

Phase 1 Dose Escalation of CTX-8371, a novel PD-1xPD-L1 bispecific antibody, in patients with advanced malignancies post checkpoint inhibition

Authors: ¹Wang, Judy S, ²Russell, Jeffery, ³Perez, Cesar A, ⁴Ott, Patrick A, ⁵Switzer, Benjamin, ⁶Viray, Hollis, ⁷Ocasio Norat, Kelly, ⁷Warholc, Natalie, ⁷Sirard, Cynthia A, ⁷Schuetz, Thomas

Affiliations: 1. Florida Cancer Specialists/Sarah Cannon Research Institute- Sarasota, Sarasota, FL 2. Greco-Hainsworth Center for Research/Tennessee Oncology, Nashville, TN 3. SCRI at Florida Cancer Specialists, Orlando, FL 4. Dana-Farber Cancer Institute Boston, MA 5. Roswell Park Comprehensive Cancer, Buffalo, NY 6. Beth Israel Deaconess Medical Center, Boston, MA 7. Compass Therapeutics, Boston, MA

#2629

Background

- Cancer therapy has been transformed by immune checkpoint inhibition with antibodies targeting programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1). However, treatment options for patients who are resistant or refractory to the approved monospecific anti-PD-1/PDL-1 agents are often limited.
- CTX-8371 is a bispecific tetravalent antibody consisting of an anti-PD-1 immunoglobulin (IgG)1 with two anti-PD-L1 Fabs fused at the C-terminus of an aglycosylated Fc fragment through (G4S)4 linkers which block the PD-1/PD-L1 pathway by simultaneously binding PD-1 and PD-L1.
- In pre-clinical studies, CTX-8371 has demonstrated enhanced T-cell activation and function in addition to potent anti-tumor efficacy compared to other approved checkpoint inhibitor agents.¹

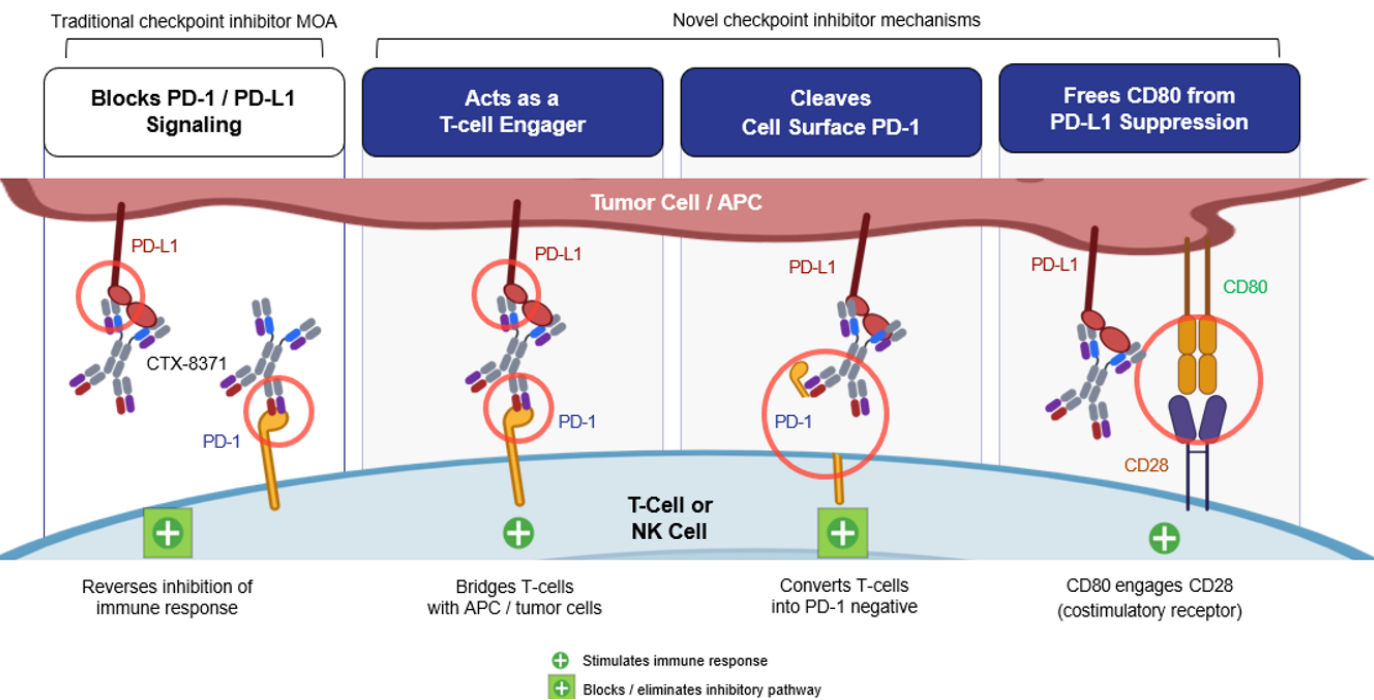


Figure 1: CTX-8371 Differentiated Mechanism of Action Leads to Enhanced T-Cell Activation

