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Society for Immunotherapy of Cancer

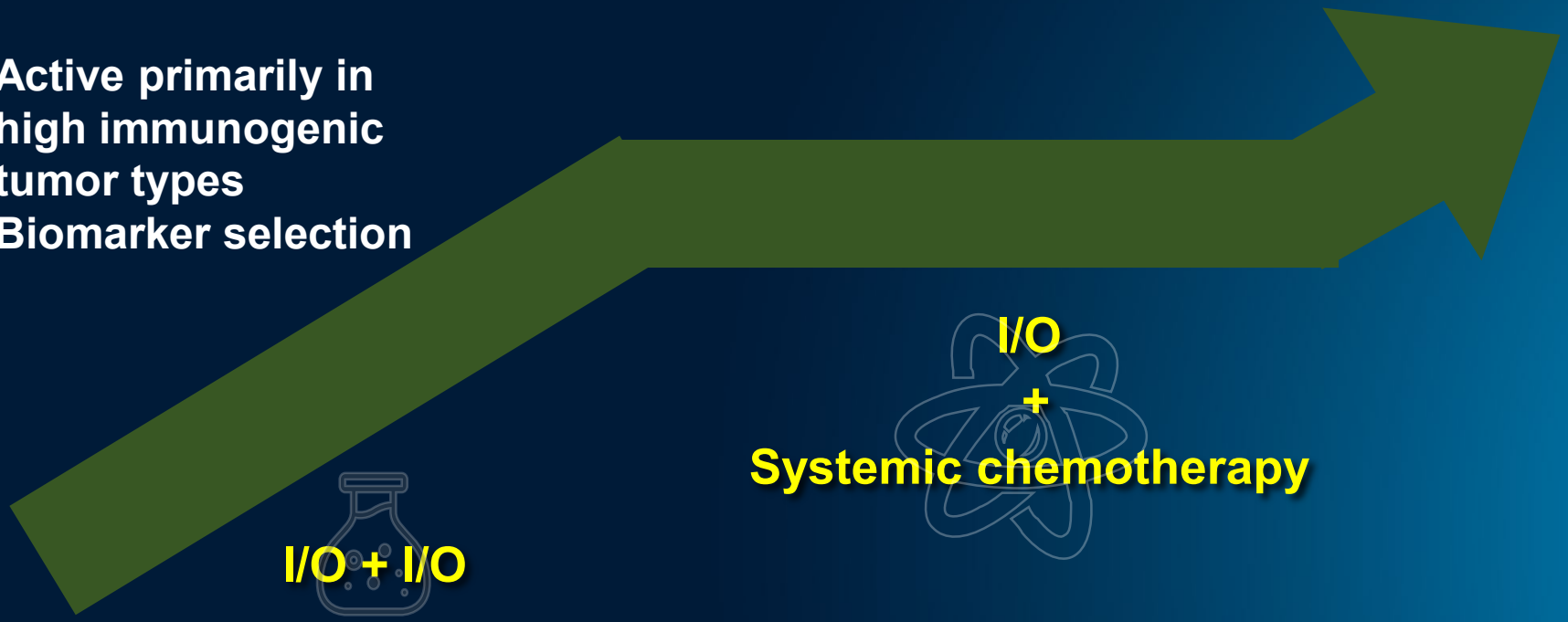
USC Norris Comprehensive Cancer Center
Keck Medicine of USC

Intratumoral INT230-6 injection into solid tumors kills tumors and induces immune cell infiltration leading to abscopal responses and prolonged disease control in multiple refractory cancer types. (NCT 03058289)

Jacob Thomas, Anthony J. Olszanski, Nilofer Azad, Lew Bender, Ian Walters, Giles Whalen, Diana Hanna, Vinay Duddalwar, Phillip Cheng, Kevin King, Lillian L. Siu, Anthony El-Khoueiry

Major limitation of Immune therapy: Immune recognition

- Active primarily in high immunogenic tumor types
- Biomarker selection



- **Approved in lung and breast cancer**
- **Immunologic cell death but suppresses the systemic immune compartment** (Mathios et al, STM 2016)

I/O
+
Local Therapy

- **Increase antigens**
- **Recruit Immune cells**

INTRATUMORAL INT230-6 FOR OPTIMAL ANTIGEN PRESENTATION

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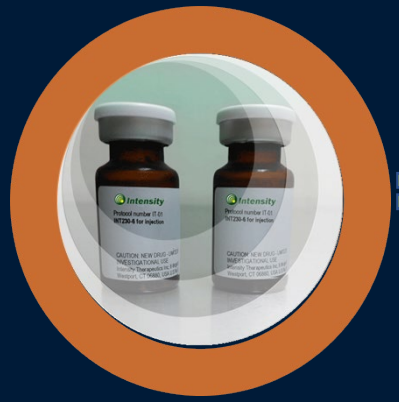
INT230-6
designed to optimize tumor dispersion and cell penetration



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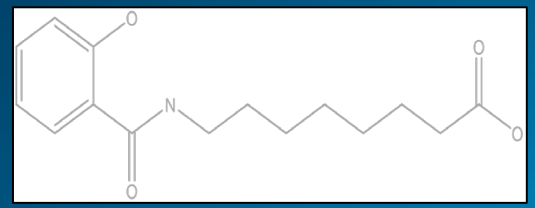
Proven anti-cancer agents co-formulated in a fixed ratio

Water	+	Cisplatin	+	Vinblastine	+	SHAO (diffusion enhancer)
						
10 mL		5mg		1mg		100mg

INT230-6 recruits immune cells by **killing cancer cells** and **sparing** central immune compartment

ONCOIMMUNOLOGY
2019, VOL. 8, NO. 10, e1625687 (15 pages)
https://doi.org/10.1080/2162402X.2019.1625687

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

Check for updates

Intratumorally delivered formulation, INT230-6, containing potent anticancer agents induces protective T cell immunity and memory

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[a]Vaccine Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA; [b]Intensity Therapeutics, Westport, CT, USA

