INTRATUMORAL INT230-6 (CISPLATIN, VINBLASTINE, SHAO) ALONE OR WITH IPILIMUMAB PROLONGED SURVIVAL WITH FAVORABLE SAFETY IN ADULTS WITH REFRACTORY SARCOMAS (NCT 03058289)

Christian Meyer, MD PhD

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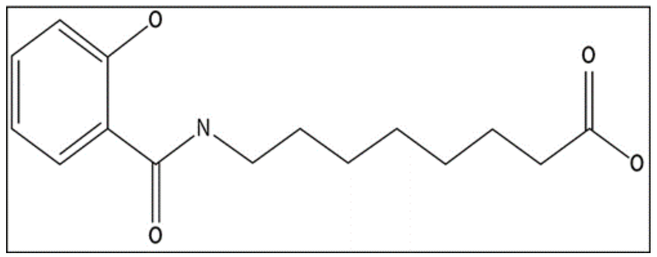
INT230-6 is a Novel Intratumoral Agent Consisting of Cisplatin, Vinblastine and SHAO

Cisplatin & Vinblastine are co-formulated in a fixed ratio with SHAO, a tissue dispersion and cell penetration amphiphilic agent

SHAO



Cisplatin

- **Direct killing**: Binds to DNA to cause apoptotic cell death
- **Immune effects**: Attracts and binds T-Cells via TL9 receptors.

Clin Cancer Res; 20(11) June 1, 2014

Vinblastine

- **Direct killing**: Destroys tubulin to stop replication
- **Immune effects**: induces dendritic cell maturation.

Cancer Res; 2009 Sept 1: 69(17): 6987-6994

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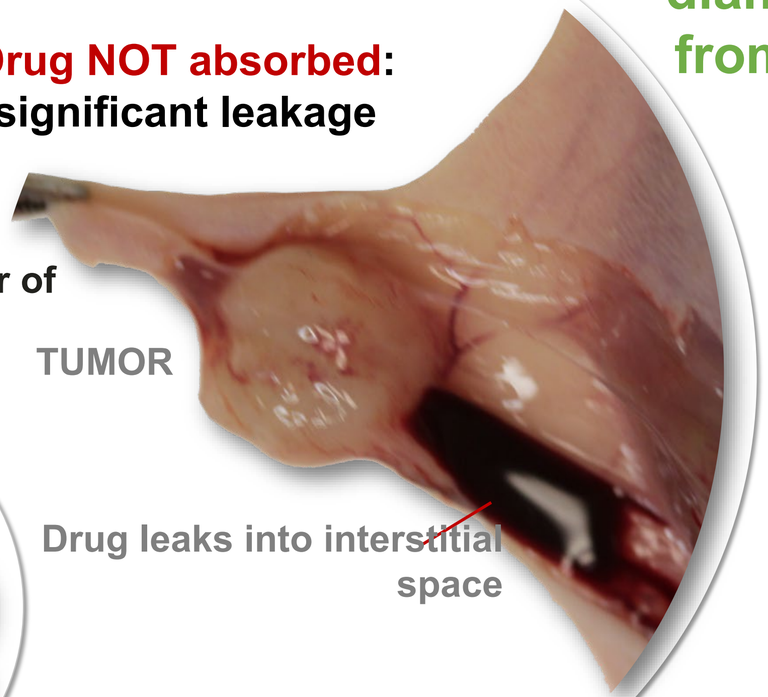
Intratumoral INT230-6 Diffuses in and is Absorbed in Tumors

