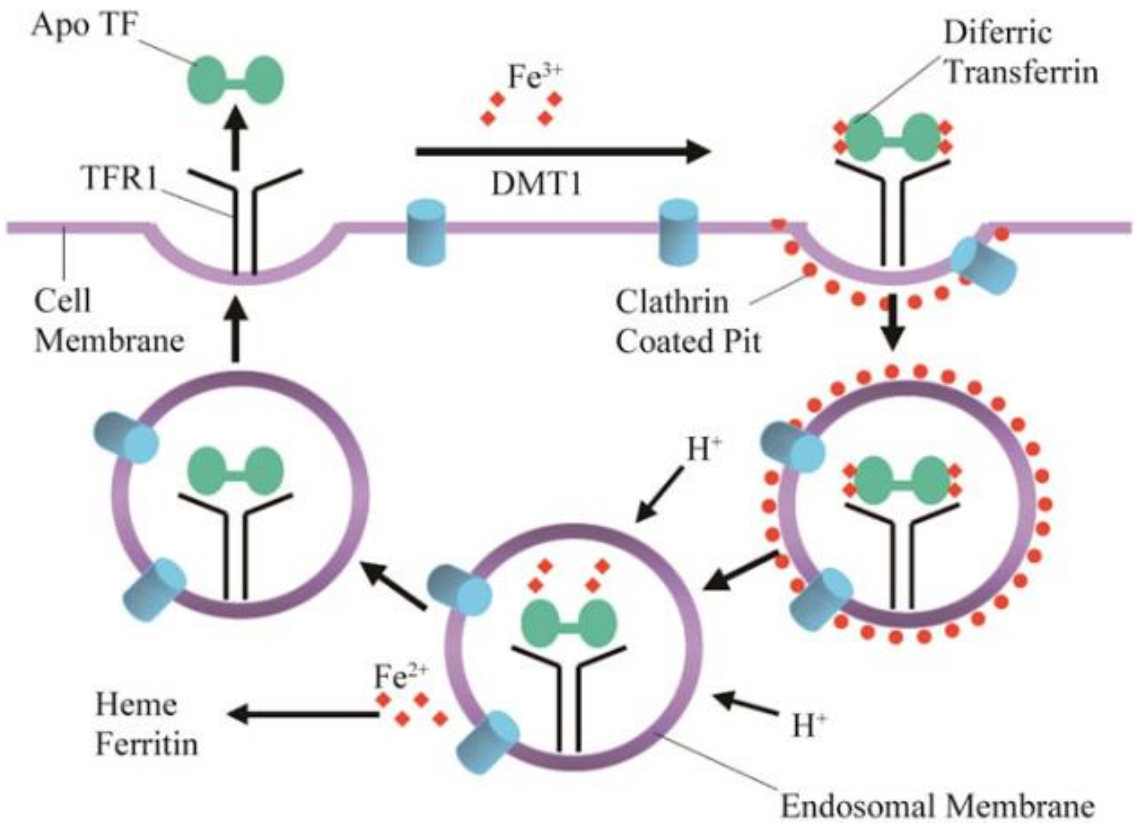
PROBODY Therapeutics: Investigating Undruggable Targets

- CD71 (transferrin receptor 1): attractive target for a PROBODY drug conjugate
  - CD71 is a transmembrane glycoprotein that efficiently internalizes iron-bound transferrin
  - Highly expressed on malignant cells
  - Expressed in healthy tissue with high iron requirements (e.g., rapidly dividing cells; hematopoietic precursors)
- CD71 expression in normal cells prohibits development of a traditional antibody drug conjugate (ADC) due to lethal on-target toxicity
- Probody therapeutics: recombinant antibody prodrugs designed to remain inactive in healthy tissue; activated in the tumor microenvironment by tumor-associated proteases



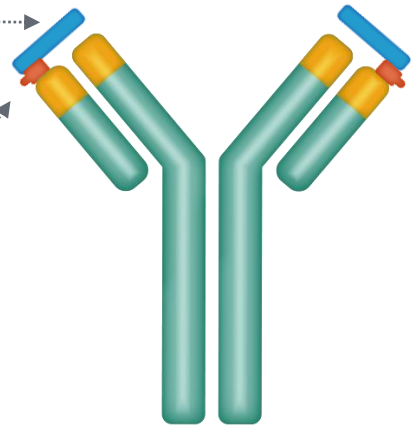
Elliott and Head. *J Cancer Ther. 2012;3:278-311.*

CX-2029: Probody Drug Conjugate Against CD71 With MMAE Warhead

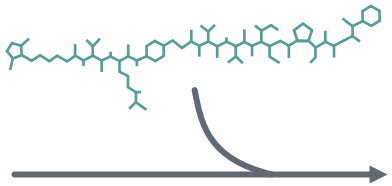
MONOMETHYL AURISTATIN E (MMAE):
POTENT CYTOTOXIC MICROTUBULE INHIBITOR, BLOCKING CELL DIVISION

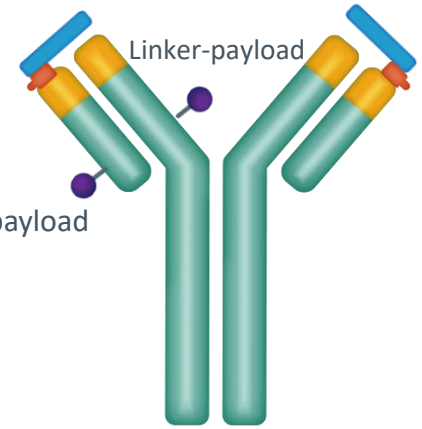
Mask prevents/ significantly reduces binding in normal tissue

Proteases cleave **substrate,** remove mask and allow target engagement in the TME