INT230-6: Absorbed by tumors when dosed intratumorally

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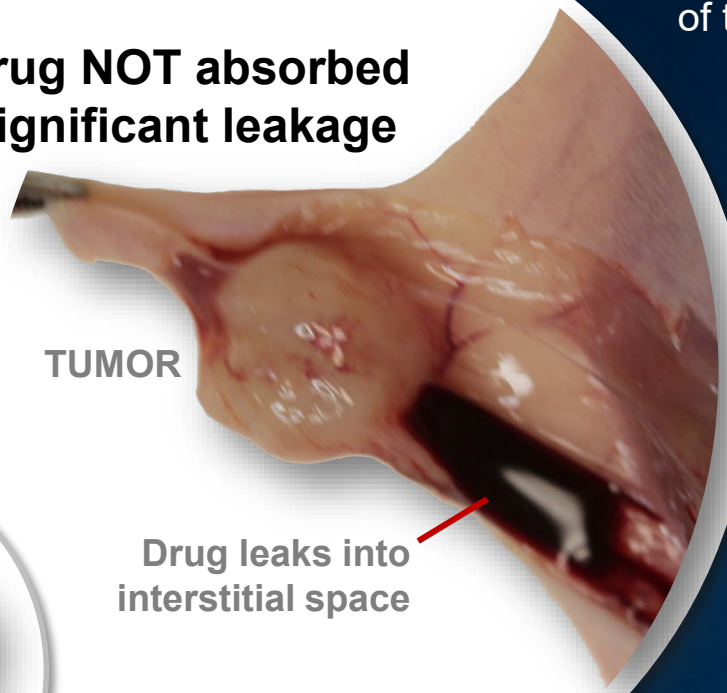
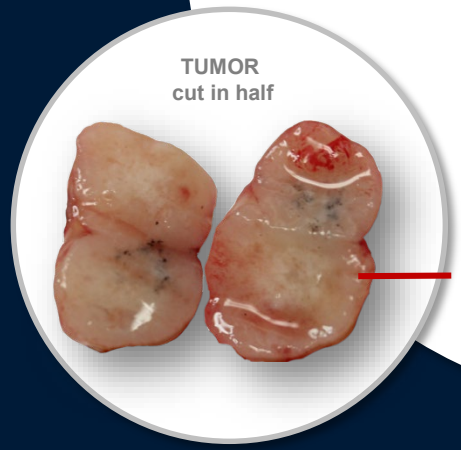
CYTOTOXIC AGENTS ALONE + *dye*

Injections made to center of tumor over 90 sec

Drug NOT absorbed significant leakage





Little to no drug dispersion in all tumors tested

INT230-6 + *dye*

INT230-6 is ABSORBED

Significant dispersion in all tumors tested

Human pancreatic cancer in mouse model

Preclinical data support direct tumor effects with augmented immune response

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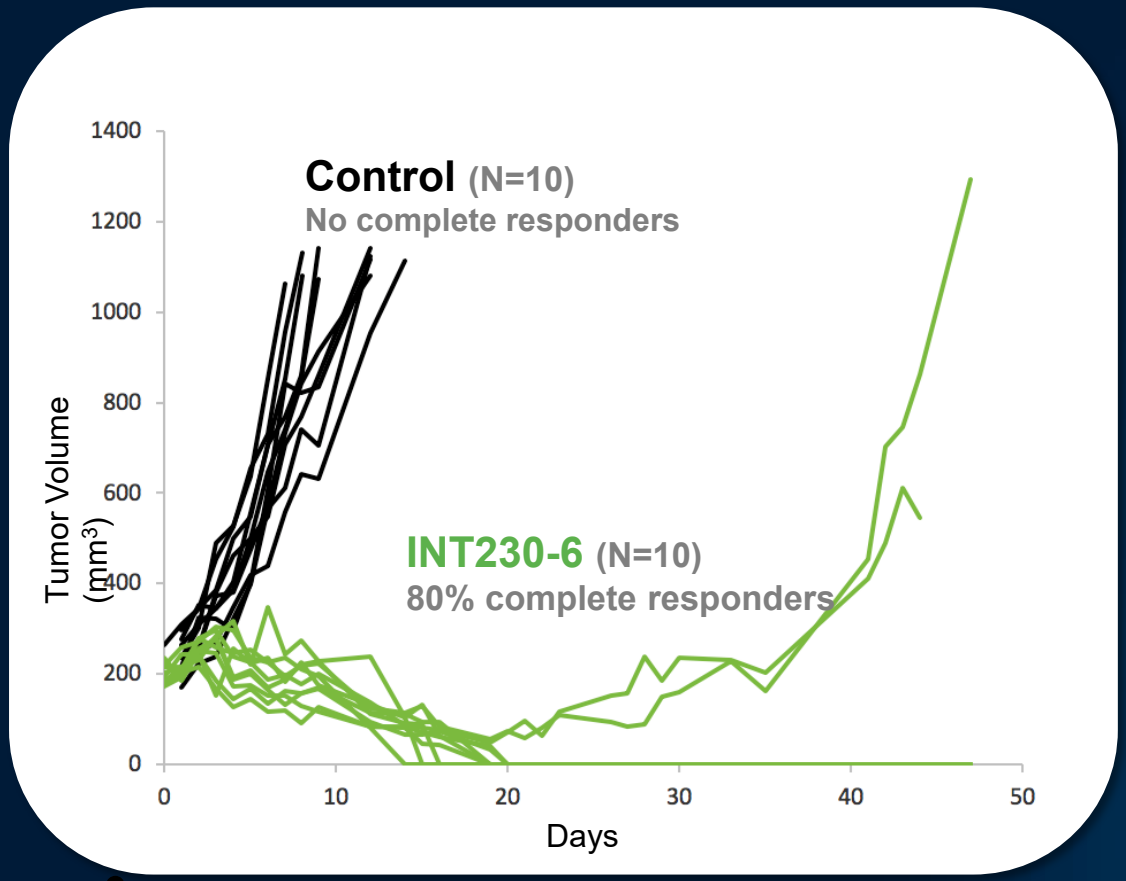
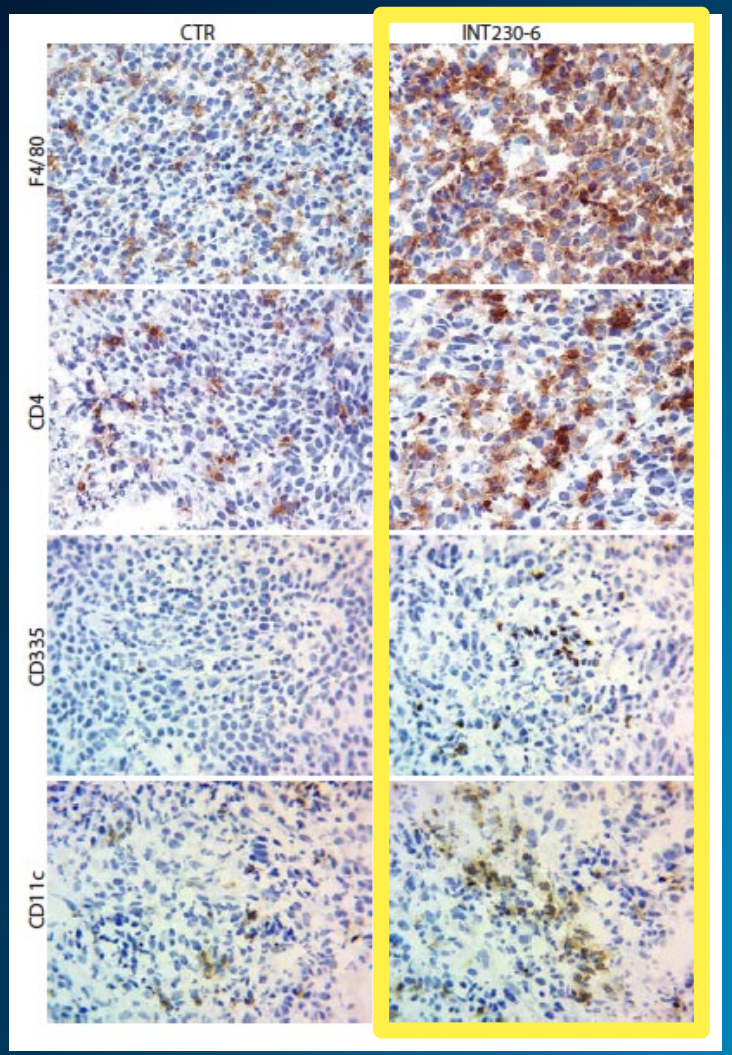


