

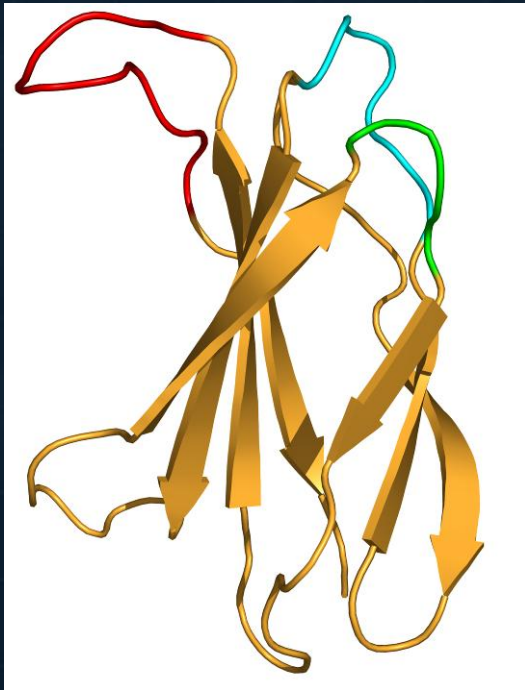
Phase 1 Study of CT-322, First Adnectin™ Protein Therapeutic and Potent Inhibitor of VEGFR-2, in Patients with Advanced Solid Tumors

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Pre-Clinical Background

Adnectins: Novel Protein-Based Therapeutic Class



10th Type III Domain (10Fn3)
of Human Fibronectin
10 kD

Protein-based therapeutics derived from a domain of **human fibronectin**

Extracellular, immune-tolerated origin

Well understood protein, stable domain

Fibronectin **designed by nature to bind**
- Natural high affinity, specific binding sites

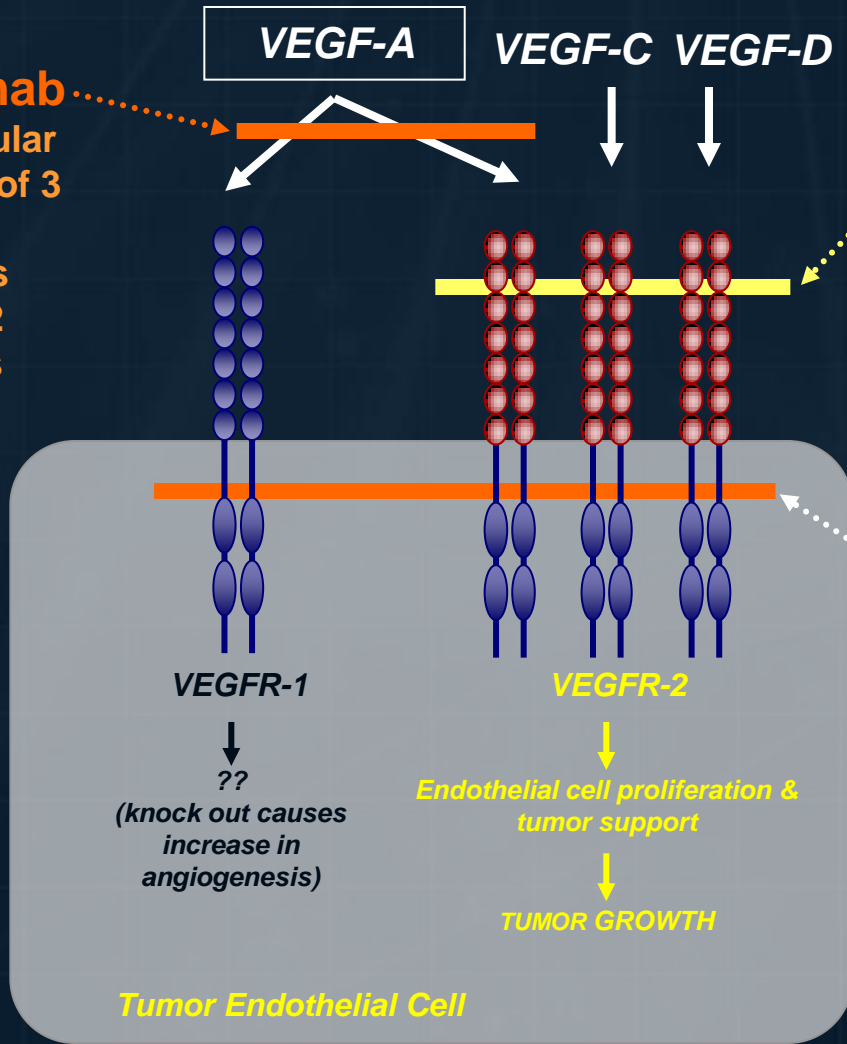
Binding loops modified to redirect binding to a drug target instead of integrin
- Loops engineered using proprietary technology

Manufactured in *E. coli*

CT-322 is a Specific and Potent Blocker of VEGFR-2

Bevacizumab

- Extracellular
- Blocks 1 of 3 VEGFR-2 activators
- Impacts 2 receptors



CT-322

- Extracellular
- Blocks 3 of 3 VEGFR-2 protein activators
- Blocks primary tumor angiogenesis pathway only (VEGFR-2)