Linker-payload
mc-vc-PAB-MMAE





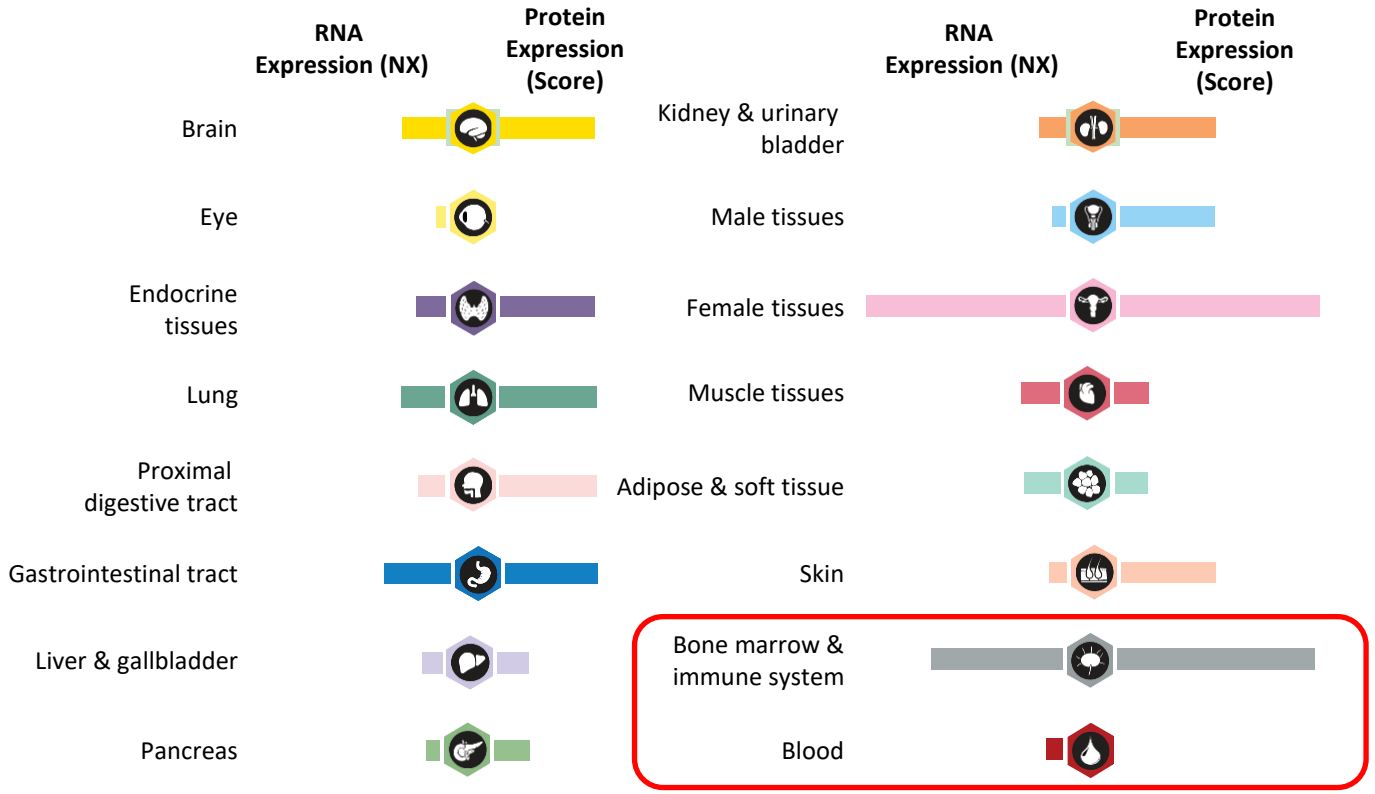
CD71- DIRECTED PROBODY

CX-2029 PDC

TME, tumor microenvironment.

Expression of CD71 in Healthy Tissue and Multiple Cancers

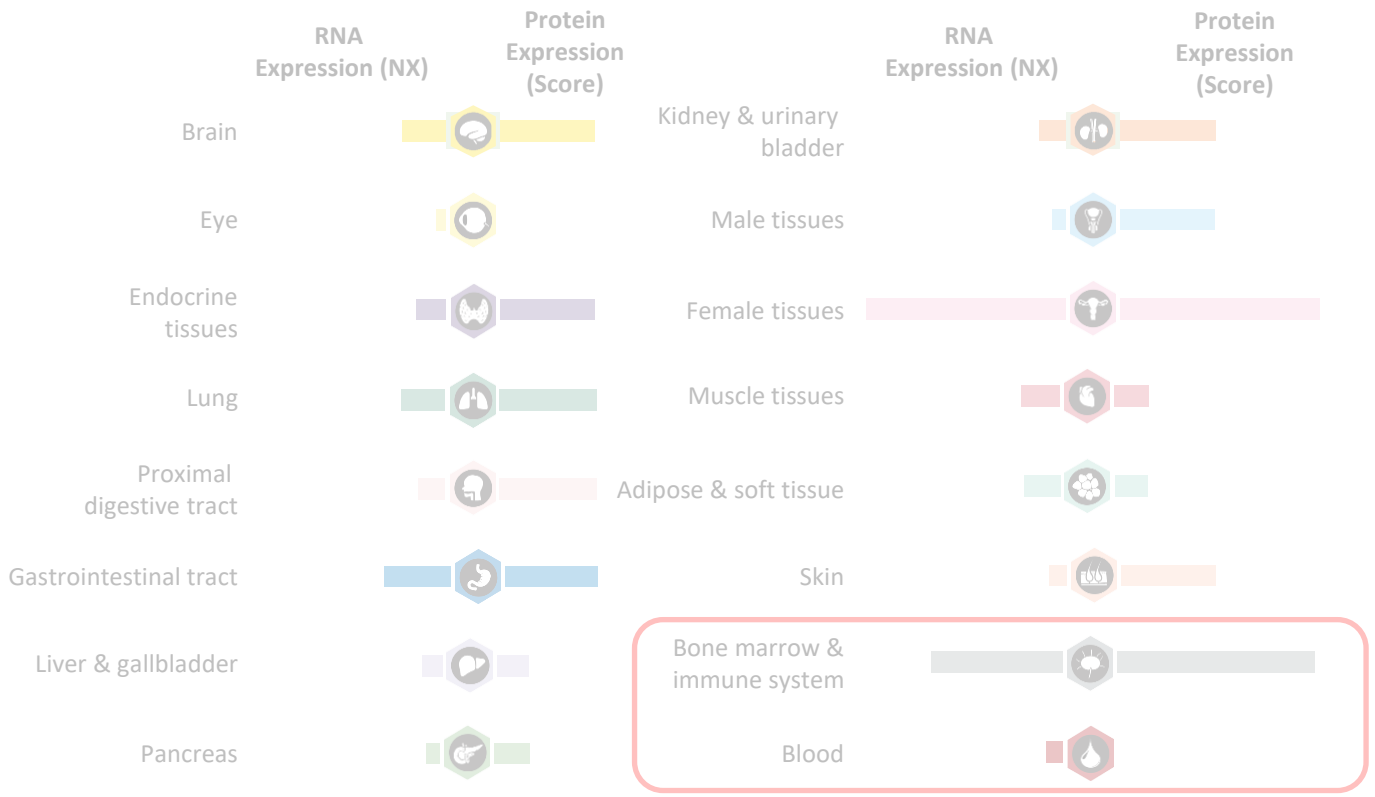
RNA and Protein Expression in Healthy Tissue



Adapted from The Human Protein Atlas
RNA and Protein Expression Summary/TRC available from proteinatlas.org/ENSG00000072274-TFRC/tissue.