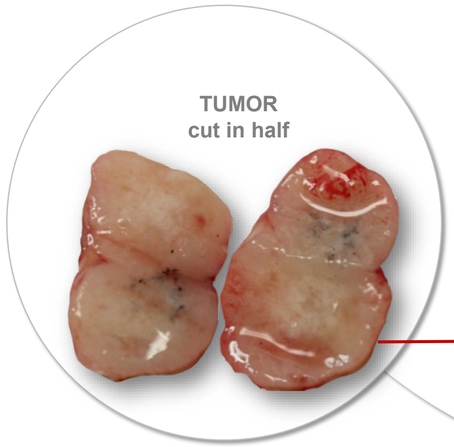
CYTOTOXICS + *dye in H_2O*
Control

Human pancreatic cancer in mouse model

Drug NOT absorbed: significant leakage

Injections made to center of tumor over 90 sec



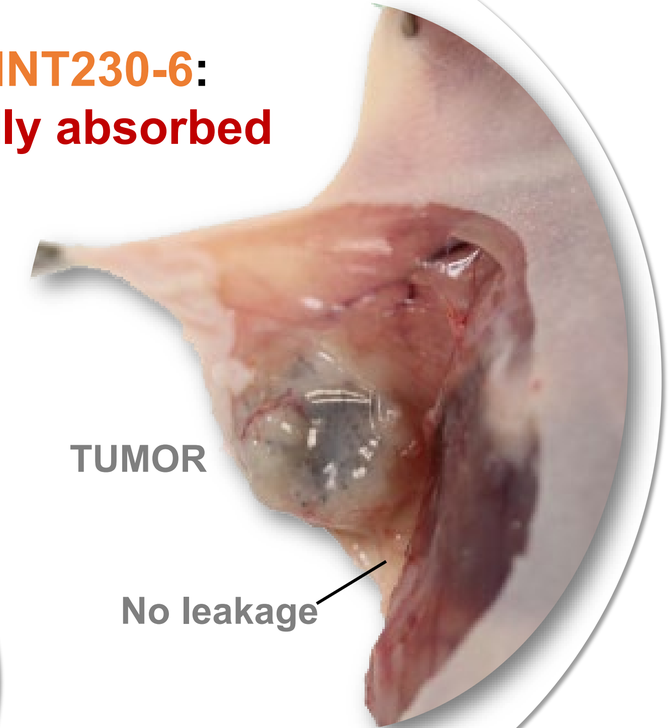


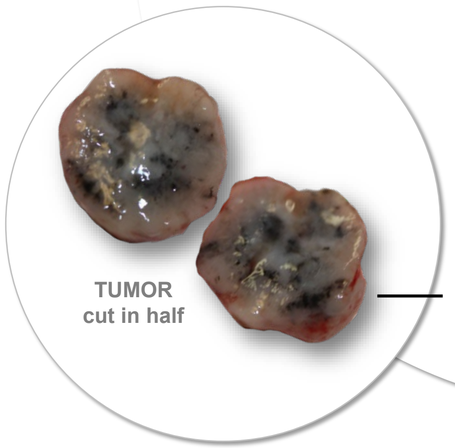
Little to no drug dispersion in all tumors tested

Tumor dose is set by the longest diameter or volume from 3 dimensions

INT230-6 + *dye in H_2O*

INT230-6: Fully absorbed





Significant dispersion in all tumors tested

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International Journal of *Molecular Sciences*
doi.org/10.3390/ijms21124493

INT230-6 Achieves Significant Cancer Killing With One or Two Doses in Multiple Types of Cancer

Breast Cancer tumors fully resected

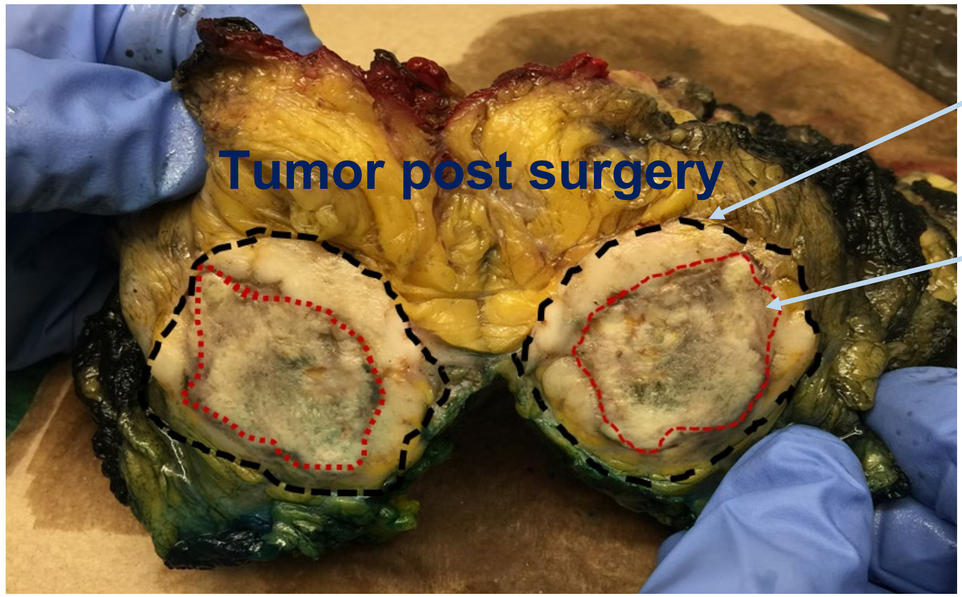
3.9 cm invasive ductal cancer: Grade 3

May 6 — May 13 — May 20

Injection #1: Dose 7.4 cc

Injection #2: Dose 14.8 cc

Surgery



Final Pathology (significant necrosis ~85%)