Phase 1 Study Design

Phase 1, open-label, first-in-human study investigating CTX-8371 in patients with metastatic or locally advanced malignancies. The study is being conducted in 2 cohorts: Dose Escalation and Dose Expansion. The study enrolled patients with Malignant Melanoma (MM), Head and Neck Squamous Cell Carcinoma (HNSCC), Non-Small Cell Lung Cancer (NSCLC), Triple-Negative Breast Cancer (TNBC), and Hodgkin's Lymphoma (HL).

CTX-8371 Administration: Patients receive CTX-8371 as an intravenous (IV) infusion at the assigned dose level once every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

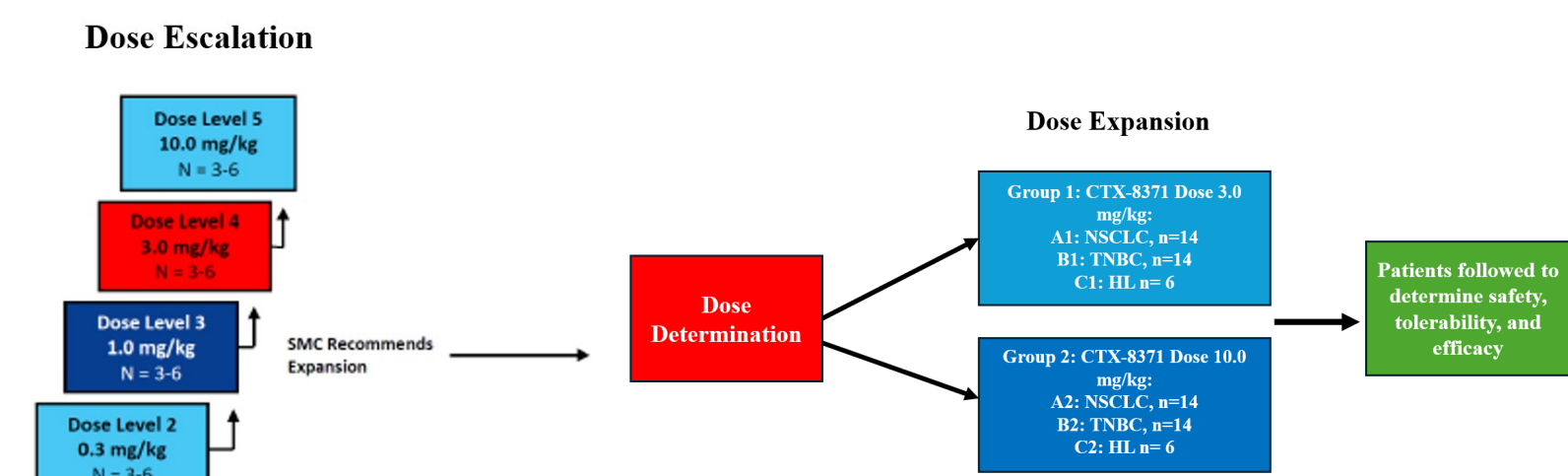


Figure 2: CTX-8371-001 Study Design

Dose Escalation Key Eligibility Criteria

- Patients with NSCLC, MM, and HNSCC must have progressed after a minimum of 2 doses of a PD-1/PD-L1 treatment, and study enrollment (C1D1) must be within 12 weeks of the last dose of the anti-PD-1/PD-L1 blocking antibody.
- Patients with TNBC must have received prior sacituzumab govitecan and if PD-L1 $\geq 10\%$ by CPS pembrolizumab with chemotherapy. Patients with HER2-low cancers (HER2 IHC 1+ or 2+/ISH negative) are excluded.
- Patients with HL must have received at least two prior systemic therapies, including brentuximab vedotin (if eligible) and a prior PD-1 inhibitor, and must have experienced less than a CR (Lugano 2014) to an anti-PD-1 treatment.
- Measurable disease per RECIST 1.1 (NSCLC, MM, TNBC, and HNSCC) or one measurable lesion > 1.5 cm for nodal, > 1.0 cm for extranodal FDG-avid disease by Lugano (2014) (HL).

Data presented has a **cut off date of 20-April-2026**. Study enrollment, baseline characteristics and safety is reported for both Dose Escalation and Dose Expansion. Dose Expansion PK and efficacy not reported as Expansion phase remains ongoing.