Sunitinib, Sorafenib

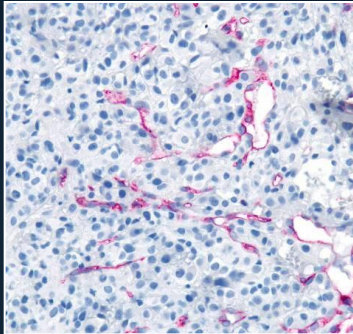
- Intracellular (ATP binding sites)
- Nonspecific: Multiple VEGFRs and TKRs
- Increased AE profile (eg, plantar palmar erythema)

CT-322 Blocks VEGFR-2 Activators: VEGF-A, C, and D

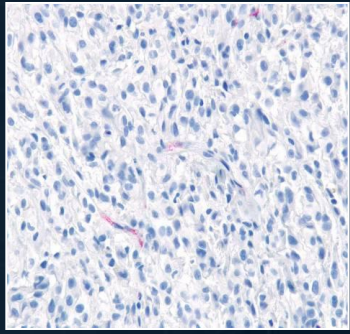
CT-322 Alters Tumor Vascular Density & Morphology

	IC ₅₀ nM (cellular assays)
Human	1
Murine	20

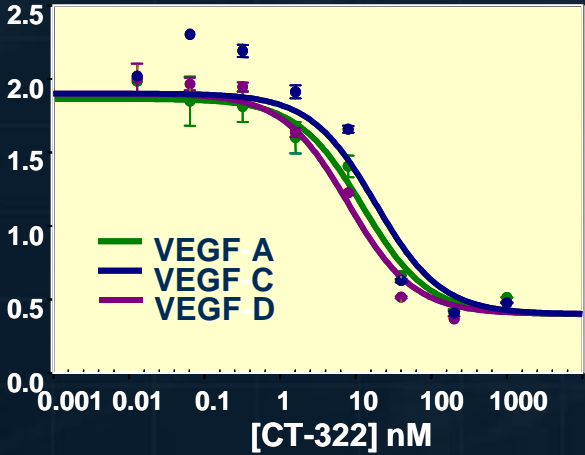
U87 Human Glioblastoma



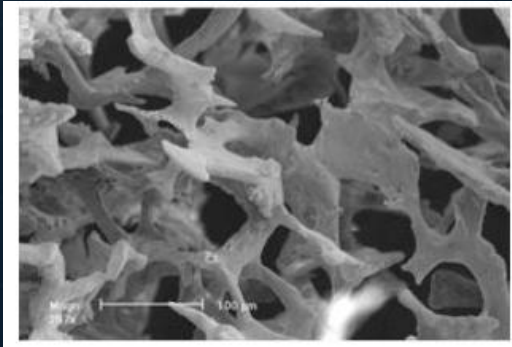
Vehicle
41.4 ± 2.2/mm²



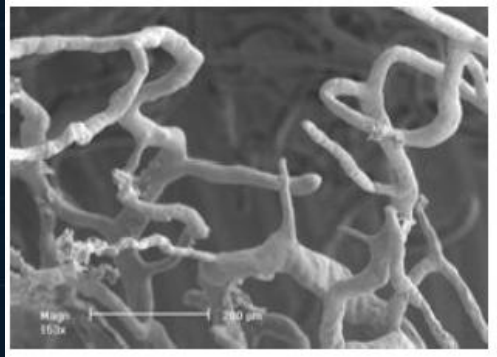
CT-322 (30 mg/kg)
6.9 ± 0.7/mm²



Colo205 Xenograft



Vehicle



CT-322 (60 mg/kg)

Quantification of intervascular and interbranching distances: Vehicle < CT-322 (p<0.0000001)