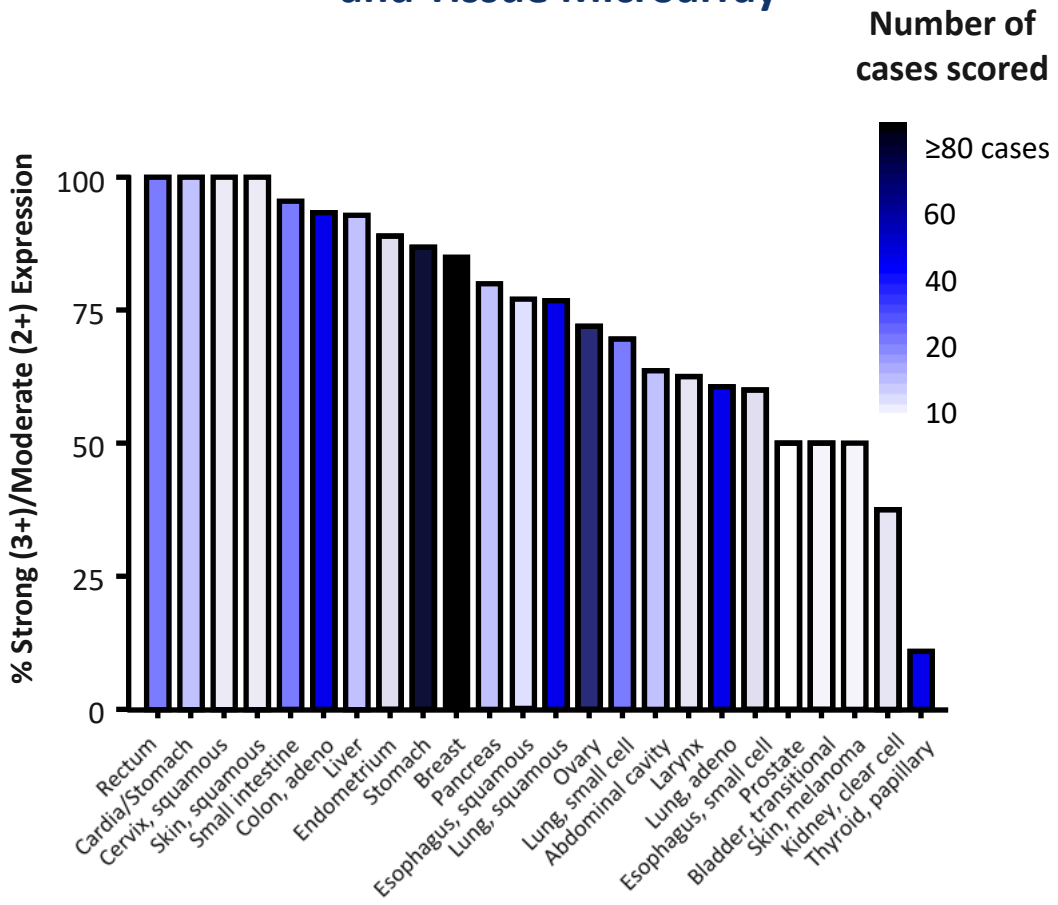
Expression of CD71 in Healthy Tissue and Multiple Cancers

RNA and Protein Expression in Healthy Tissue



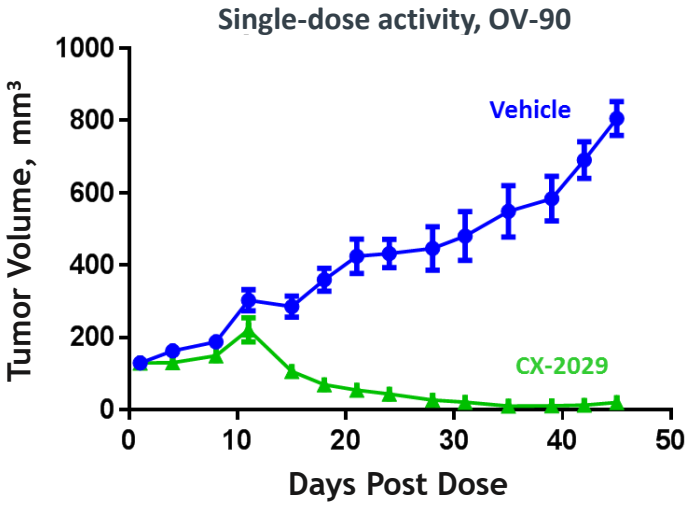
Adapted from The Human Protein Atlas
RNA and Protein Expression Summary/TRC available from proteinatlas.org/ENSG00000072274-TFRC/tissue.

Expression by IHC using Commercial Antibody and Tissue Microarray



Probody Platform: Enabling CD71 as a Drug Conjugate Target

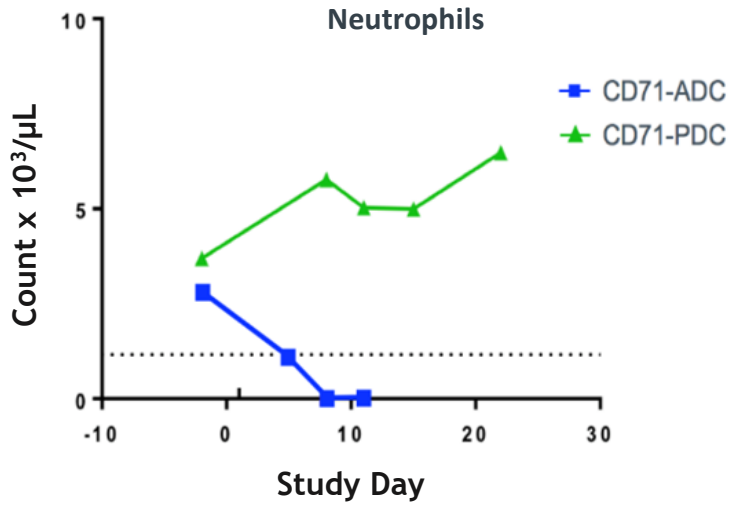
PDC REGRESSES TUMORS AFTER A SINGLE DOSE IN MICE



PDC HAS EFFICACY ACROSS MULTIPLE CELL LINE / PDX NON-CLINICAL MODELS

Models Type	Regression or Stasis
Cell-line derived (unselected)	15/21 (71%)
Patient-derived (high expressing)	30/36 (83%)