Baseline and Cancer Characteristics

Dose	Dose Escalation (n, %)					Dose Expansion			
	0.1 mg/kg (n=3)	0.3 mg/kg (n=4)	1.0 mg/kg (n=3)	3.0 mg/kg (n=8)	10 mg/kg (n=3)	3.0 mg/kg (n=4)	10 mg/kg (n=3)	Overall (n=7)	
Age years (median, range)	80 (72,81)	67 (60,75)	79 (74,86)	60 (45,62)	61 (61,78)	67 (45,86)	73 (62,82)	69.5 (67,72)	71 (62,82)
Sex									
Male	1 (33.3)	2 (50)	2 (66.7)	2 (50)	1 (33.3)	8 (47)	-	1 (33.3)	1 (14)
Female	2 (66.7)	2 (50)	1 (33.3)	2 (50)	2 (66.7)	9 (53)	4 (100)	2 (66.7)	6 (86)
Ethnicity									
Hispanic or Latino	--	--	--	2 (50)	1 (33.3)	3 (18)	1 (25)	1 (33.3)	2 (29)
Not Hispanic or Latino	3 (100)	4 (100)	3 (100)	2 (50)	2 (66.7)	14 (82)	3 (75)	2 (66.7)	5 (71)
Race									
White	3 (100)	4 (100)	3 (100)	4 (100)	3 (100)	17 (100)	3 (75)	2 (66.7)	5 (71)
African American	--	--	--	--	--	--	1 (25)	--	1 (14)
Other	--	--	--	--	--	--	1 (33.3)	1 (33.3)	1 (14)
ECOG									
0	--	--	1 (33.3)	--	1 (33.3)	2 (12)	--	--	--
1	3 (100)	4 (100)	2 (66.7)	4 (100)	2 (66.7)	15 (88)	4 (100)	3 (100)	7 (100)
DLT evaluable	3 (100)	3 (75)*	3 (100)	3 (75)*	3 (100)	15 (88)	N/A	N/A	N/A
Primary Malignancy									
NSCLC	2 (67.7)	1 (25)	1 (33.3)	1 (25)	2 (66.7)	7 (41)	2 (50)	1 (33.3)	3 (43)
TNBC	--	2 (50)	--	2 (50)	--	4 (24)	2 (50)	2 (66.7)	4 (57)
Melanoma	--	--	2 (66.7)	1 (25)	--	3 (18)	N/A	N/A	N/A
HNSCC	1 (33.3)	1 (25)	--	--	--	2 (12)	N/A	N/A	N/A
HL	--	--	--	1 (33.3)	--	1 (6)	--	--	--
Time since Diagnosis (median, range)	930 (751,3321)	783 (530,1011)	1284 (909,1558)	566 (436,932)	695 (446,3788)	783 (436,3788)	1695 (1392,4753)	2366 (1711,3020)	2030 (1392,4753)
Prior Therapies									
Systemic therapy (median, range)	2 (1.0,3.0)	2 (1.0,6.0)	1 (1.0,3.0)	6.0 (1.0,3.0)	2 (1.0,3.0)	2 (1.0,6.0)	3.5 (2.0,6.0)	4 (3.0,5.0)	3.75 (2.0,6.0)
Prior anti-PD1	3 (100)	4 (100)	3 (100)	4 (100)	3 (100)	17 (100)	2 (50)	1 (33.3)	3 (43)
Stem Cell Transplant	--	--	--	--	1 (33.3)	1 (6)	--	--	--

*1 pt in 0.3 and 3.0 mg/kg cohort not DLT evaluable due to receiving only one dose and discontinuing for unrelated SAEs

Safety

Safety Summary:

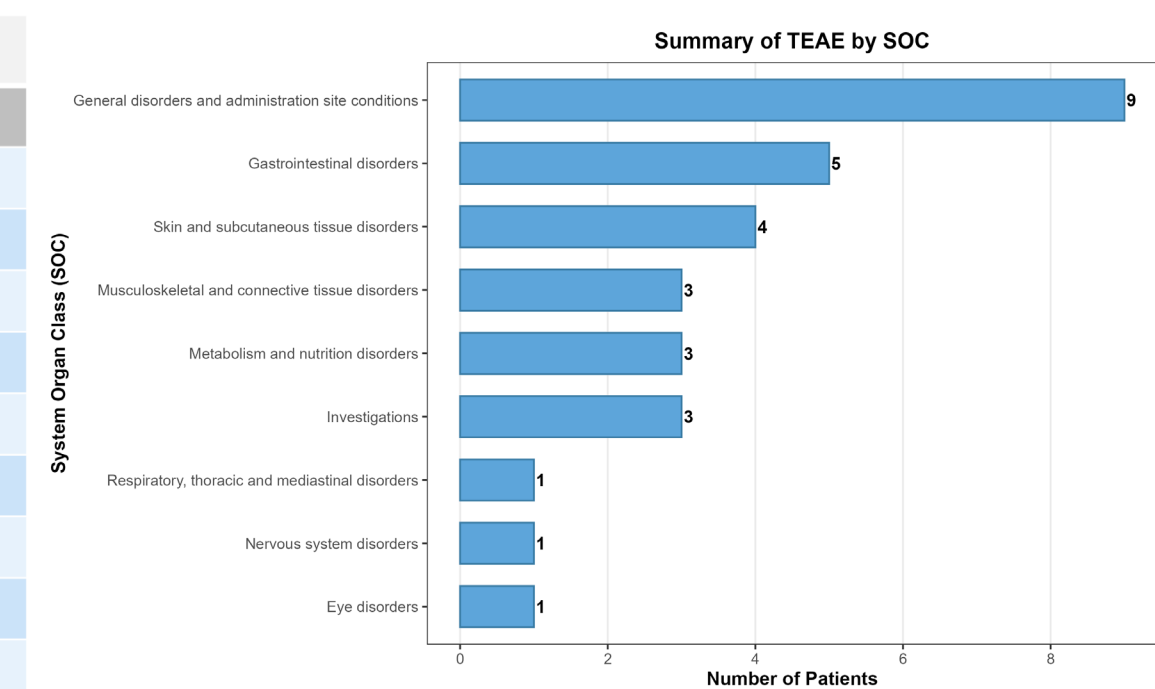
- No DLTs or Related Serious Adverse Events (SAEs)
- One Related Grade 3 TRAE of Lipase Increase
- One Related irAE of Grade 2 Pneumonitis