Tumor Extent

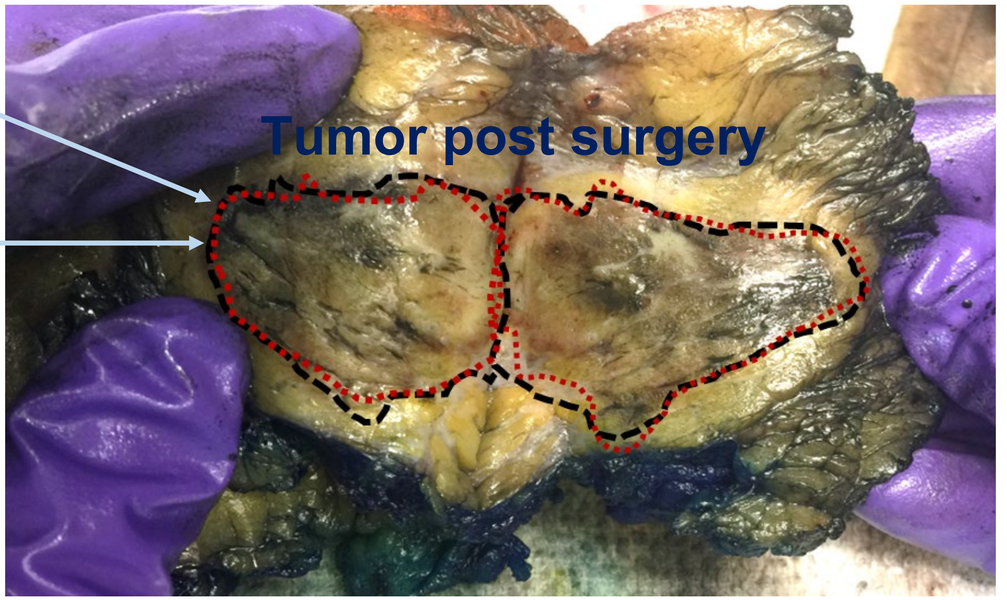
Extent of Necrosis within Tumor

4.4 cm invasive lobular cancer: Grade 2

May 27 — June 16

Injection #1 (only) Dose 21.3 cc

Surgery



Final Pathology (significant necrosis ~95%)

Percent tumor death is dependent on total dose given per treatment per size of tumor

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IT-01: *A Phase 1/2 Study of Intratumoral (IT) INT230-6 in Adult Subjects with Advanced Refractory Cancers, incl. Soft Tissue Sarcomas*

Study Enrollment Completed
INT230-6 monotherapy dose escalation by increasing the frequency, dose volume, number of tumors, and concentration of drugs in the tumors.

- ≥ 18 years
- ECOG PS ≤ 1 for Combo and PS ≤ 2 for Mono
- Advanced solid tumors, relapsed/ refractory

Dose expansion

Ipilimumab combination
Breast cancer, sarcoma, HCC
- INT230-6 dosing as in monotherapy
- Ipi q3 weeks x 4 doses

INT230-6 monotherapy
Any Others
-INT230-6 1 mL per 3 cc of tumor vol., up to 175 mL: q2 weeks x 5 doses
-Maintenance q9 weeks x 2 years

Primary endpoint
Safety

Secondary endpoints
PK measurements
Disease control rate
Overall survival

- INT230-6 IT is proportional to the tumor's volume.
- Dosing was Up to 175 mL (86mg cis, 17.2 mg vin)
- INT230-6 is given every 2 weeks (up to 5x)
- Retreatment or maintenance therapy with INT230-6 was allowed.