IN NON-HUMAN PRIMATES, PDC CREATES THERAPEUTIC WINDOW



- CX-2029 demonstrates broad potent activity in mouse tumor models, suggesting proteolytic cleavage, unmasking, and subsequent CD71 target engagement with effective MMAE delivery
- Unmasked CD71 ADC is tolerated in cynomolgus monkeys at 0.6 mg/kg but is lethal (neutropenic sepsis) at 2.0 mg/kg; CX-2029 is well tolerated up to 6 mg/kg, demonstrating an improved safety window
- Toxicities observed in monkey were predominantly hematopoietic, consistent with a MMAE payload

Phase 1 Dose-Escalating Clinical Trial

Starting Dose

- Given nonclinical toxicity, broad expression of CD71, and novelty of target and platform, the starting dose was ~1/20 the HNSTD in the monkey
- Predicted toxicities (based on MMAE payload): hematopoietic suppression, neuropathy
- Nonclinical PK and toxicology predicted dose range of 2–4 mg/kg in patients

Key Eligibility Criteria

- Metastatic or locally advanced unresectable solid tumor
- ECOG 0 or 1
- Archival tissue or biopsy available for tissue analyses
- Stable brain metastases permitted

Exclusions:

- Transfusion-dependent anemia or iron metabolism disorders
- Grade 2 or higher neuropathy

Intravenous Dose (every 3 weeks)	TOTAL (n)
0.1 mg/kg	3
0.25 mg/kg	3
0.5 mg/kg	6
1.0 mg/kg	3
2.0 mg/kg	**8**
3.0 mg/kg	**12**
4.0 mg/kg	**6**
5.0 mg/kg	4

HNSTD: Highest non severely toxic dose.

Demographics and Exposure

	All Cohorts (n=45)
Age, median (min, max)	60 (31, 75)
Sex, male / female (%)	62 / 38
Number of prior cancer treatments, median (min, max)	3 (1, 16)
Baseline ECOG 0 / 1, %	29 / 71
CD71 staining,* n (%)	
High expression [2+/3+ by IHC]	15 (33)
Low expression [0/1+ by IHC]	16 (36)
Unknown	14 (31)
Tumor types, n (%)	
NSCLC	9 (20)
HNSCC	8 (18)
Colorectal cancer	7 (16)
Soft tissue sarcoma	4 (9)
Prostate cancer	3 (7)
Other**	14 (31)
Number of CX-2029 doses administered, median (min, max)	3 (1, 12)
Duration of exposure in weeks, median (min, max)	9 (3, 36)

*CD71 expression was defined by overall tumor staining using a proprietary antibody.
**Other tumor types include adenoid cystic carcinoma of parotid gland (n=2); ovarian cancer (n=2); cutaneous melanoma (n=1); endometrial cancer (n=1); hepatocellular carcinoma (n=1); mesothelioma (n=1); ocular melanoma (n=1); oncocytic carcinoma of parotid gland (n=1); pancreatic cancer (n=1); perivascular epithelioid cell tumor (n=1); thymoma/thymic cancer (n=1); thyroid cancer (n=1).

Adverse Event Overview

	Patients, n (%)				
	CX-2029 0.1–1.0 mg/kg (n=15)	CX-2029 2.0 mg/kg (n=8)	CX-2029 3.0 mg/kg (n=12)	CX-2029 4.0 mg/kg (n=6)	CX-2029 5.0 mg/kg (n=4)
Any TEAE, n (%)	15 (100)	8 (100)	12 (100)	6 (100)	4 (100)
Related to CX-2029	14 (93.3)	8 (100)	12 (100)	6 (100)	4 (100)
TEAE grade 3+	6 (40)	6 (75)	11 (92)	6 (100)	4 (100)
Related to CX-2029	4 (27)	5 (63)	8 (67)	5 (83)	4 (100)
TEAE leading to CX-2029 discontinuation	2 (13)	0	0	0	0
Related to CX-2029	1 (7)*	0	0	0	0
Cycle 1 dose-limiting toxicity	0	0	0	2 (33)[1,2]	2 (50) [3,4]
Late-onset dose-limiting toxicity**	3/15 (20)	2/7 (29)	3/12 (25)	4/5 (80)	1/2 (50)
Serious TEAE	3 (20)	2 (25)	5 (42)	3 (50)	4 (100)
Related to CX-2029	2 (13)	0	1 (8)	2 (33)	3 (75)
TEAE leading to death	0	0	0	0	0

*One patient with hypoxia treated at a dose of 0.1 mg/kg.
**Percentages are based on number of subjects who had received at least 2 infusions

1. Grade 3 infusion-related reaction >6 hours
2. Grade 4 neutropenia; cycle 2 delayed 23 days due to persistent grade 3 anemia; ECOG status declined to 2
3. Grade 3 pancytopenia (thrombocytopenia, anemia, neutropenia) >7 days
4. Grade 3 febrile neutropenia

Treatment-Related AEs (>10% of Patients; N=45)

	Patients, n (%)				
	CX-2029 1.0 mg/kg (n=3)	CX-2029 2.0 mg/kg (n=8)	CX-2029 3.0 mg/kg (n=12)	CX-2029 4.0 mg/kg (n=6)	CX-2029 5.0 mg/kg (n=4)
Infusion-related reaction	3 (100)	8 (100)	9 (75)	6 (100)	3 (75)
Anemia	2 (67)	6 (75)	9 (75)	5 (83)	4 (100)
Neutropenia	0	0	4 (33)	3 (50)	3 (75)
Fatigue	1 (33)	2 (25)	2 (17)	2 (33)	2 (50)
Leukopenia	1 (33)	0	3 (25)	2 (33)	2 (50)
Nausea	0	1 (13)	4 (33)	2 (33)	0
Decreased appetite	1 (33)	0	1 (8)	1 (17)	1 (25)
Vomiting	0	0	3 (25)	0	1 (25)

Infusion-related reactions (IRRs): not dose-dependent

- Starting in 0.5 mg/kg cohort, pre-medications were required (H_1/H_2 blockers, acetaminophen, methylprednisolone)
- 39 of 45 patients (87%) experienced a total of 68 IRRs (3 patients with Grade 3)
  - ~Half of these (19 patients) had only 1 IRR at the first infusion
- In general, IRRs occur within 2–3 hours from start of infusion and resolve within 2–3 hours; supportive care: antihistamines, meperidine, corticosteroids and slowing the rate of infusion

Analysis combines Preferred Terms (e.g., “neutropenia” and “decreased neutrophil count”).