Treatment Emergent Adverse Events (TEAEs) in ≥ 3 Patients

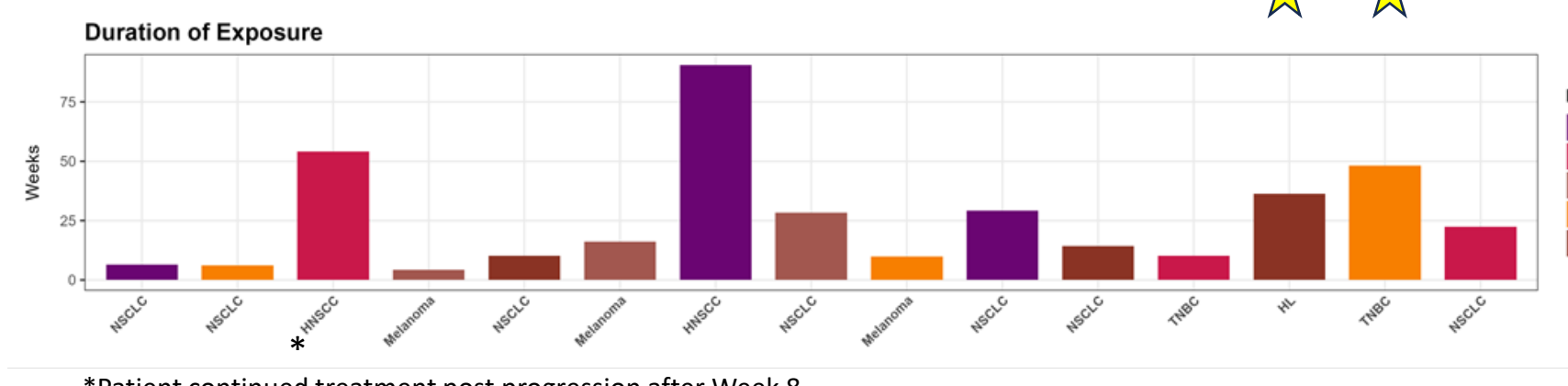
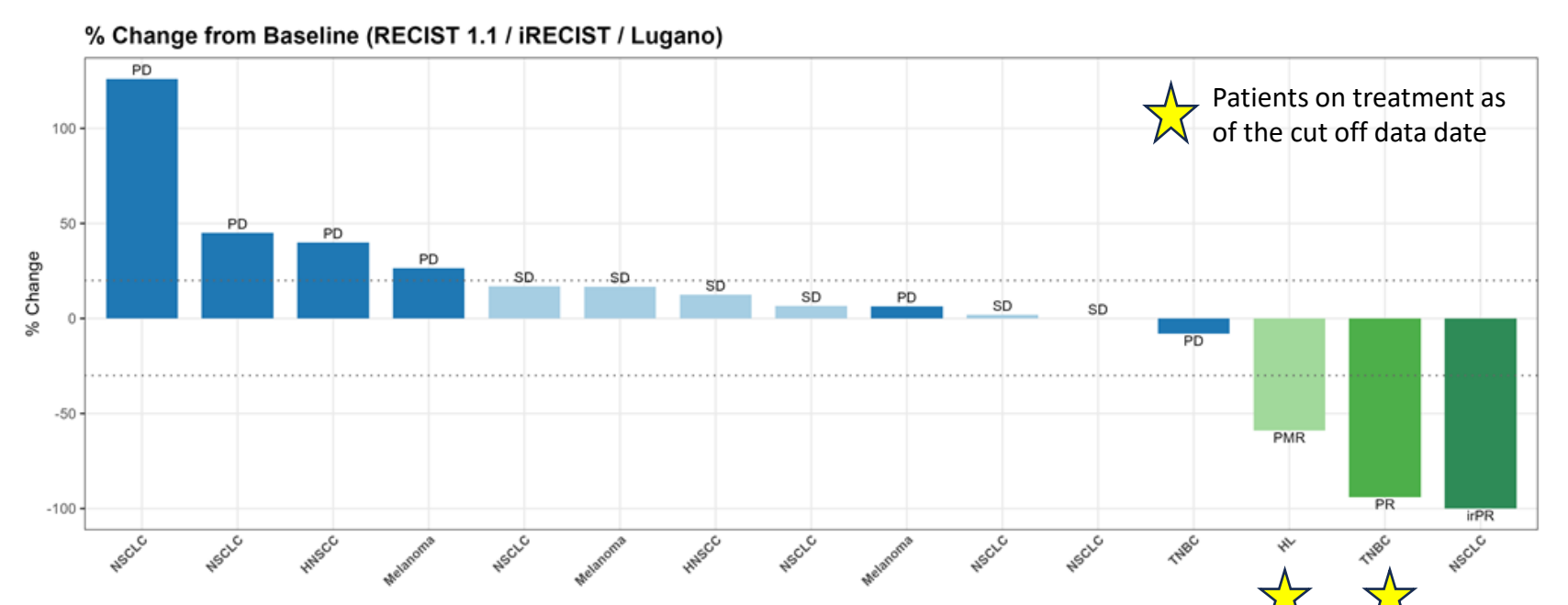
Preferred Term	Treatment Emergent Adverse Events (n, %)					
	0.1 mg/kg (n=3)	0.3 mg/kg (n=4)	1.0 mg/kg (n=3)	3.0 mg/kg (n=8)	10 mg/kg (n=6)	Total (n=24)
Fatigue	1 (33.3)	2 (50.0)	1 (33.3)	1 (12.5)	1 (16.7)	6 (25.0)
Arthralgia	1 (33.3)	2 (50.0)	1 (33.3)	--	--	4 (16.7)
Nausea	--	--	1 (33.3)	2 (25.0)	1 (16.7)	4 (16.7)
Dehydration	1 (33.3)	1 (25.0)	1 (33.3)	--	--	3 (12.5)
Diarrhea	1 (33.3)	1 (25.0)	--	1 (12.5)	--	3 (12.5)
Headache	--	--	1 (33.3)	1 (12.5)	1 (16.7)	3 (12.5)
Influenza like illness	1 (33.3)	--	1 (33.3)	1 (12.5)	--	3 (12.5)
Oedema peripheral	1 (33.3)	1 (25.0)	--	1 (12.5)	--	3 (12.5)
Pain in extremity	--	--	--	2 (25.0)	1 (16.7)	3 (12.5)

- Majority of TEAEs were Grade 1 and 2
- Most common related events by SOC were General disorders [Fatigue (n= 4), Influenza like illness (n= 2) Pyrexia, Malaise, Chills (n= 1 of each)]

Summary of TEAEs Related to CTX-8371 by SOC



Dose Escalation Efficacy



*Patient continued treatment post progression after Week 8

- The response evaluable population was defined as patients who completed the DLT period (28 days from C1D1) and had at least one post-baseline scan.
- 15 patients met this criteria.
- Overall Response Rate (ORR): 20% [one pt each with NSCLC (irPR), TNBC (PR) and HL (PMR)]
- Disease Control Rate (DCR): 60%

Best Overall Response (n, %)	
Response evaluable	N=15
Progressive Disease*	7 (47.67)
Partial Response	2 (13.3)
Stable Disease	6 (40.0)

* One NSCLC patient developed pseudoprogression which converted to an irPR per IRECIST