ClinicalTrials.gov Identifier: NCT03058289

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Demographics of Sarcoma Patients as of 9/1/2022

DEMOGRAPHICS		
	INT230-6	INT230-6 + IPI
Median Age	64 (42-76)	63 (33-82)
Gender	11 male, 4 female	7 male, 7 female
ECOG	13.3% ECOG 0 80.0% ECOG 1 6.7% ECOG 2	13.3% ECOG 0 80.0% ECOG 1 6.7% ECOG 2
Median number of prior therapies (range)	3 (0-8)	4 (0-9)

Type of Cancer	# of prs
Sacral chordoma	5
Liposarcoma	3
Pleomorphic	2
Chondrosarcoma	1
Kaposi's	1
Leiomyosarcoma	1
Myofibroblastic	1
Osteosarcoma	1

Type of Cancer	# of prs
Leiomyosarcoma	4
Sacral chordoma	2
Chordoma	2
Spindle cell	2
Fibrosarcoma	1
Liposarcoma	1
Langerhan's	1
Pleomorphic	1

- There were 266 injections into the 29 sarcoma patients with 158 (59.3%) into deep visceral tumors

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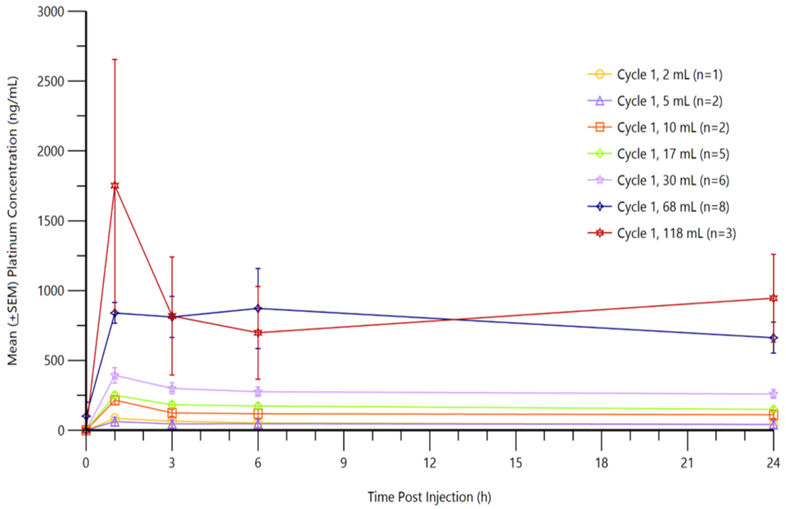
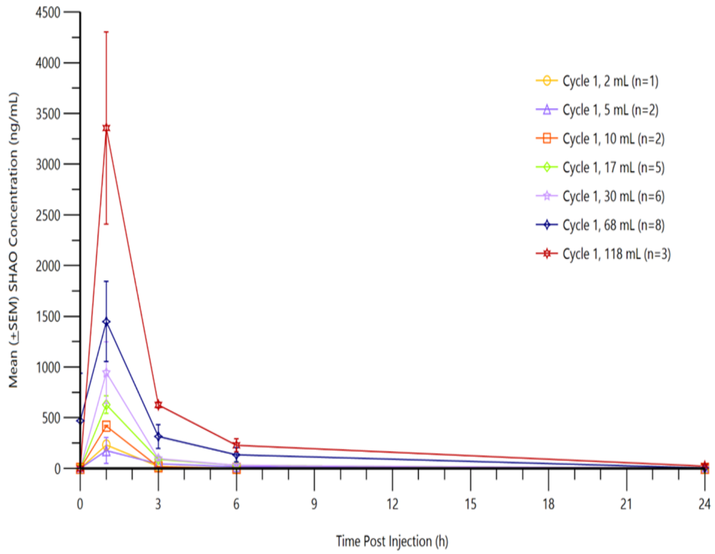
Pharmacokinetics 3 Primary Ingredients of INT230-6 Sarcoma (29 samples)

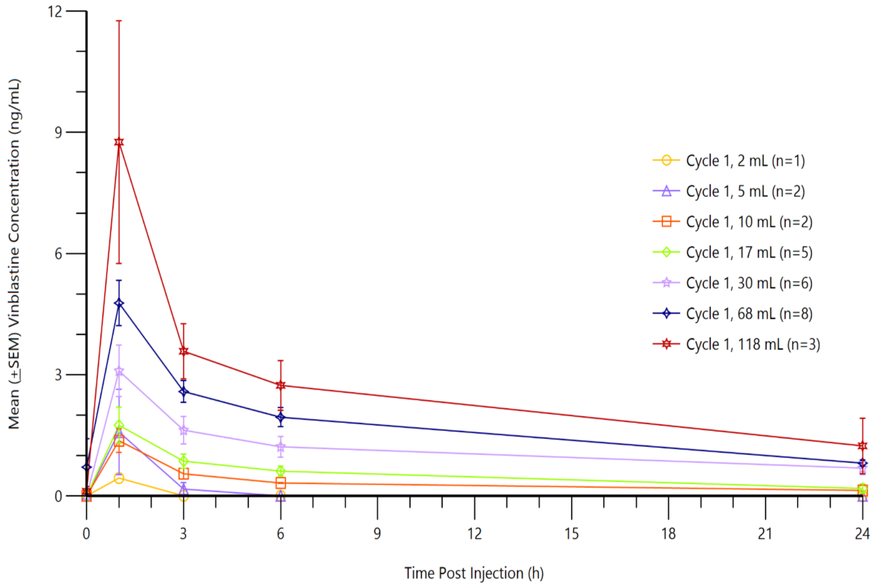
PK of platinum metal first 24 hours following the first INT230-6 dose.