Treatment-Related AEs (>10% of Patients; N=45)

	Patients, n (%)				
	CX-2029 1.0 mg/kg (n=3)	CX-2029 2.0 mg/kg (n=8)	CX-2029 3.0 mg/kg (n=12)	CX-2029 4.0 mg/kg (n=6)	CX-2029 5.0 mg/kg (n=4)
Infusion-related reaction	3 (100)	8 (100)	9 (75)	6 (100)	3 (75)
Anemia	2 (67)	6 (75)	9 (75)	5 (83)	4 (100)
Neutropenia	0	0	4 (33)	3 (50)	3 (75)
Fatigue	1 (33)	2 (25)	2 (17)	2 (33)	2 (50)
Leukopenia	1 (33)	0	3 (25)	2 (33)	2 (50)
Nausea	0	1 (13)	4 (33)	2 (33)	0
Decreased appetite	1 (33)	0	1 (8)	1 (17)	1 (25)
Vomiting	0	0	3 (25)	0	1 (25)

MMAE-predicted toxicity: anemia, neutropenia, thrombocytopenia

- Polatuzumab (grade 3 neutropenia 40%, anemia 11%)[1]
- Brentuximab (grade 3 neutropenia 20%, anemia 6%)[2]

MMAE-associated neuropathy: rarely seen to date (1 patient each with grade 1–2 neuropathy at 1 and 3 mg/kg)

- May be confounded by limited duration of CX-2029 therapy

1. Palanca-Wellis et al. *Lancet Oncol.* 2015;16:704. **2.** Younes et al. *J Clin Oncol.* 2012;30(18):2183.

Analysis combines Preferred Terms (eg, "neutropenia" and "decreased neutrophil count").

Treatment-Related Grade 3+ AEs; Transfusions

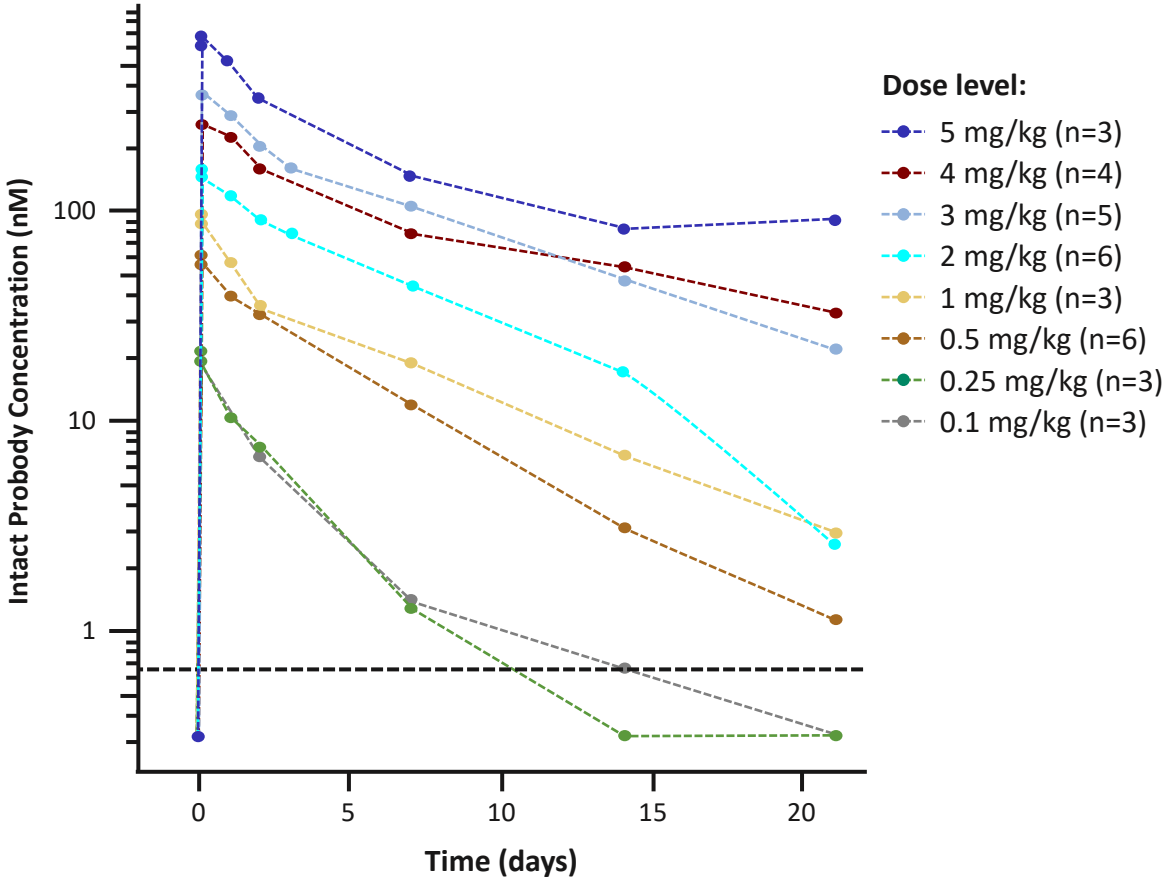
Treatment-Related Grade 3+ AEs (≥2 patients)	Patients, n (%)				
	CX-2029 1.0 mg/kg (n=3)	CX-2029 2.0 mg/kg (n=8)	CX-2029 3.0 mg/kg (n=12)	CX-2029 4.0 mg/kg (n=6)	CX-2029 5.0 mg/kg (n=4)
Anemia	1 (33)	5 (63)	7 (58)	5 (83)	4 (100)
Neutropenia	0	0	4 (33)	3 (50)	3 (75)
Leukopenia	0	0	1 (8)	2 (33)	2 (50)
Infusion-related reaction	0	1 (13)	0	1 (17)	0
PRBC Transfusions					
Patients with ≥1 RBC transfusion , n (%)	1 (33)	6 (75)	10 (83)	5 (83)	4 (100)
Number of RBC transfusions received, median	1	2	2	2	2
Time to first RBC transfusion, median, days	36	38	34	37	15

- No treatment-related deaths occurred
- Etiology of anemia is under active investigation