- LARGE ESTABLISHED COLON 26 MODEL
- 80% CURE(CR WITH IMMUNITY TO RECHALLENGE)



- Increases in Dendritic cells, macrophage, T-cells and NK cells after 1 week
- Select immune depletion abrogates therapeutic effect
- Increased antigen specific CD8 in tumor/spleen

Bloom et al, *OncoImmunology* 2019

Bender et al Manuscript submitted

PHASE 1/2 DESIGN

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Patient Population

- First superficial tumors
- Then deep and/or superficial
- Metastatic or locally advanced solid tumors

Dosing

- Dose determined by volume of tumor to be injected
- 3+3 design
- **Intra**patient dose escalation
- Can inject multiple tumors over 5 total sessions
- Retreatment possible

Endpoints

- Safety, defined by ≥Gr 3 related AEs
- Pharmacokinetics
- Biomarkers in blood/tissue
- Injected and non injected tumor responses

TRIAL PROGRESS

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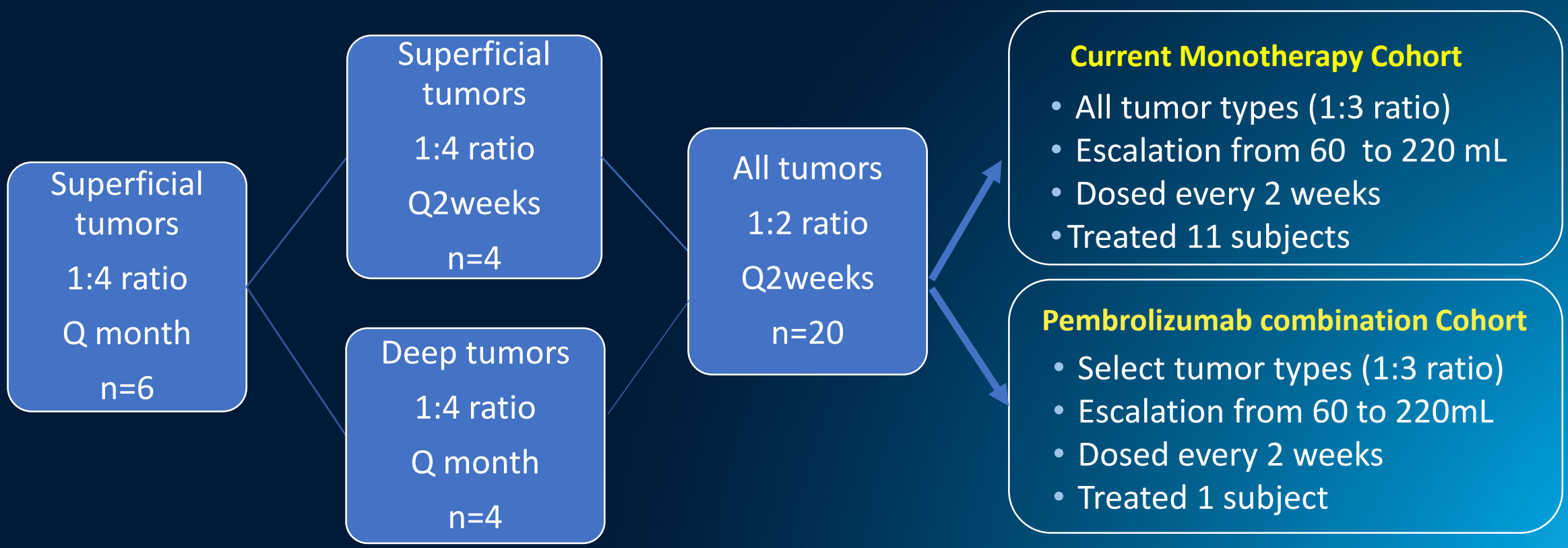

Progress Dose and Schedule

START 5mL

UP TO 220 mL

45 patients treated to date (17 cancer types)