PK of SHAO first 24 hours following the first INT230-6 dose.



PK of vinblastine first 24 hours following the first INT230-6 dose.



>95% of the active agents remain in the tumor relative to IV dosing at 1 to 6 hours

Retention is independent of cancer type, location, or tumor size
(Data reported at ASCO 2022 abstract 2520 poster 176)

Cisplatin levels are not measured - only (non-toxic) platinum metal is seen in the blood

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Treatment-Related AEs in Sarcoma of INT230-6 Alone or With IPI

Monotherapy INT230-6 NCI-CTCAE Toxicity Grade n (%) (N = 15)

MedDRA Coded Preferred Term	1	2	3	Total
Any	3(20.0%)	8(53.3%)	3(20.0%)	14(93.3%)
Localized tumor-related pain	7 (46.7%)	4 (26.7%)	1 (6.7%)	12 (80.0%)
Nausea	3 (20.0%)	3 (20.0%)	0	6 (40.0%)
Fatigue	0	4 (26.7%)	1 (6.7%)	5 (33.3%)
Decreased appetite	0	4 (26.7%)	0	4 (26.7%)
Vomiting	2 (13.3%)	1 (6.7%)	0	3 (20.0%)
Anaemia	1 (6.7%)	1 (6.7%)	1 (6.7%)	3 (20.0%)
Blood creatinine increased	2 (13.3%)	0	0	2 (13.3%)
Hypomagnesaemia	1 (6.7%)	1 (6.7%)	0	2 (13.3%)
Injection site reaction	0	2 (13.3%)	0	2 (13.3%)
Hyponatraemia	1 (6.7%)	0	1 (6.7%)	2 (13.3%)

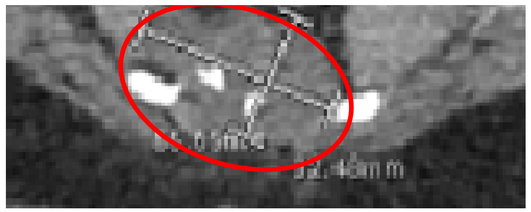
Combination with IPI NCI-CTCAE Toxicity Grade n (%) (N = 14)

MedDRA Coded Preferred Term	1	2	3	Total
Any	4(28.6%)	7(50.0%)	0(0.0%)	12(85.7%)
Localized tumor-related pain	4 (28.6%)	2 (14.3%)	0	6 (42.9%)
Fatigue	3 (21.4%)	2 (14.3%)	0	5 (35.7%)
Nausea	4 (28.6%)	0	0	4 (28.6%)
Vomiting	2 (14.3%)	1 (7.1%)	0	3 (21.4%)
Rash maculo-papular	3 (21.4%)	0	0	3 (21.4%)
Pruritus	3 (21.4%)	0	0	3 (21.4%)
Pyrexia	2 (14.3%)	0	0	2 (14.3%)
Headache	2 (14.3%)	0	0	2 (14.3%)
Chills	1 (7.1%)	1 (7.1%)	0	2 (14.3%)
Decreased appetite	1 (7.1%)	1 (7.1%)	0	2 (14.3%)
Anaemia	0	1 (7.1%)	1 (7.1%)	2 (14.3%)