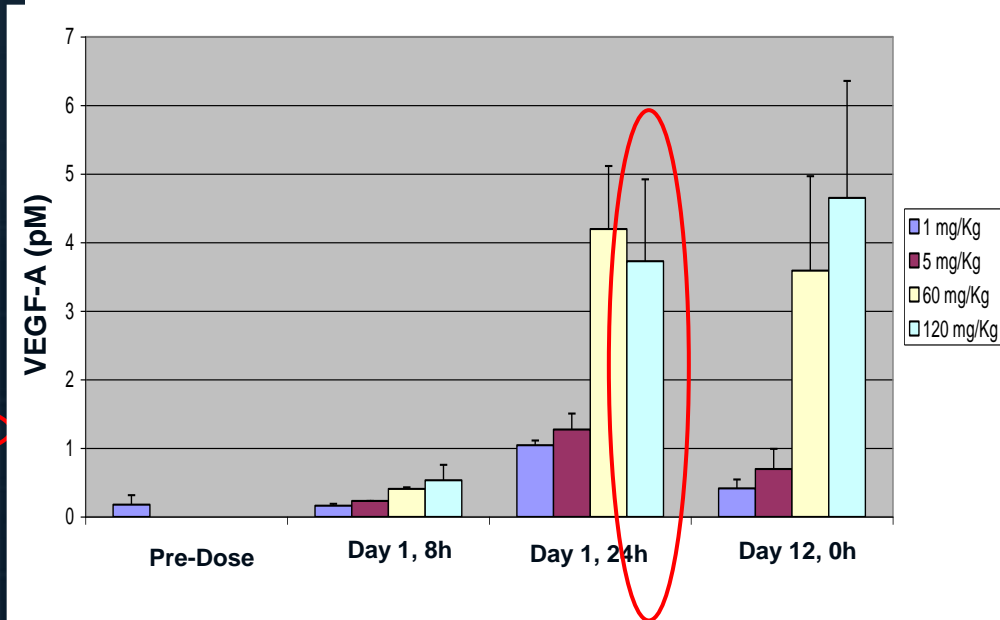
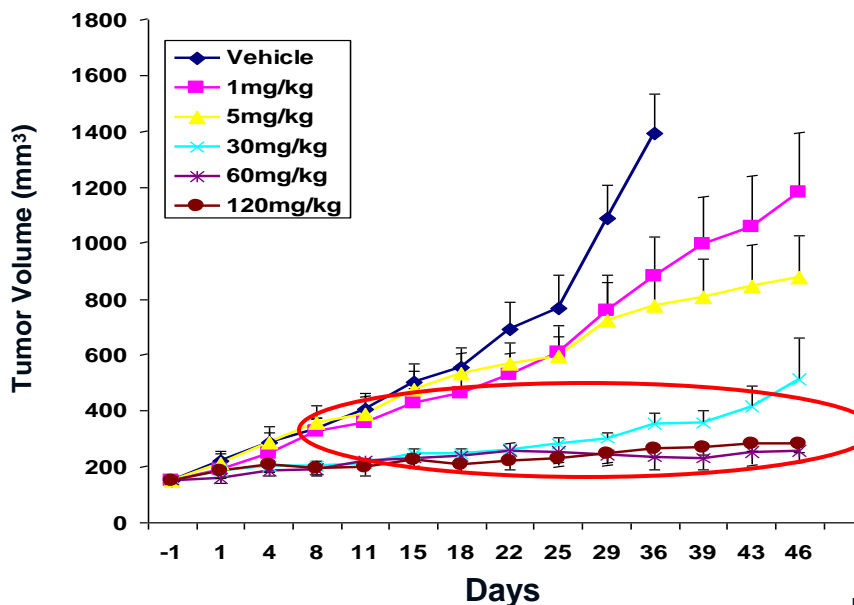
[unpublished data courtesy Prof. Morris Konitz, Univ of Mainz]

Concordance of Maximal Anti-Tumor Activity and VEGF-A Response

Colo205 xenografts (60mpk TIW)

60 mg/kg TIW is maximally efficacious dose of CT-322

CT-322-Induced VEGF-A Levels are saturated at 60 mg/kg TIW



First in Human Phase 1 Clinical Trial

Phase I Dose-Escalating Study of CT-322

Advanced Solid Tumor and Non-Hodgkin's Lymphoma

Primary Objective

- Safety and Tolerability
- Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose

Secondary Objectives

- PK, PD (Biologic Activity), Immunogenicity responses
 - Biomarkers: plasma VEGF-A, proteinuria and blood pressure

Phase I Dose-Escalating Study of CT-322 (Monotherapy) Advanced Solid Tumor and Non-Hodgkin's Lymphoma Pts

Design

- Sequential escalating dose cohorts (“Classic 3+3”)
- QW and Q2W dosing schedules
- 39 patients treated, 3 US centers
- 28-d initial safety assessment with extension for pts with CR/PR & SD

Subject Eligibility

INCLUSION

- Histologically proven solid tumor or NHL having failed standard therapies
- ECOG \leq 2
- Standard organ function
- 24 hr urine protein < 500 mg
- Neg pregnancy test
- Informed consent

EXCLUSION

- CNS metastasis
- Arterial vascular events or procedures within 12 months
- Uncontrolled HTN
- Therapeutic anti-coagulation
- Non-healing wound or fracture
- Central squamous cell NSCLC

Methods

CT-322 Pharmacokinetics

- CT-322 plasma concentrations assayed by ELISA following capture using a CT-322 specific murine mAb with detection by an anti-PEG IgM mAb

Plasma VEGF-A

- Plasma VEGF-A assayed using a commercially available sandwich ELISA assay (R&D systems Inc)

PK-PD modeling to explore the relationship of:

- CT-322 concentration to absolute plasma VEGF-A levels
- CT-322 trough concentration to the trough:peak ratio of VEGF-A

DEMOGRAPHICS (N = 39)

CHARACTERISTIC		NO. OF PATIENTS
GENDER	MALE	22 (56%)
	FEMALE	17 (44%)
AGE, YRS	MEDIAN	58
	RANGE	(32 - 86)
ECOG	0	10 (26%)
	1	27 (69%)
	2	2 (5%)
PRIOR CHEMO	0	2 (5%)
	1	4 (10%)
	2	9 (23%)
	3+	24 (59%)
PRIOR RADIATION		19
PRIOR ANTI-VEGF		12

SUBJECT CHARACTERISTICS: CANCER TYPE

(n = 1 each)

Colorectal (10; 26%)

HRPC (6; 15%)

Metastatic Neuroendocrine (3; 8%)

Kaposi Sarcoma (2; 5%)

Renal Cell Carcinoma (2; 5%)

- Clear cell (1)
- Collecting duct (1)