Dose Escalation Pharmacokinetics

CTX-8371 Serum Pharmacokinetics Profile

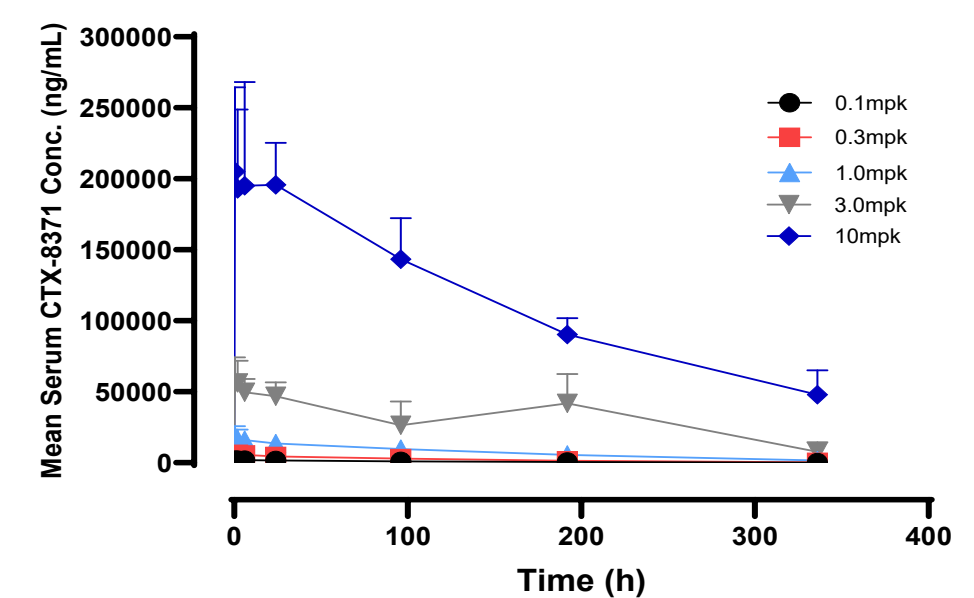


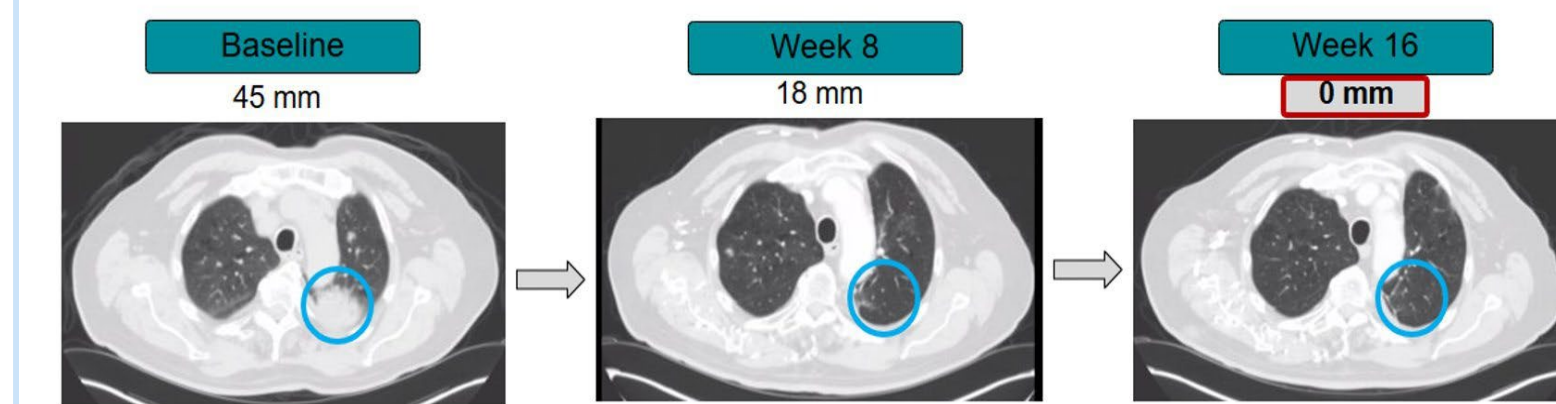
Figure 3: CTX-8371 Mean Serum Concentration-Time Profiles (Cycle 1)

PK Summary:

- C_{max} demonstrated dose-dependent and dose-proportional increases
- Mean $T_{1/2}$ generally ranged from 2.5 to 7.9 days.