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DEMOGRAPHICS	
Age Median (range)	60 (42-76)
Gender	20 male, 25 female
Race	82% Caucasian
	7% African American
	11% Asian
ECOG (0/1/2)	31% / 62 % / 7%
Median # of prior therapies (range)	3 (0,10)
# with prior Platinum	49%
# with prior PD1	44%
TUMOR TYPES	Melanoma, Lung, Adrenocortical, Cholangio, Chordoma, Ovarian, Breast, CRC, SCC, Anal, RCC, Pancreatic, Sarcoma, H&N, Thyroid, Urothelial, Psuedomyxoma Perintoneii

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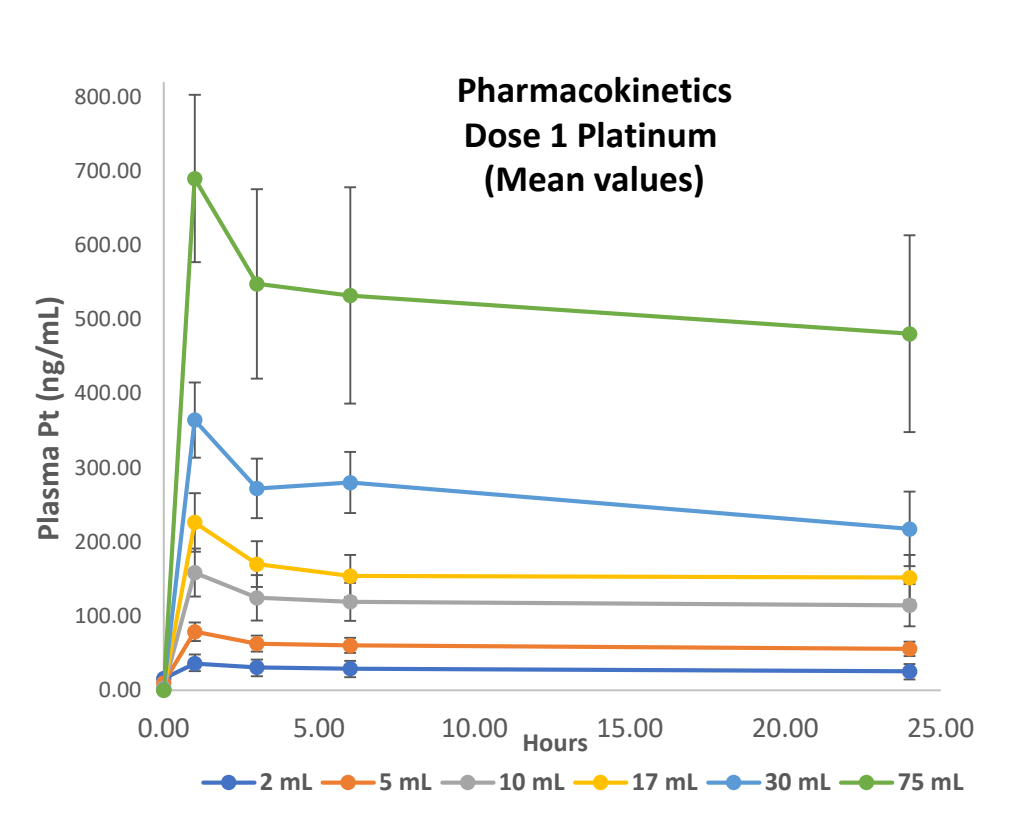
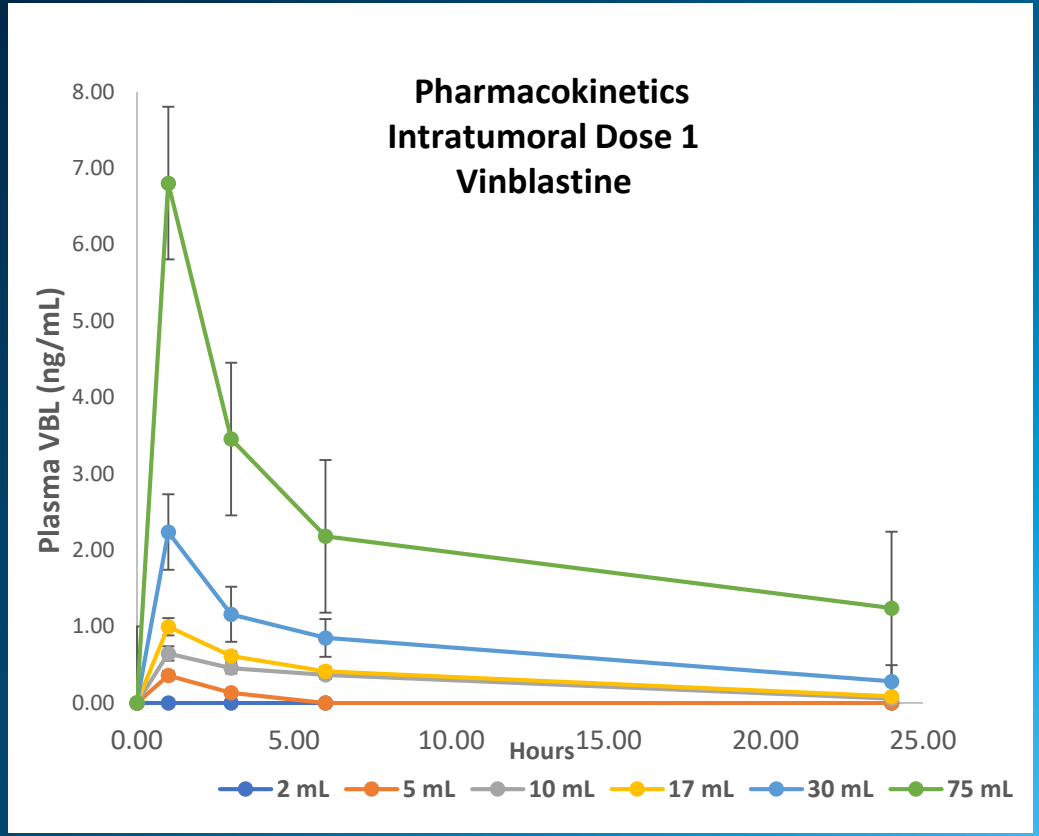
Dose proportional Pk