Adenoid Cystic submandibular gland

Anal canal, squamous

Chondroblastic Osteosarcoma

Endometrial

Gastric

Head and Neck (laryngeal)

Large Cell Lymphoma

Lung Adenocarcinoma

Ovarian

Pancreatic

Sarcoma

Signet Ring Cell CA (unknown primary)

Thymoma, epithelial

Thyroid

Tonsillar

Transitional Cell CA, kidney

Uterine Leiomyosarcoma

Dose Escalation Schema and DLT Determination

Dose (mg/kg)	Schedule	N	DLT or 'DLT Equivalents' (**)
1	QW	6	Lipase Elevation; Pancreatitis (Grade 4)
3	QW	6	Proteinuria (Grade 3) LV dysfunction (Grade 3)*

* Prior mitoxantrone

Dose Escalation Schema and MTD Determination

Dose (mg/kg)	Schedule	N	DLT or 'DLT Equivalents' (**)
1	QW	6	Lipase Elevation; Pancreatitis (Grade 4)
3	QW	6	Proteinuria (Grade 3) LV dysfunction (Grade 3)*
2	QW	8 (6 eval.)	MTD NONE
3	Q2W	6	Proteinuria (1 Grade 3 DLT) RPLS** (n = 2) Retinal vascular occlusion** (n = 1)

Dose Escalation Schema and MTD Determination

Dose (mg/kg)	Schedule	N	DLT or 'DLT Equivalents' (**)
1	QW	6	Lipase Elevation; Pancreatitis (Grade 4)
3	QW	6	Proteinuria (Grade 3) LV dysfunction (Grade 3)*
2	QW	8 (6 eval.)	MTD
3	Q2W	6	Proteinuria (1 Grade 3 DLT) RPLS** (n = 2) Retinal vascular occlusion** (n = 1)
0.1 or 0.3→1	QW	7 (6 eval.)	NONE
2	Q2W	6	NONE

Time on Study

Dose (mg/kg)	Schedule	Median (Pt-Wks)	Range (Pt-Wks)
1*	QW	6.6	0 – 66
2	QW	7.3	0 – 27.4
3	QW	4.4	2.3 – 15.7
2**	Q2W	8.1	2.1 – 34.4
3	Q2W	4.9	2 – 13
Total		6.3	0 – 66

Number with CT-322 Exposure ≥	
4 wks	26
8 wks	13
12 wks	8
16 wks	7
24 wk	4

* 1 subject de-escalated from 3 mg/kg QW

** 1 subject de-escalated from 3 mg/kg Q2W

RESULTS: Safety, Tolerability

Generally well tolerated at 1 & 2 mg/kg/wk

- *No* acute infusion reactions (1 h infusion)
- *No* pre-medication required
- *No* fatigue > grade 2 (no relationship to dose)
- *No* chronic cutaneous toxicity (i.e. *no* hand-foot syndrome; *no* hemangiomas)

Observable and manageable VEGF pathway-related clinical effects

VEGF Pathway-Related Grade 3 or 4 Adverse Events at Anytime on Therapy

GRADE 3/4 ADVERSE EVENT	1mg/kg*	2mg/kg**	3mg/kg**
	N = 13	N = 14	N = 12
Hypertension	0	1	1
VTE	0	1 (Gr 2; port)	0
Retinal v./a. Occlusion	0	0	1
LV Dysfunction	0	0	1 [^]
Lipase inc.	1	0	0
RPLS	0	0	2
Proteinuria	0	0	2

Unaudited data

* includes 'low-dose' 0.1 and 0.3 mg/kg cohort

** includes subjects treated QW or Q2W

[^] prior treatment with mitoxantrone

CT-322 Effect on Blood Pressure & Proteinuria

Event	Dose Level (mg/kg)		
	1*	2**	3**
Any Grade AE of Hypertension (n)	N=13 3	N=14 3	N=12 5
Proteinuria: Urine Prot:Creat ≥ 1.0	2	2	3