No grade 4 or 5 related adverse events

In Metastatic Disease Injected Tumors Shrink Over Time

55.65 mm x 32.48 mm
47.5 mm x 18.78 mm



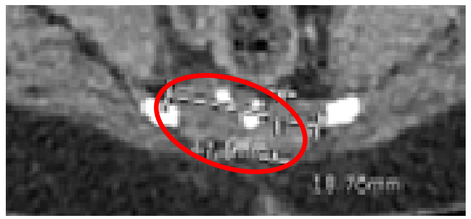
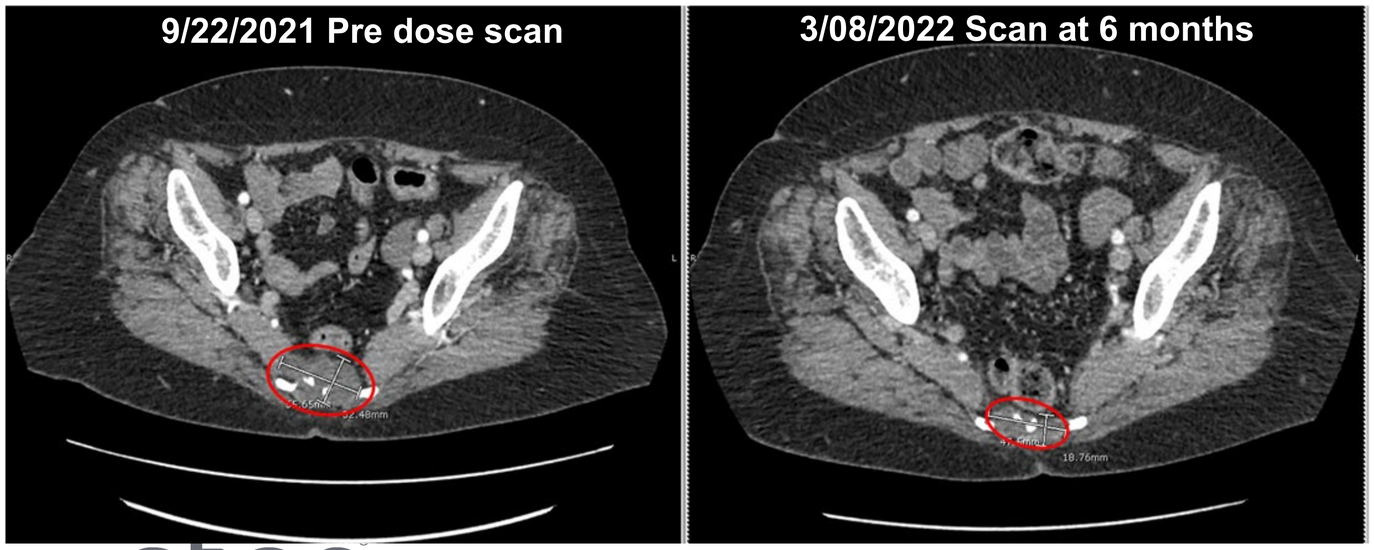


Figure 3 55.65 mm x 32.48 mm 47.5 mm x 18.78 mm



A scan of a chordoma treated with monotherapy highlights tumor regression.