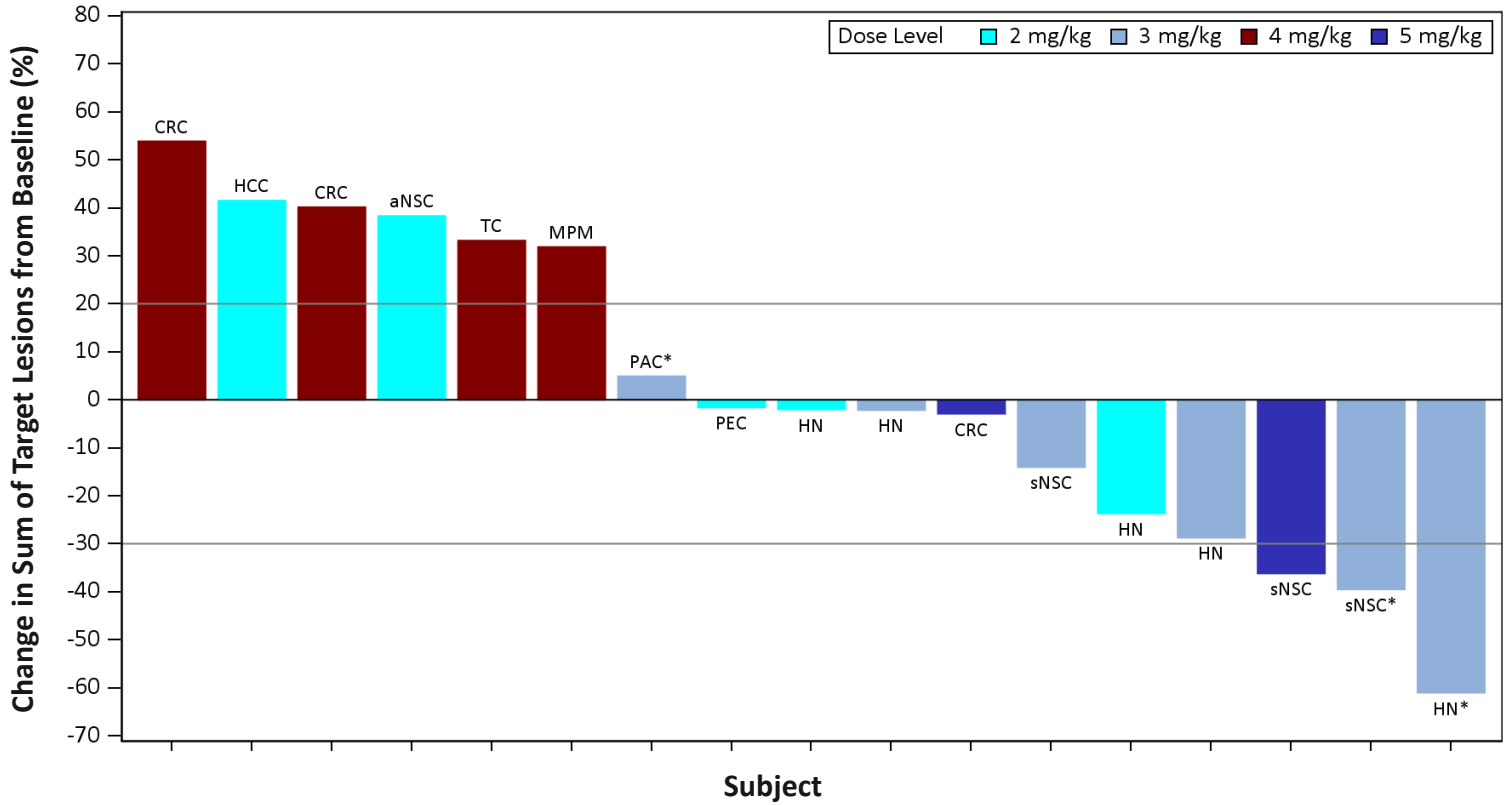
Analysis combines Preferred Terms (eg, “neutropenia” and “decreased neutrophil count”).

Pharmacokinetics

- Following 0.25–5.0 mg/kg, CX-2029 circulates predominantly as intact CX-2029 (>90%)
- For intact CX-2029:
  - No trends from dose-proportionality
  - Clearance 0.55–2.7 L/day
  - Volume of distribution 3.2–10.6 L
  - Terminal half-life 2.3–9.8 days
- Free MMAE circulates <4.3% of Total CX-2029



Waterfall Plot (Doses 2–5 mg/kg)



aNSC = non–small cell lung cancer (adenocarcinoma), CRC = colorectal cancer, HCC = hepatocellular carcinoma, HN = head and neck squamous cell carcinoma, MPM = malignant pleural mesothelioma, PAC = pancreatic cancer, PEC = perivascular epithelioid cell tumor, sNSC=non–small cell lung cancer (squamous cell carcinoma), TC = thyroid carcinoma.

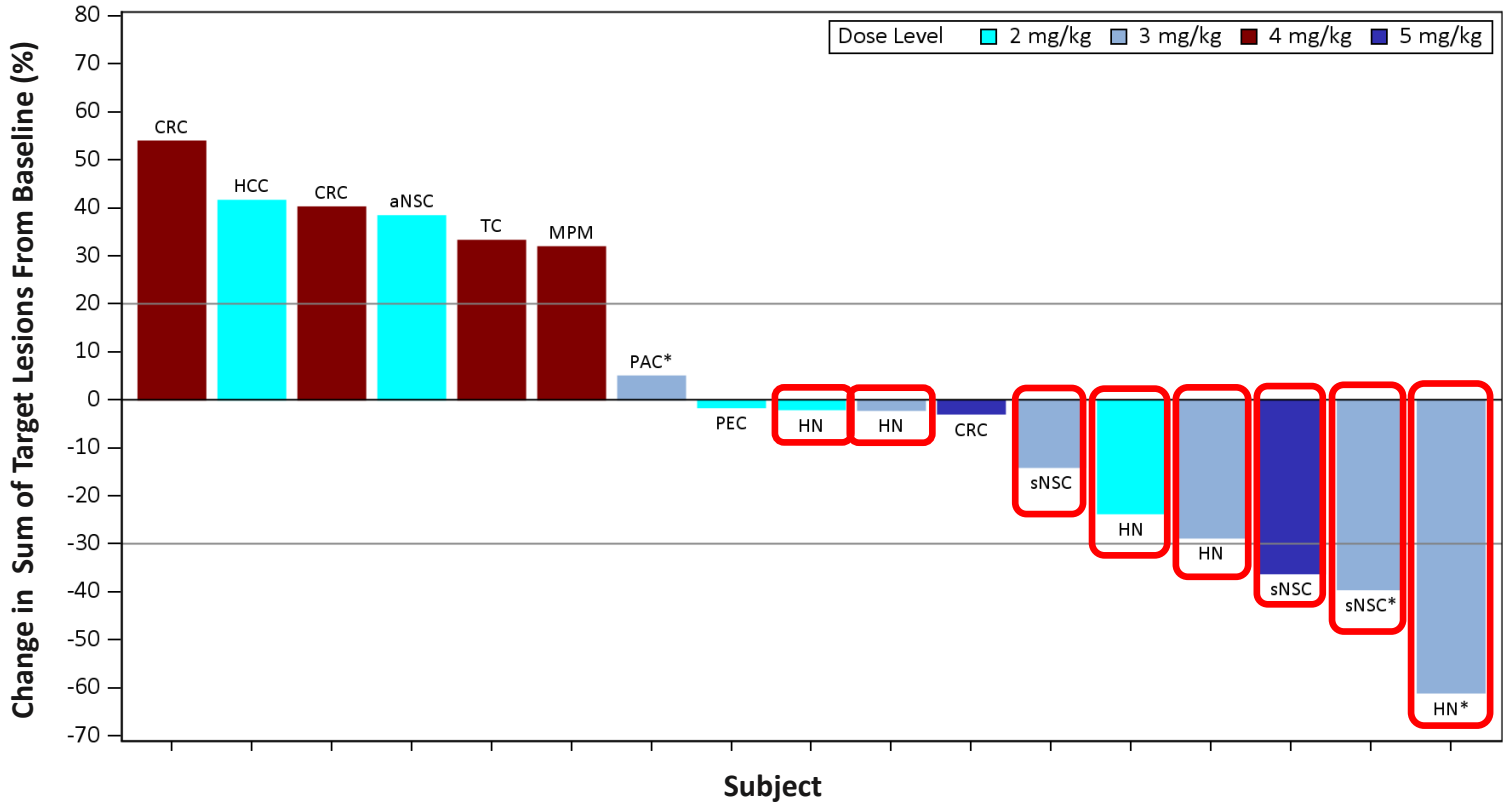
*Denotes subjects still on treatment.