Unaudited data

* includes 'low-dose' 0.1 and 0.3 mg/kg cohort

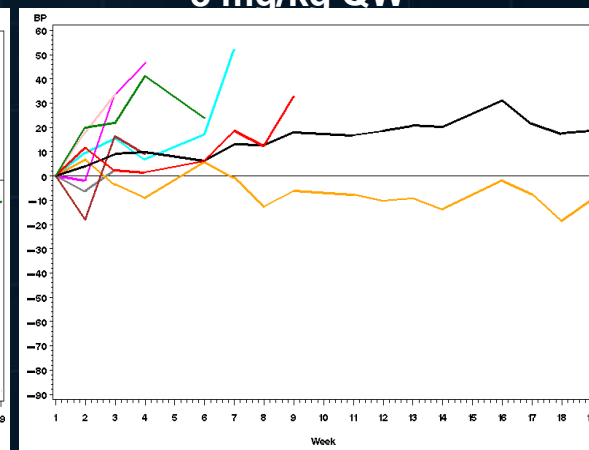
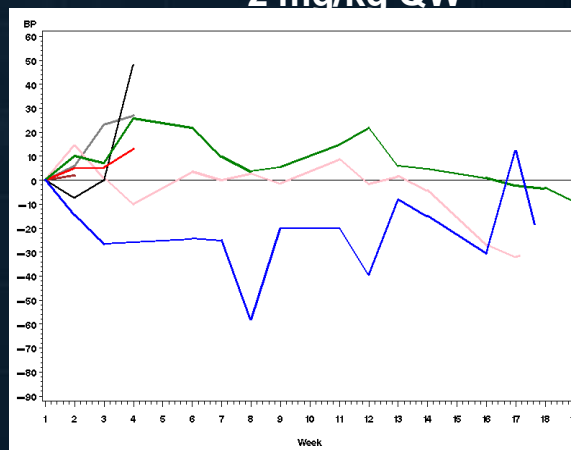
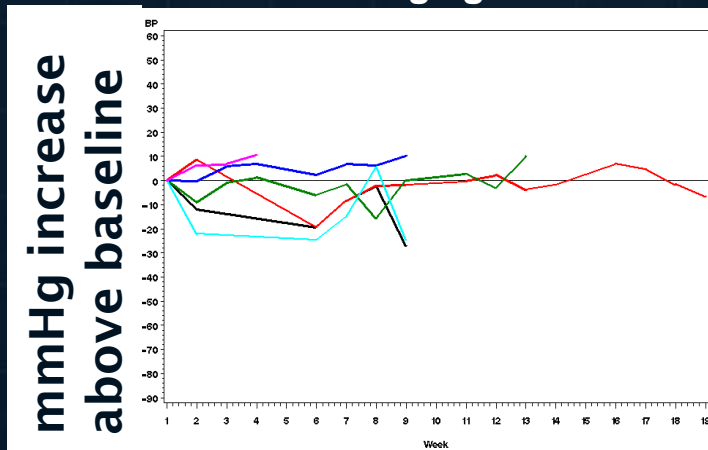
** includes subjects treated QW or Q2W