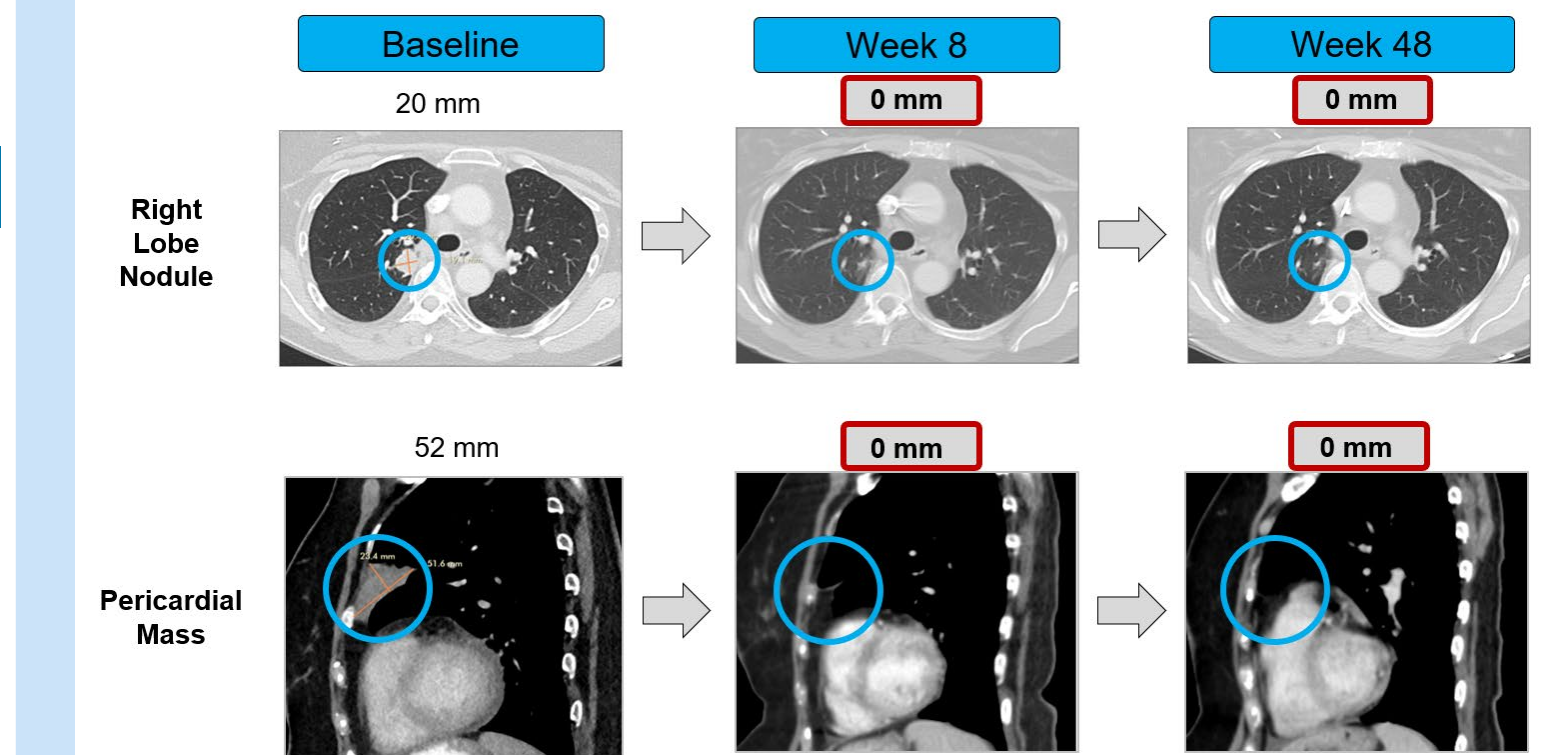
Dose Escalation Efficacy: Responders

Patient with NSCLC (0.3 mg/kg) Complete resolution of target lesions after initial pseudo-progression (irPR)