- **Majority of drug stays in tumor**

(<4% compared to the historical 120 ng/mL Cmax for IV vinblastine 3.8mg/m²)

- **Minimal systemic levels consistent across many tumor types**





75ml cohort: Vinblastine (approx. 7.5 mg dose) Cmax 6.8 ng/ml, AUC = 53 (ng/ml)h

RELATED ADVERSE EVENTS IN MORE THAN 2 SUBJECT

NCI-CTCAE Toxicity Grade n (%)

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PT	1	2	3	4 or 5	Total
Any	10 (22.2%)	20 (44.4%)	8 (17.8%)	0	38 (84.4%)
Localized tumor-related pain	12 (26.7%)	8 (17.8%)	2 (4.4%)	0	22 (48.9%)
Fatigue	5 (11.1%)	11 (24.4%)	1 (2.2%)	0	17 (37.8%)
Nausea	14 (31.1%)	3 (6.7%)	0	0	17 (37.8%)
Vomiting	11 (24.4%)	2 (4.4%)	0	0	13 (28.9%)
Decreased appetite	4 (8.9%)	7 (15.6%)	0	0	11 (24.4%)
Anaemia	2 (4.4%)	4 (8.9%)	3 (6.7%)	0	9 (20.0%)
Abdominal pain	1 (2.2%)	1 (2.2%)	2 (4.4%)	0	4 (8.9%)
Back pain	3 (6.7%)	1 (2.2%)	0	0	4 (8.9%)
Chills	4 (8.9%)	0	0	0	4 (8.9%)
Dizziness	4 (8.9%)	0	0	0	4 (8.9%)
Myalgia	3 (6.7%)	1 (2.2%)	0	0	4 (8.9%)
Blood creatinine inc.	2 (4.4%)	1 (2.2%)	0	0	3 (6.7%)
Dry mouth	2 (4.4%)	1 (2.2%)	0	0	3 (6.7%)
Dysgeusia	2 (4.4%)	1 (2.2%)	0	0	3 (6.7%)

- > 150 deep tumor injections conducted to date; straight or multipronged needles used
- As much as 160 mL dosed in a single session

MANY SUBJECTS SHOW PROLONGED SD

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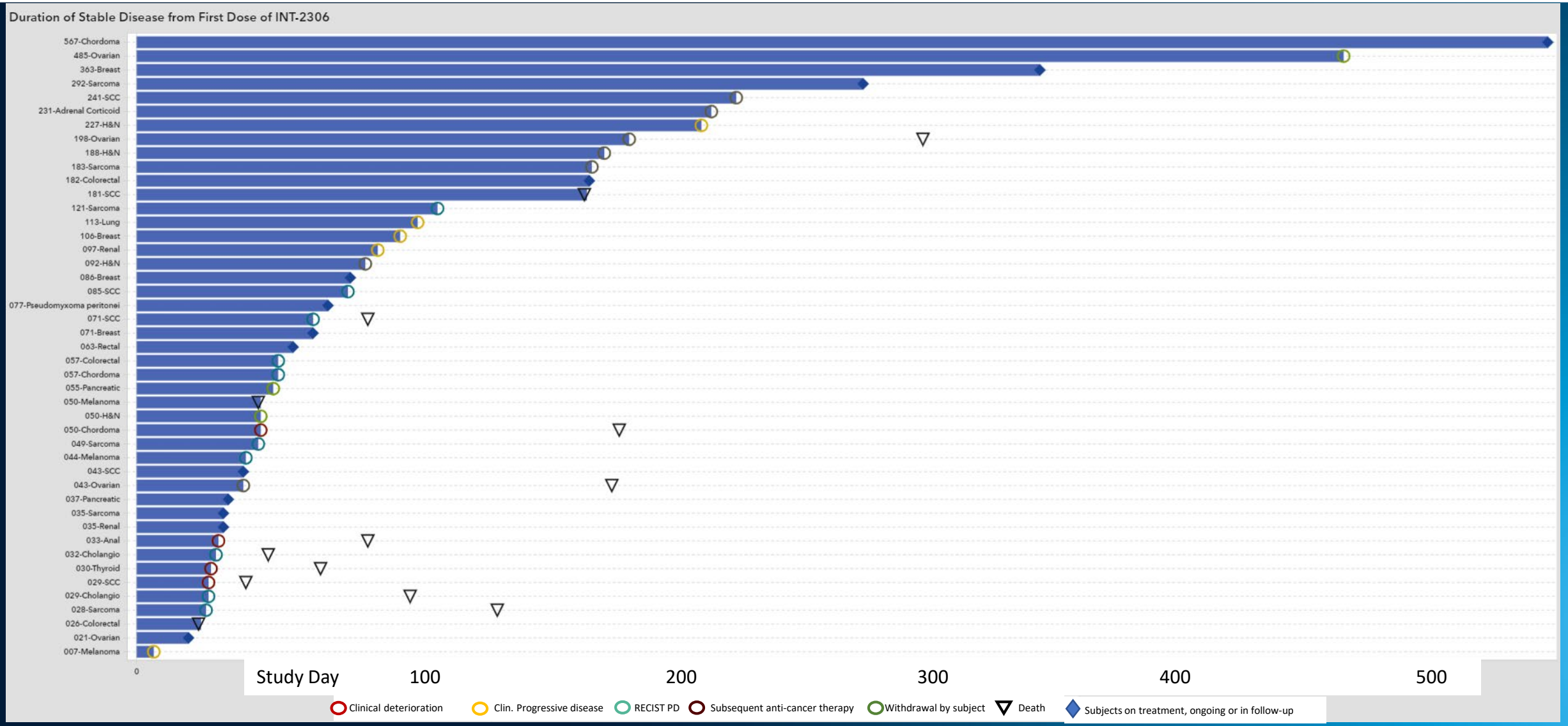