Systolic Blood Pressure Responses by Dose

1 mg/kg QW

2 mg/kg QW

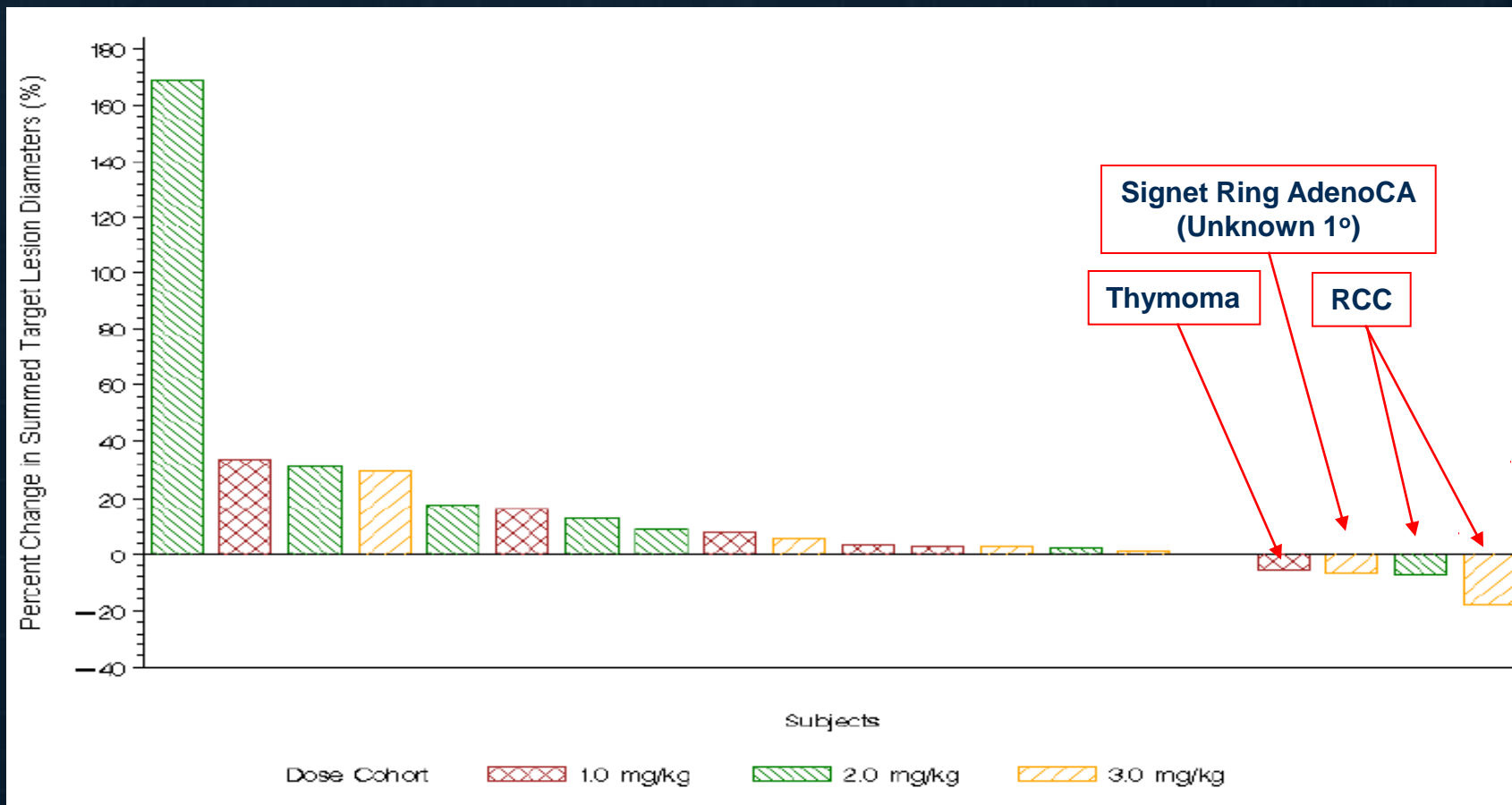
3 mg/kg QW



Waterfall Plot: Best Tumor Response by Subject

PD

Stable Disease



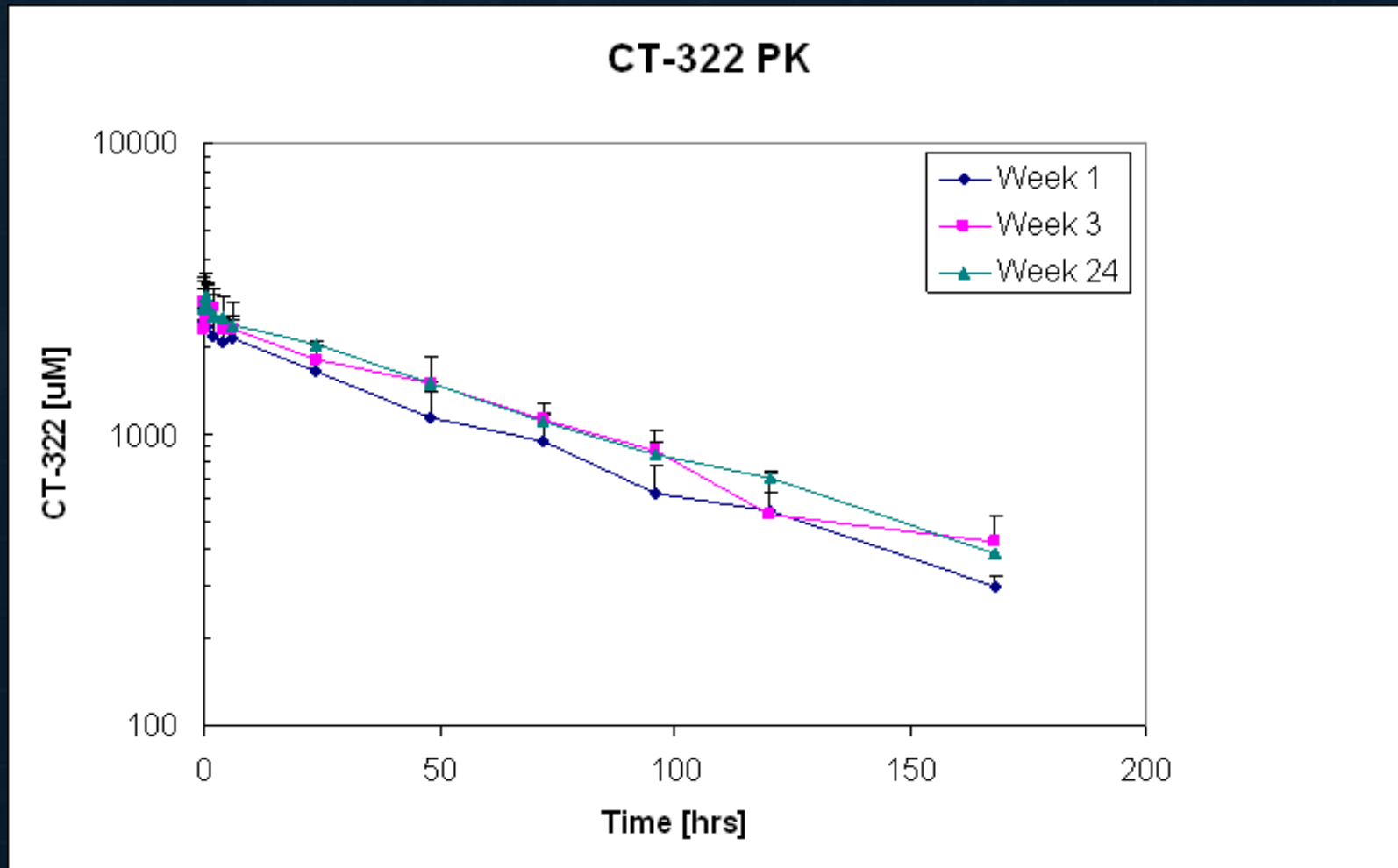
Pharmacokinetics of CT-322 in Humans

DOSE	1 mg/kg QW (n = 6)	2 mg/kg QW (n = 6)	3 mg/kg QW (n = 6)
C_{max} (uM/L) mean (range)	2.7 (2.0-3.8)	5.2 (3.9-6.0)	8.7 (7.2-10.8)
AUC (uM*day) mean (range)	9.1 (8.0-10.6)	15.7 (9.7-22.8)	29.1 (25.4-33.8)
T_{1/2} (h) median (range)	68.7 (56.9 - 157.2)	65.1 (55.8-81.2)	61.1 (49.4 - 89.3)
CL (L/day/kg) mean (SD)	0.011 (0.001)	0.014 (0.004)	0.010 (0.001)