Longest diameter declines 15%, whereas 2nd longest diameter declines 42%

Using WHO Criteria: Partial Response
Using RECIST Criteria: Stable Disease

Shrinkage of uninjected tumors observed

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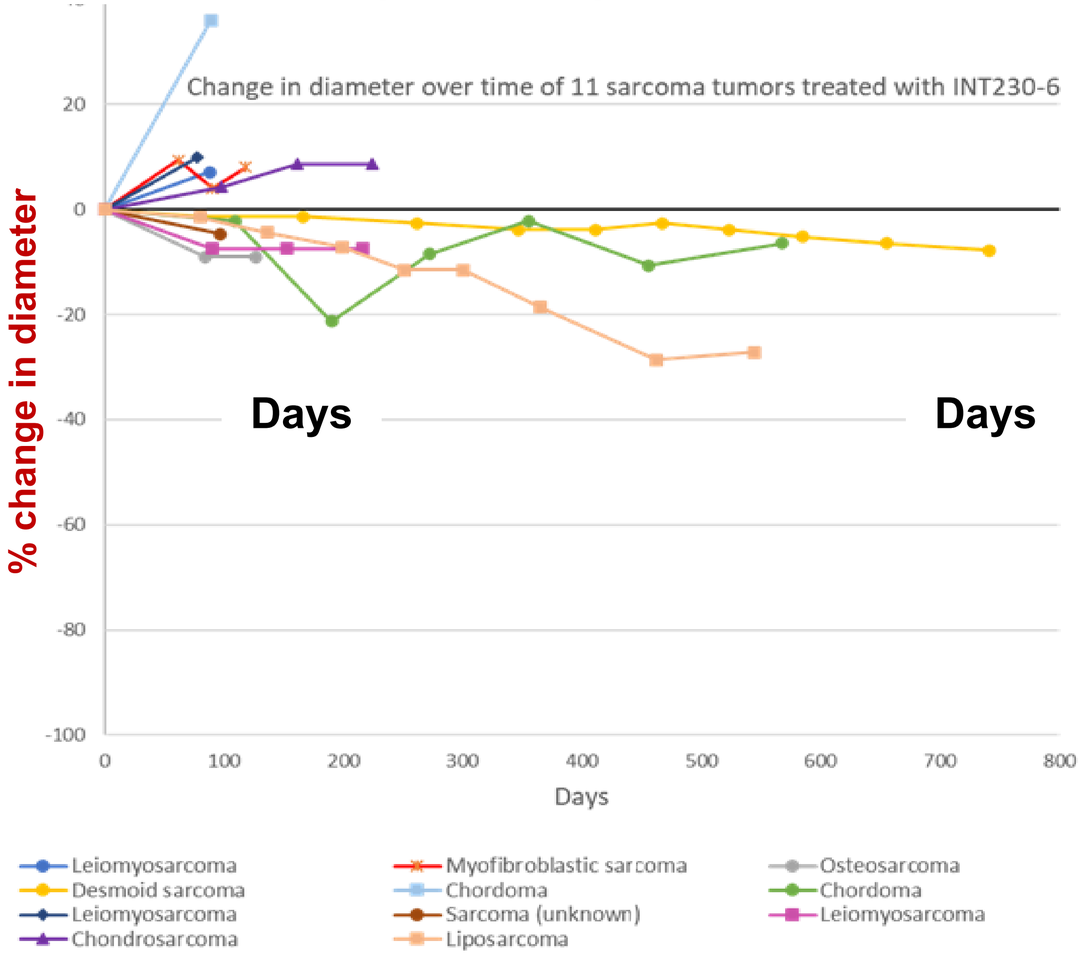
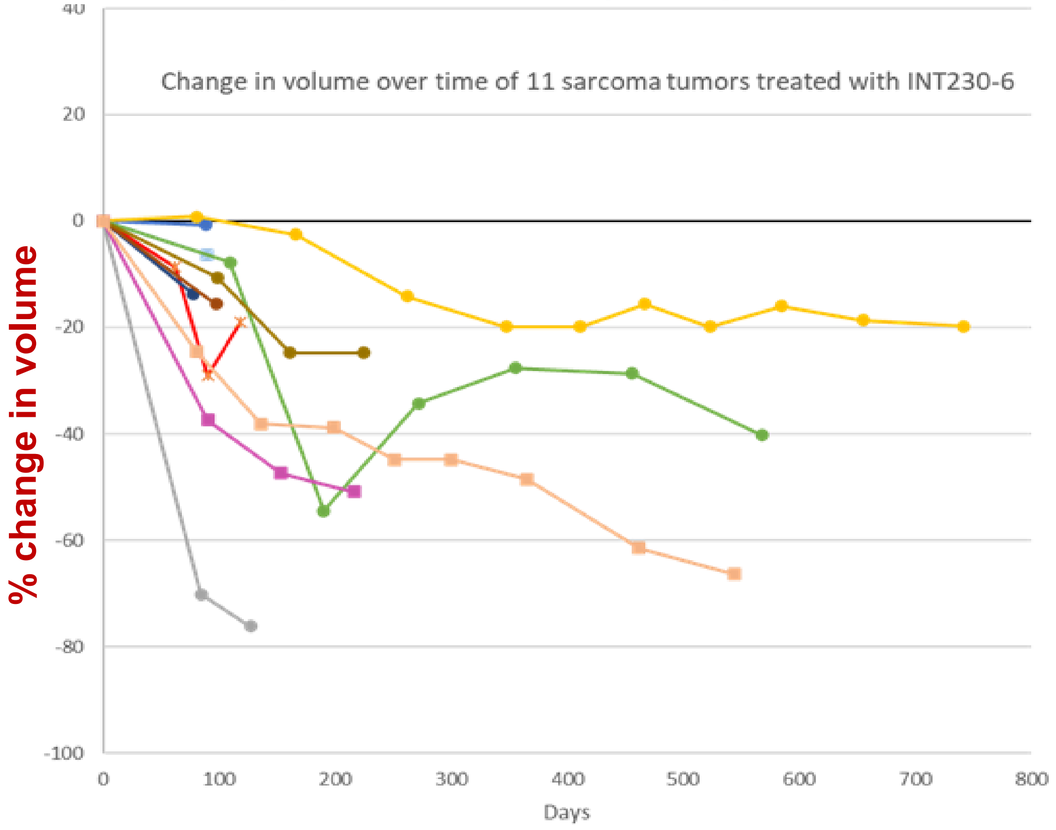
Use of RECIST in Sarcoma May Not Capture Efficacy