DISEASE CONTROL APPEARS TO IMPROVE WITH INCREASING CUMULATIVE DOSE AND PERCENT OF TUMORS TREATED

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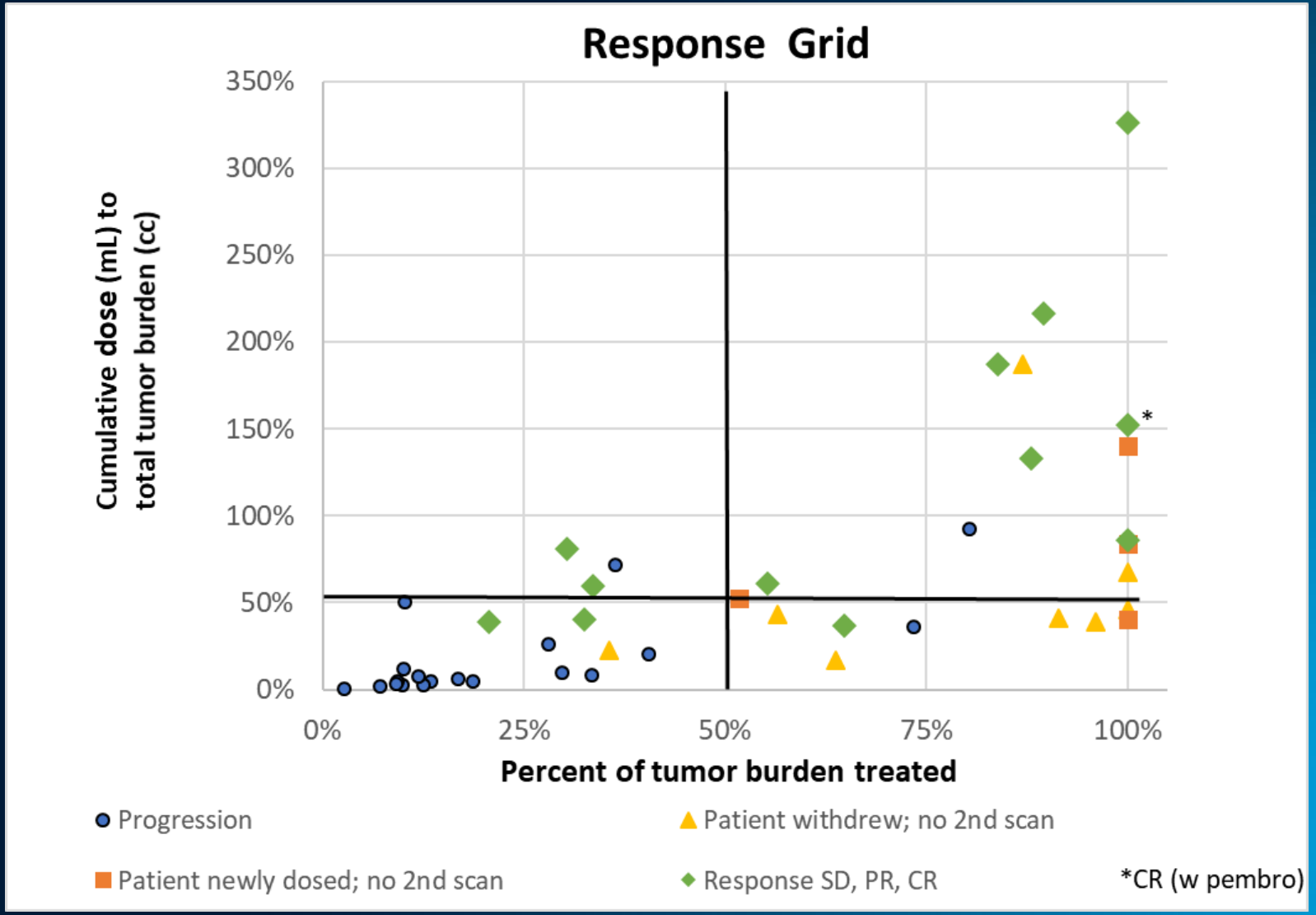
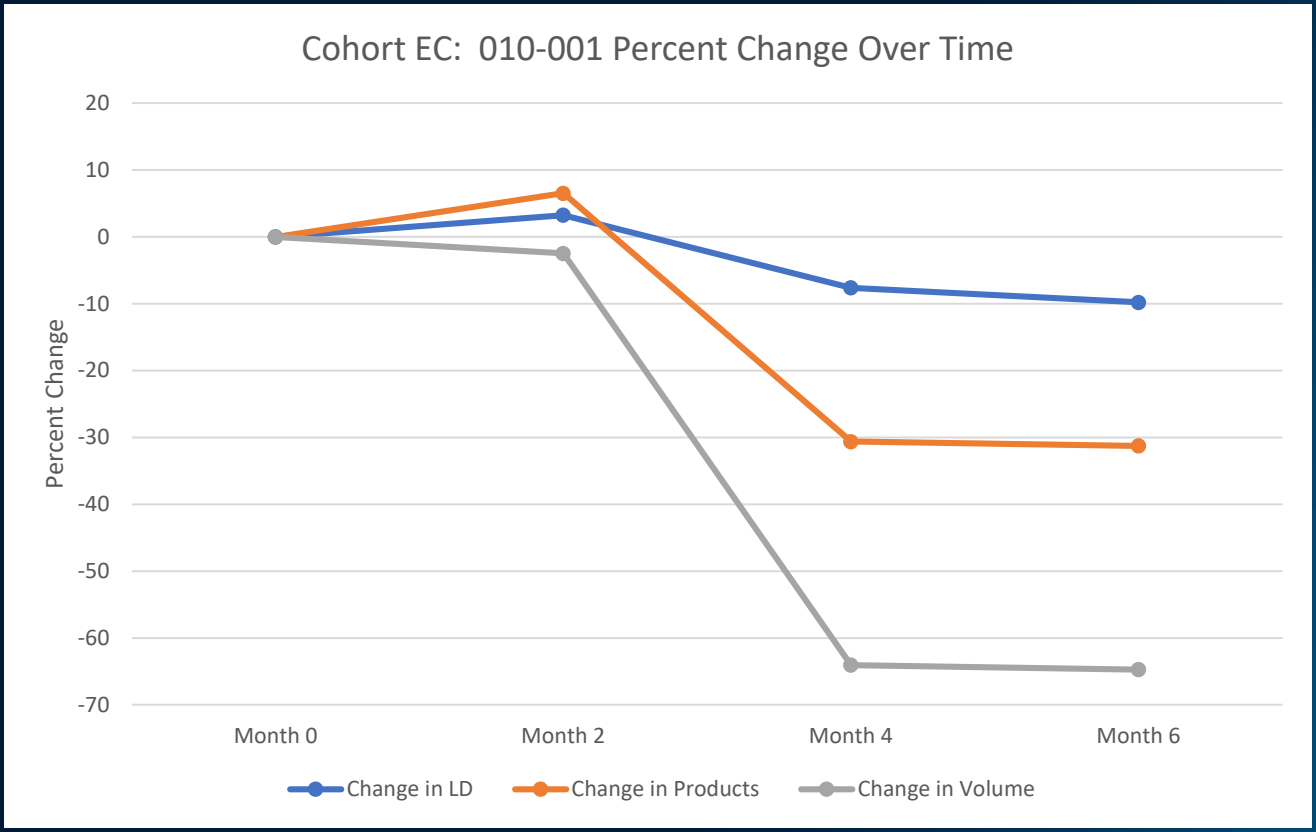
Disease control for:

- Adrenocortical
- Breast (4/4)
- Chordoma
- H&N
- Lung
- Sarcoma
- Squamous cell



RECIST MAY NOT ACCURATELY ASSESS BENEFIT

DCR=39% in evaluable patients, 88% in patients who had > 50% of tumor dosed
7 non-injected tumors reduced in size in 6 patients, 2 tumors > 30%



BY RECIST =10% reduced

BY WHO = 30% reduced

BY VOLUME = 65% reduced

Ellipsoid Criteria (L x W x H)*0.63, > 30% cutoff for **PR**

CIRCULATING BLOOD BIOMARKERS

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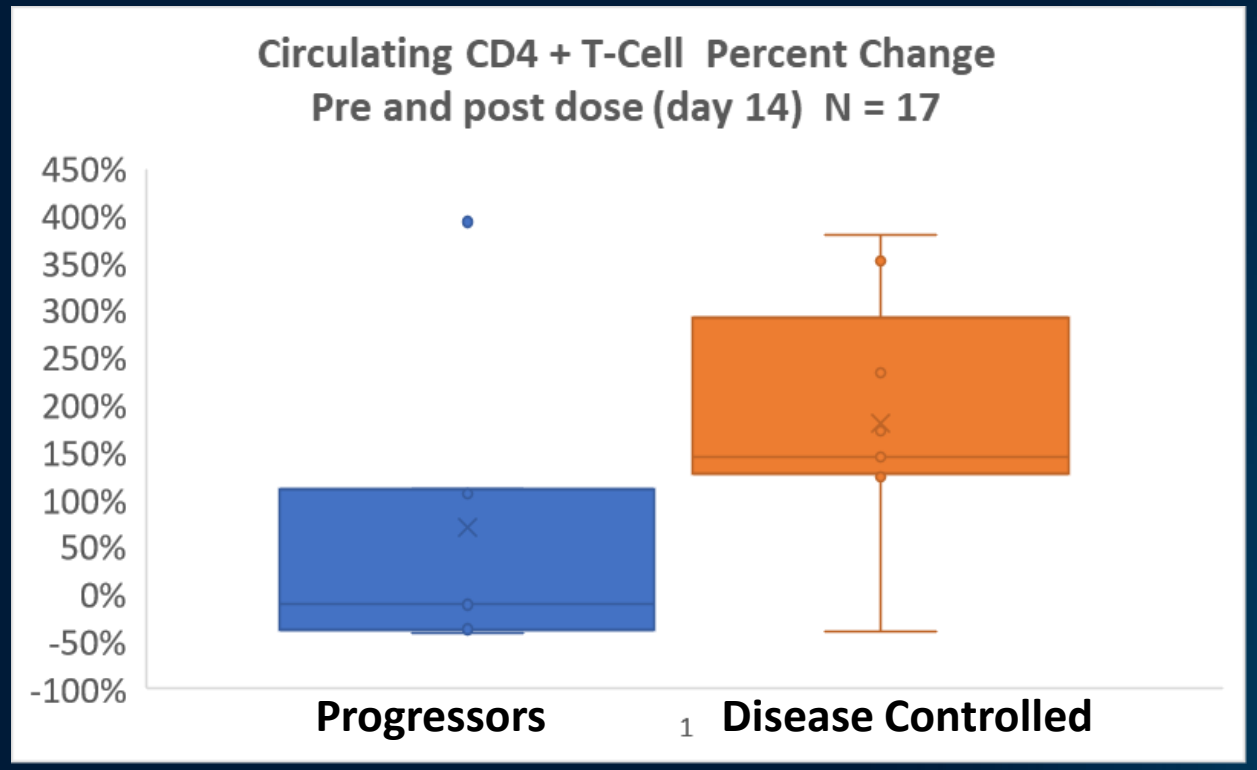
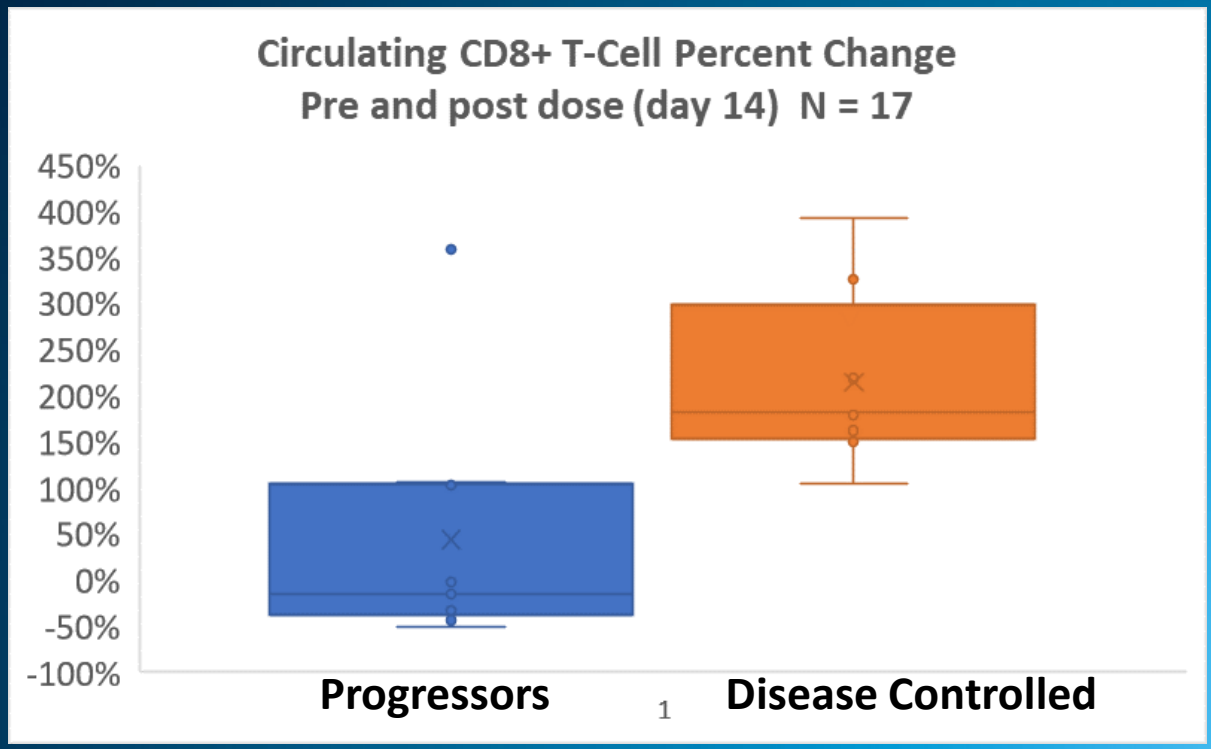
Flow Cytometry (n=17 pts)
Evaluable patients for which samples were collected pre and post dose (day 14)