Pharmacokinetics of CT-322 in Humans

DOSE	1 mg/kg QW (n = 6)	2 mg/kg QW (n = 6)	3 mg/kg QW (n = 6)	3 mg/kg Q2W (n = 4)
Accumulation Ratio (1 st vs last)				
Peak Conc. (mean; SD) n	1.18 (0.32) n = 6	1.22 (0.09) n = 6	1.12 (0.12) n = 6	1.15 (0.18) n = 4
Trough Conc. (mean; SD) n	1.09 (0.29) n = 6	1.47 (0.37) n = 6	1.30 (0.27) n = 6	0.98 (0.19) n = 4
Time of Last Peak/Trough Range (wk)	4 - 24	4 - 24	4 - 14	5 - 21

Dose Normalized CT-322 Concentration-Time Profiles Over 6 Months Continued Treatment (n = 4)



VEGFR-2 Blockade-Related Biomarker Assessment

VEGF-A Levels & CT-322 Pharmacologic Activity

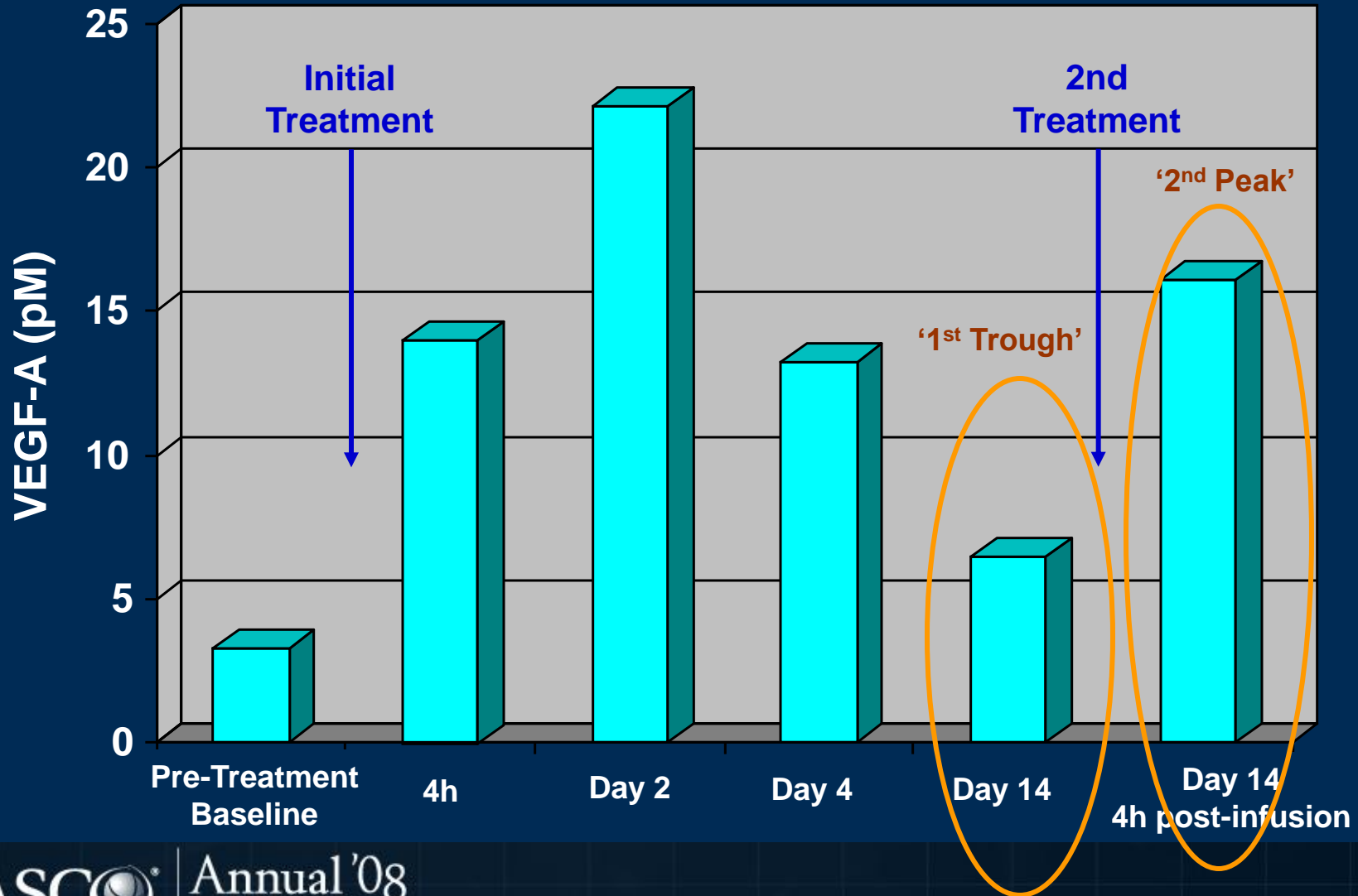
VEGF-A response: potentially useful PD marker to estimate optimal dose for drugs that block VEGF-A binding to VEGFR-2 extra-cellular domain

- Pre-clinical Observations:
 - Rapid elevation by a VEGFR-2 antibody (Bocci et al. Cancer Res, 2004)
 - Rapid elevation by CT-322 (unpublished data; Kerbel and Adnexus)
- Clinical Observations:
 - Rapid VEGF-A elevation by a VEGFR-2 mAb (Cohen et al, 2006 ASCO abstract #647)