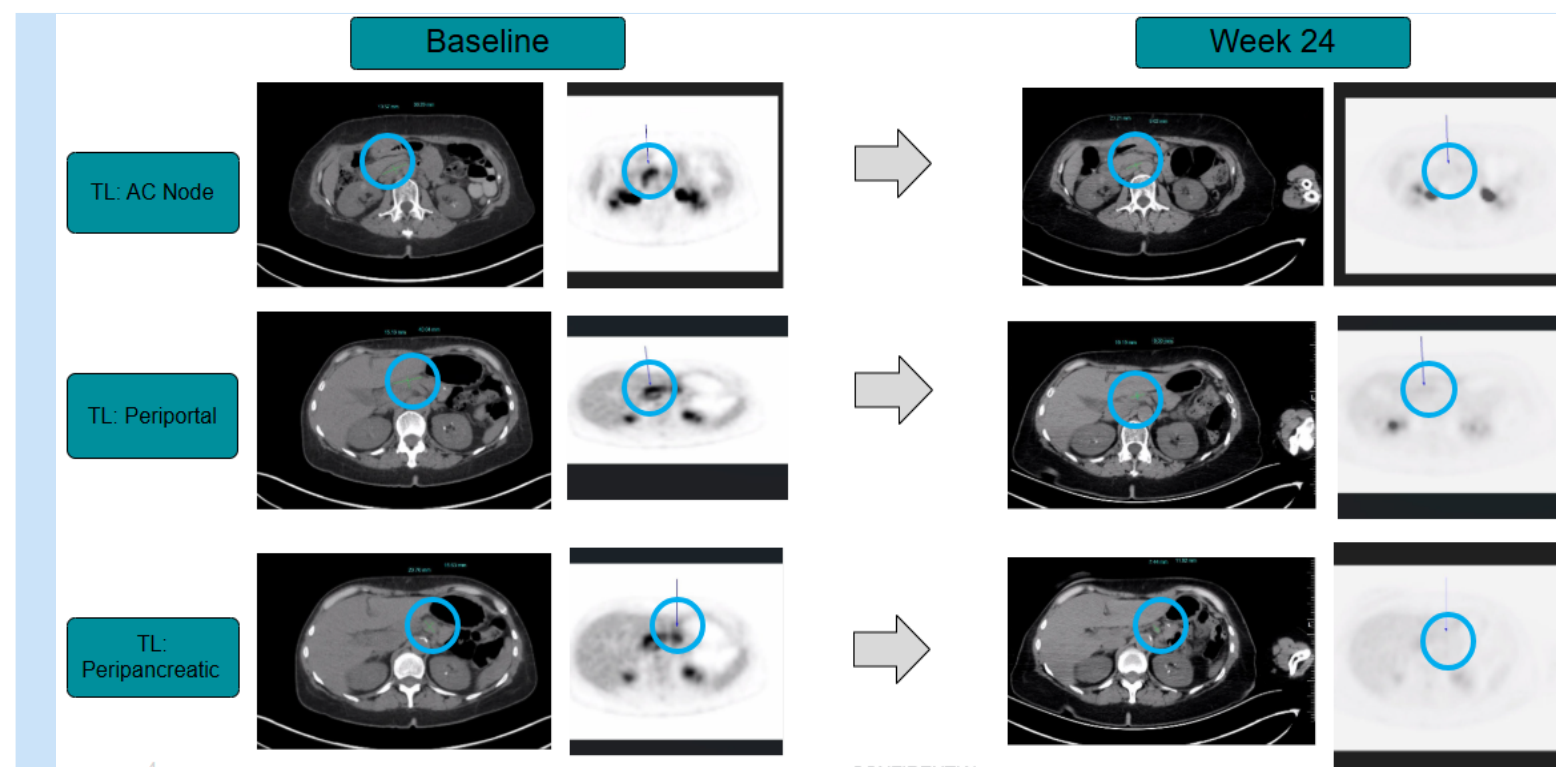
- 74 yo male with squamous NSCLC, MSS, TMB 2.87, PD-L1 TPS <1%
- Prior systemic therapies (4 total, 3 prior IOs): carboplatin + paclitaxel \rightarrow durvalumab \rightarrow pembrolizumab \rightarrow nivolumab + ipilimumab
- Total duration of therapy 6 months

Patient with TNBC (3.0 mg/kg) >90% Reduction of target lesions in 4th line setting (PR)



- 60 yo female with TNBC, MSS, PD-L1 CPS 1
- Neoadjuvant treatment: paclitaxel + pembrolizumab followed by right lumpectomy
- Adjuvant treatment: doxorubicin + pembrolizumab
- Prior Systemic therapy (3 prior): sacituzumab govitecan \rightarrow capecitabine \rightarrow gemcitabine
- Patient remains on treatment at 12+ months

Patient with Hodgkin Lymphoma (10.0 mg/kg) Decrease in metabolic activity of target lesions at Week 24 (PMR)



- 61 yo female with HL
- Adjuvant treatment: ABVD
- BEAM conditioning for autologous stem cell transplant (ASCT)
- Prior systemic therapy: nivolumab + brentuximab
- Patient remains on treatment at 10+ months

Conclusions

- CTX-8371, a novel bispecific antibody targeting both PD-1 and PD-L1, was well tolerated (No DLTs, MTD not reached) and demonstrated promising clinical activity as a monotherapy in advanced patients resistant to prior immune checkpoint inhibitors; greater depth and longer durability of responses at higher doses.
- CTX-8371 demonstrated a PK profile typical of bispecific antibodies with expected C_{max} , $T_{1/2}$ and systemic exposure.
- Dose Expansion is enrolling NSCLC, TNBC and HL in disease specific cohorts at two CTX-8371 dose groups (3.0 mg/kg and 10.0 mg/kg). The evaluation of two doses will help to inform dose optimization in support of an RP2D for further development.

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Email Contact: CTX-8371-001@compasstherapeutics.com

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