13 patients not included due to (a) 5 patients ongoing without first on-study scan; (b) 6 patients discontinued without on-study scan; (c) 1 patient without measurable disease at baseline, and (d) 1 patient diagnosed with new lesion without target lesion(s) assessed.

All 3 patients with Target Lesions Shrinkage >30% are confirmed partial responses

Data cut-off: April 20, 2020.

Waterfall Plot (Doses 2–5 mg/kg)



Activity predominantly seen in patients with tumors of squamous histology

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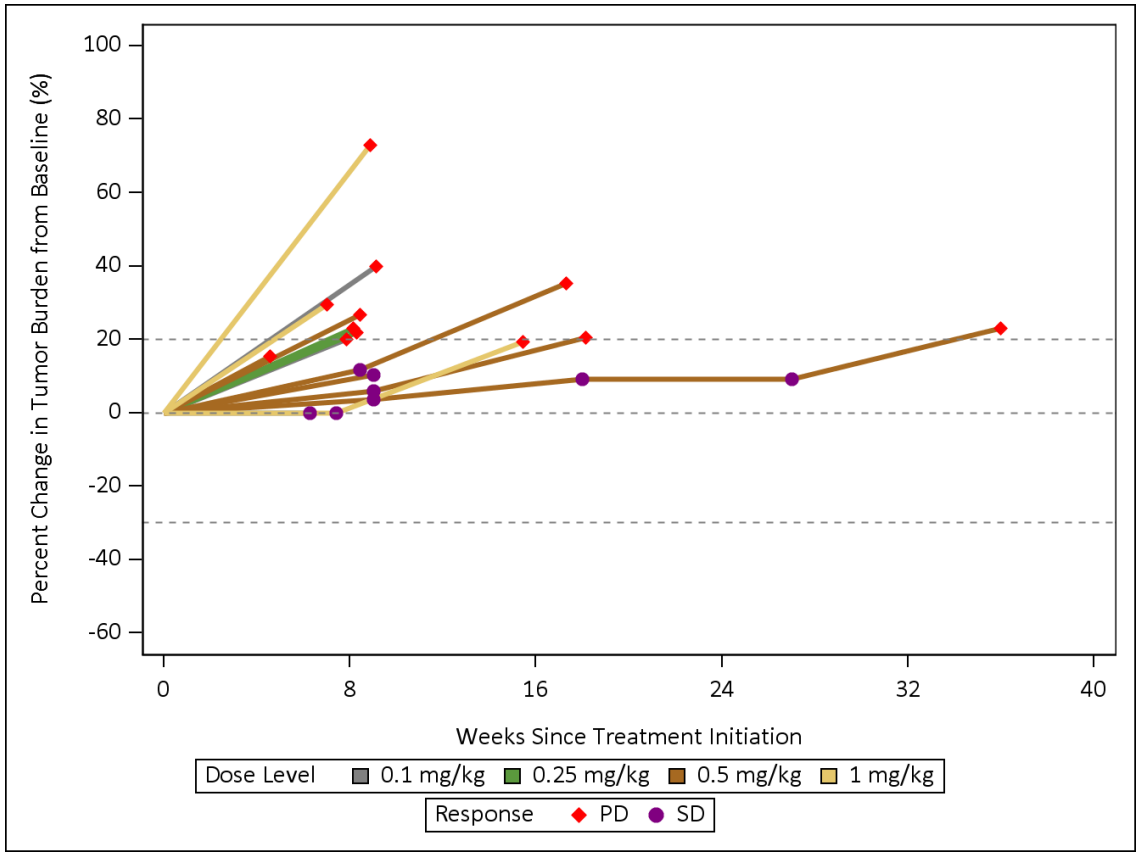
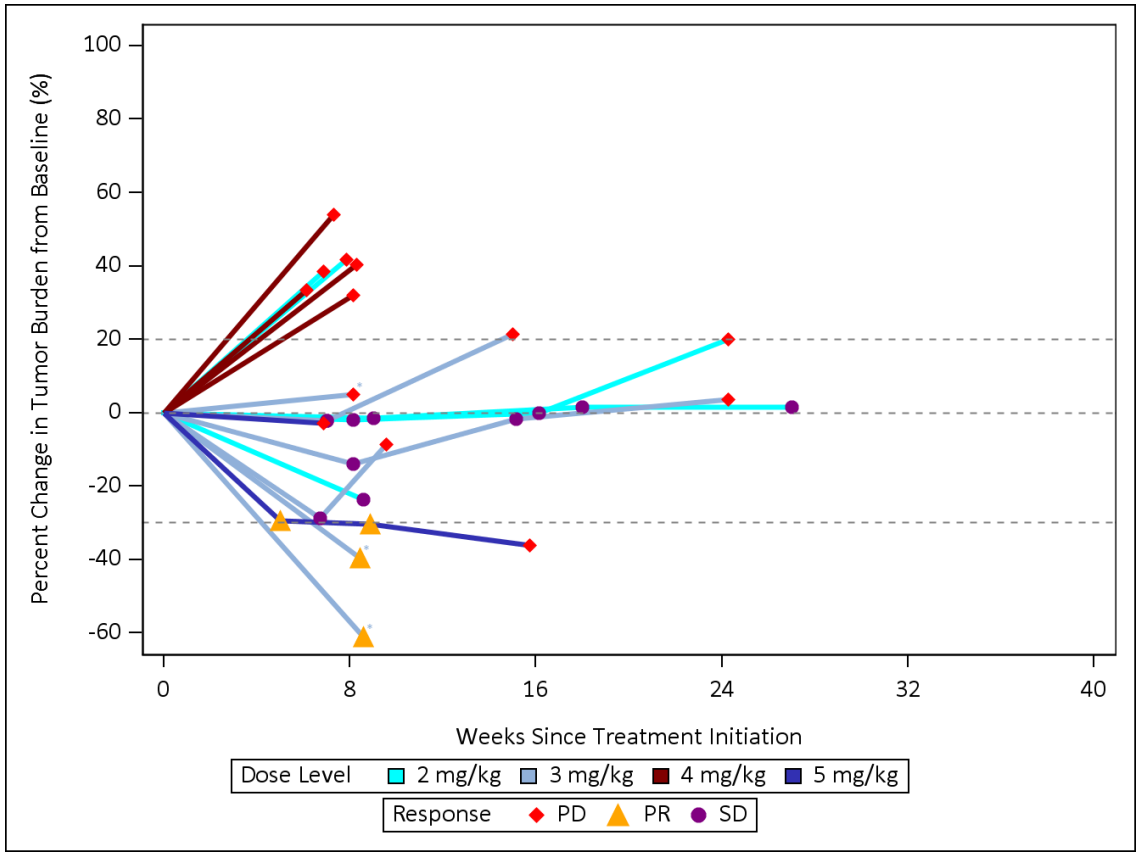
Spider Plot (Doses 0.1–1 and 2-5 mg/kg)