Rapid increase in circulating VEGF-A probably related to:

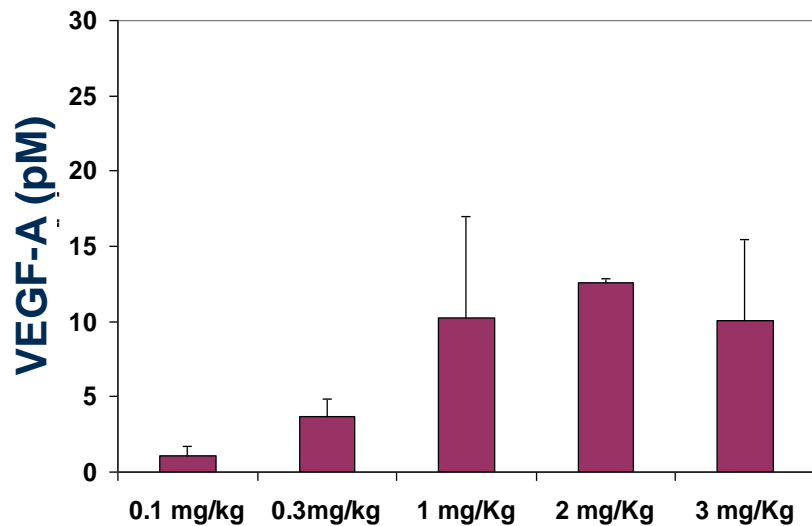
- Receptor binding with displacement of VEGF-A from VEGFR-2
- Subsequent changes in VEGF-A kinetics and clearance

Estimates of VEGFR-2 Pathway Blockade After CT-322 Treatment (Subject 1002; 1 mg/kg QW)

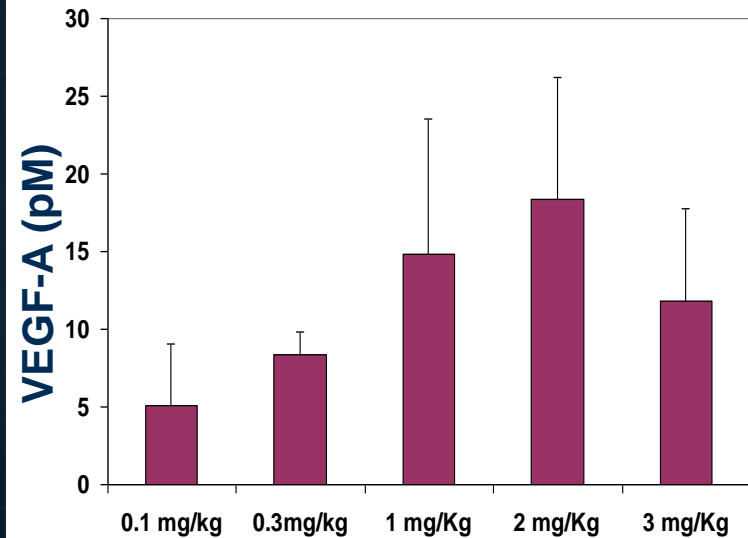


Human VEGF A plasma concentration dose responses show a plateau at 1 mg/kg

1st Trough



2nd Peak



Assessment of Clinically Significant Antibody Response to CT-322

Evaluate for anti-CT-322 Ab

- Reactivity to wild-type Adnectin?

No Ab to Adnectin backbone

Safety

- Local infusion reactions
- Systemic infusion reactions

None of Significance to Date

Pharmacokinetics

- Ab-mediated drug clearance

No Attenuation of Exposure

Target-related functional activity

- Biomarker response: VEGF-A
- Physiologic VEGFR-2 Class Effects

VEGF-A Response Sustained

BP Increases at 2 and 3mg/kg

Conclusions (I)

1. CT-322 is a novel, specific, and potent inhibitor of VEGFR-2 that completely blocks all activating ligands in the VEGFR-2 pathway
 - First of novel Adnectin-based class of protein therapeutics, to reach clinic
2. CT-322 is well-tolerated at doses and schedules of 1 & 2 mg/kg QW and 2 mg/kg Q2W
 - No acute hypersensitivity or infusion reactions
 - No clinically significant immunogenicity observed
 - Excellent patient tolerability without dose-limiting fatigue or other constitutional symptoms

Conclusions (II)

3. Clinical observations consistent with VEGFR-2 blockade
 - Reversible proteinuria and manageable HTN is observed and is an expected class effect of VEGFR-2 inhibition
4. CT-322 demonstrates predictable, linear PK with no substantial accumulation or attenuation in exposure when administered for up to 6 months on continuous QW and Q2W dosing schedules

Conclusions (III)

5. Saturable pharmacodynamic effects of CT-322 on the VEGFR-2 system are demonstrated in studies of plasma biomarkers (VEGF-A)
6. Stable disease demonstrated in advanced, refractory malignancies
7. These data provide key validation for the Adnectin class of biologics as human therapeutics with competitive drug properties

Acknowledgements

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Squibb R&D Company

PRA International

***Our participating patients
and their supportive families!***