TUMOR BIOMARKERS FROM BIOPSY

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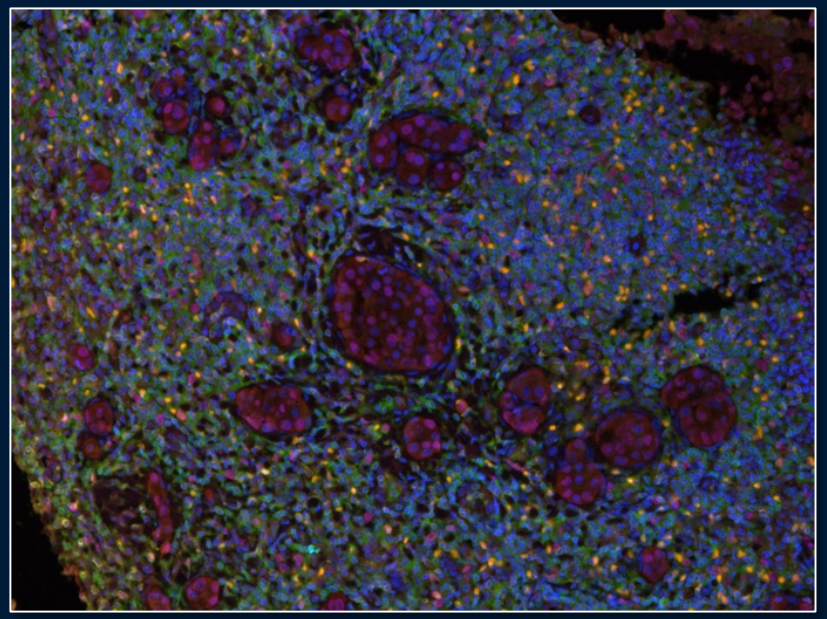
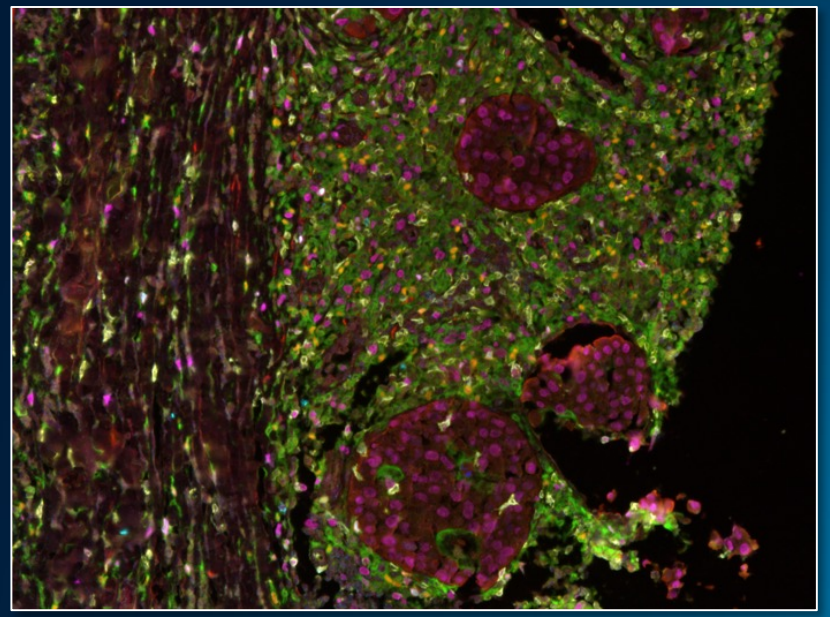
Representative example of a breast cancer subject

PRE



1 Month



Marker	Opal	Color
CD4	520	Green
CD8	620	Yellow
FoxP3	540	Orange
CD25	570	Cyan
Ki67	650	Magenta
CK	690	Red
DAPI		Blue

Multiplex IHC shows:
75% Decrease in Ki67
73% Decrease in Treg
Increase in CD4 and CD8

CONCLUSIONS

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- ✓ INT230-6 was well tolerated at doses up to 160 mL in multiple deep and superficial tumor injections, No related AE led to treatment discontinuation
- ✓ PK suggests that the majority of the drug remains in the tumor
- ✓ INT230-6 shows early signs of clinical benefit. RECIST measurements may not predict clinical benefit accurately with this modality.
- ✓ In addition to tumor cell reduction, Increases in tumor and circulating CD8 and CD4 T-cells and abscopal responses in non-injected tumors support preclinical findings of immune cell engagement following INT230-6 treatment
- ✓ INT230-6 + pembrolizumab cohort ongoing

ACKNOWLEDGEMENTS

Thank you to my co-investigators

Thank you to the patients and families who participated in this study