Clinical Activity at CX-2029 Doses ≥2 mg/kg





PD, progressive disease; PR, partial response; SD, stable disease.
*Patient on treatment as of data cut-off.

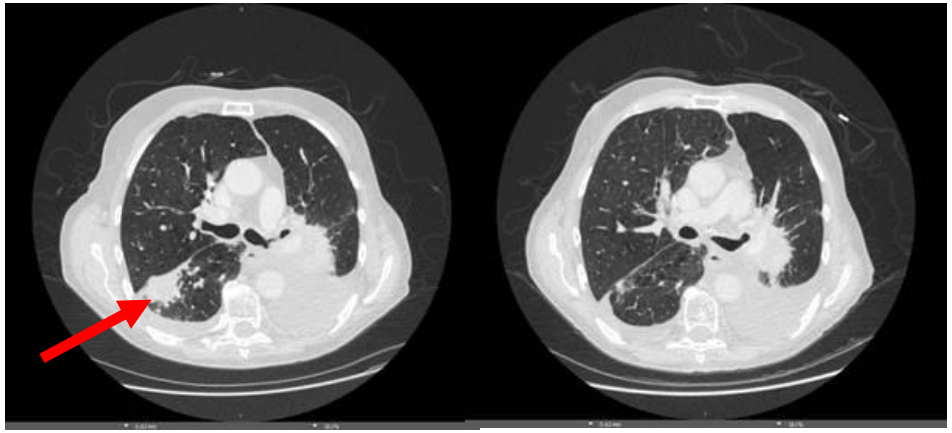
Data cut-off: April 20, 2020.

75-Year-Old Patient With Squamous NSCLC (3 mg/kg)

- **Patient:** diagnosed with stage III squamous NSCLC in August 2017
- **Prior therapy**: Carboplatin/paclitaxel with radiation (2 mo); durvalumab (10 mo); gemcitabine (2 mo); docetaxel/ramucirumab (8 mo; SD then PD)
- **Toxicity**: Cycle 2 and cycle 3 grade 3 anemia
- **Response**: confirmed partial response seen on Week 8 (12Mar10) and Week 16 (4May20) scans

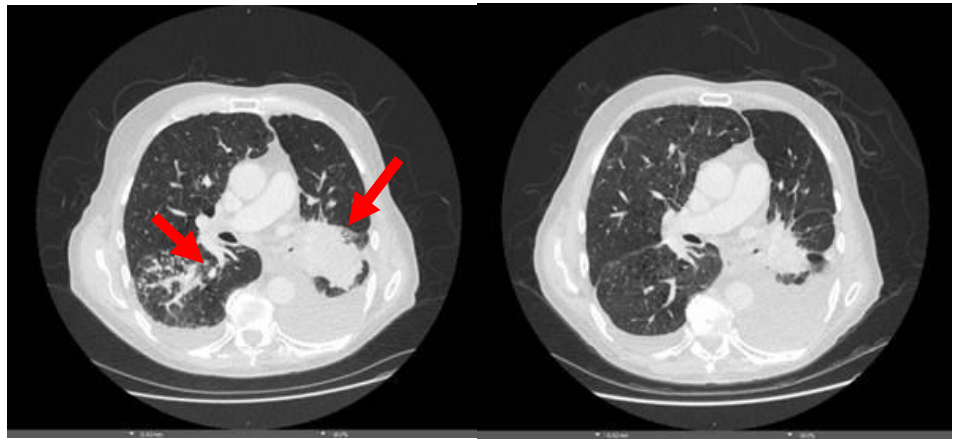
20Jan2020 12Mar2020

Near-resolution of right perifissural lesion (target lesion #2)



20Jan2020 12Mar2020

Improvement in LLL lesion (target lesion #1),
with marked improvement in RLL nodular lesions (nontarget lesions)



(Images are courtesy of Navid Hafez, MD)

Summary of Phase 1 Results

- Safety:
  - CX-2029 produces dose-dependent hematologic toxicities consistent with MMAE payload
  - Anemia: most common hematologic toxicity, also seen in non-clinical species

- CX-2029 at 3 mg/kg will be studied in the dose-expansion phase
  - No cycle 1 DLT; no discontinuation for toxicity
  - Manageable Grade 3 anemia; delayed/recurrent toxicity in 3 of 12 patients

- Clinical activity: observed at doses of 2 mg/kg and higher; consistent with PK predictions *(activity to date was observed in squamous histologies: head and neck; non–small cell lung cancers)*

Conclusions

- The results of first-in-human trial validates CD71 (transferrin receptor 1) as a viable therapeutic target in cancer

- Probody technology enables administration of a CD71 directed antibody drug conjugate at tolerable doses with clinical anti-tumor activity
  - CD71: a previously undruggable ADC target

- Safety profile and clinical activity support dose-expansion including cohorts of HNSCC and squamous NSCLC
  - Work ongoing regarding CD71 expression *vs* tumor regression

Acknowledgments

- We would like to extend our grateful thanks to our co-investigators, their research personnel, and our colleagues at CytomX Therapeutics, AbbVie and ICON
- Our sincere thanks to all patients and their caregivers who took part in this clinical trial

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Nehal Lakhani	START Midwest
Randy Sweis	University of Chicago

Investigator	Clinical site
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Rachel Sanborn	Providence Portland Medical Center
Hirva Mamdani	Barbara Ann Karmanos Cancer Institute
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