Change in Longest Diameter



Change in Volume (using 3 dimensions)



The lack of correlation between diameter and volume indicates that RECIST may be unreliable for IT INT230-6 as a metric of efficacy

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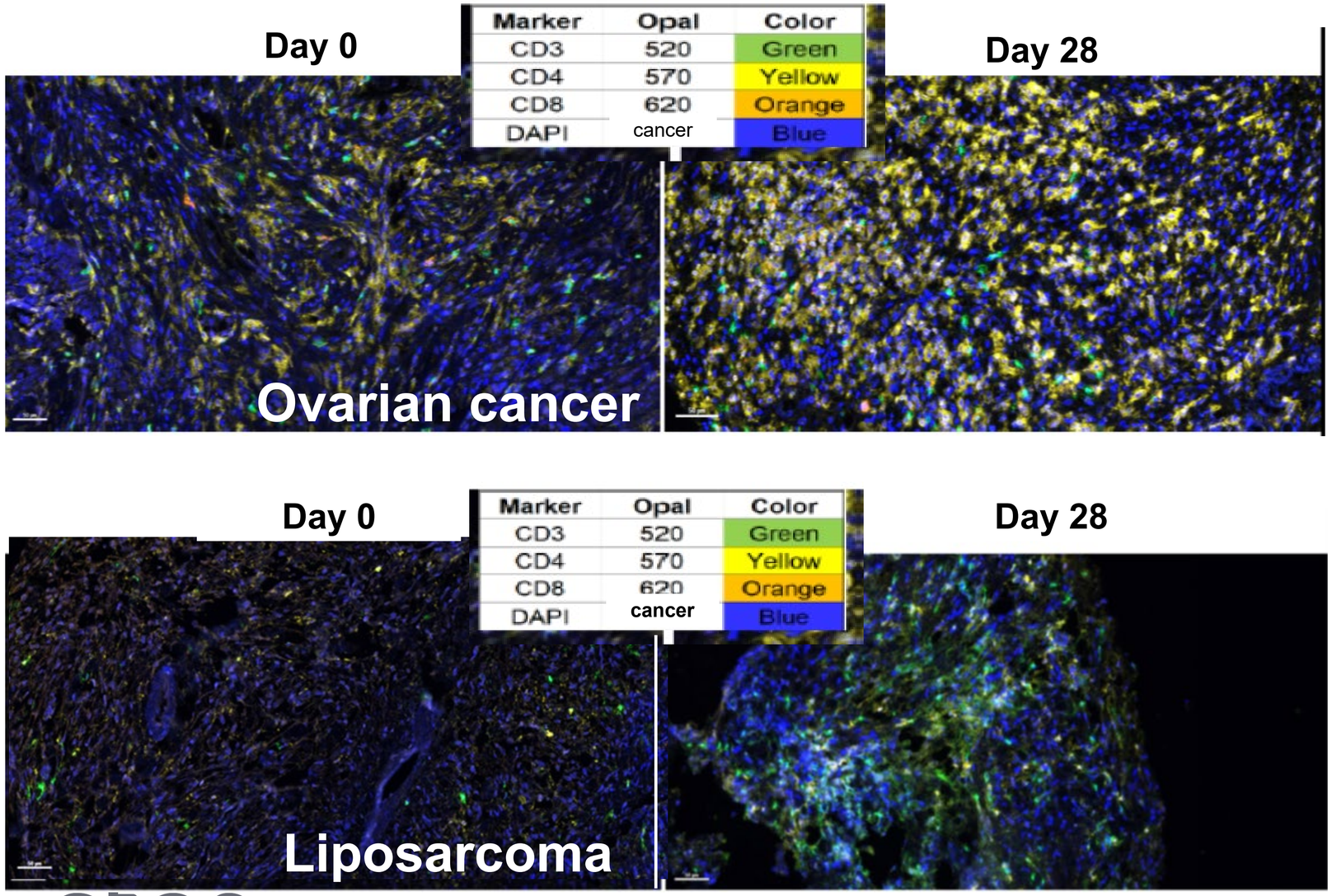
Multiplex IHC from Matched Pair Biopsies Using INT230-6 Monotherapy Reveals Immune Activation in Non-Immunogenic Cancers



2 doses increase CD3, CD4, and CD8 T-cells within the tumor (DAPI)

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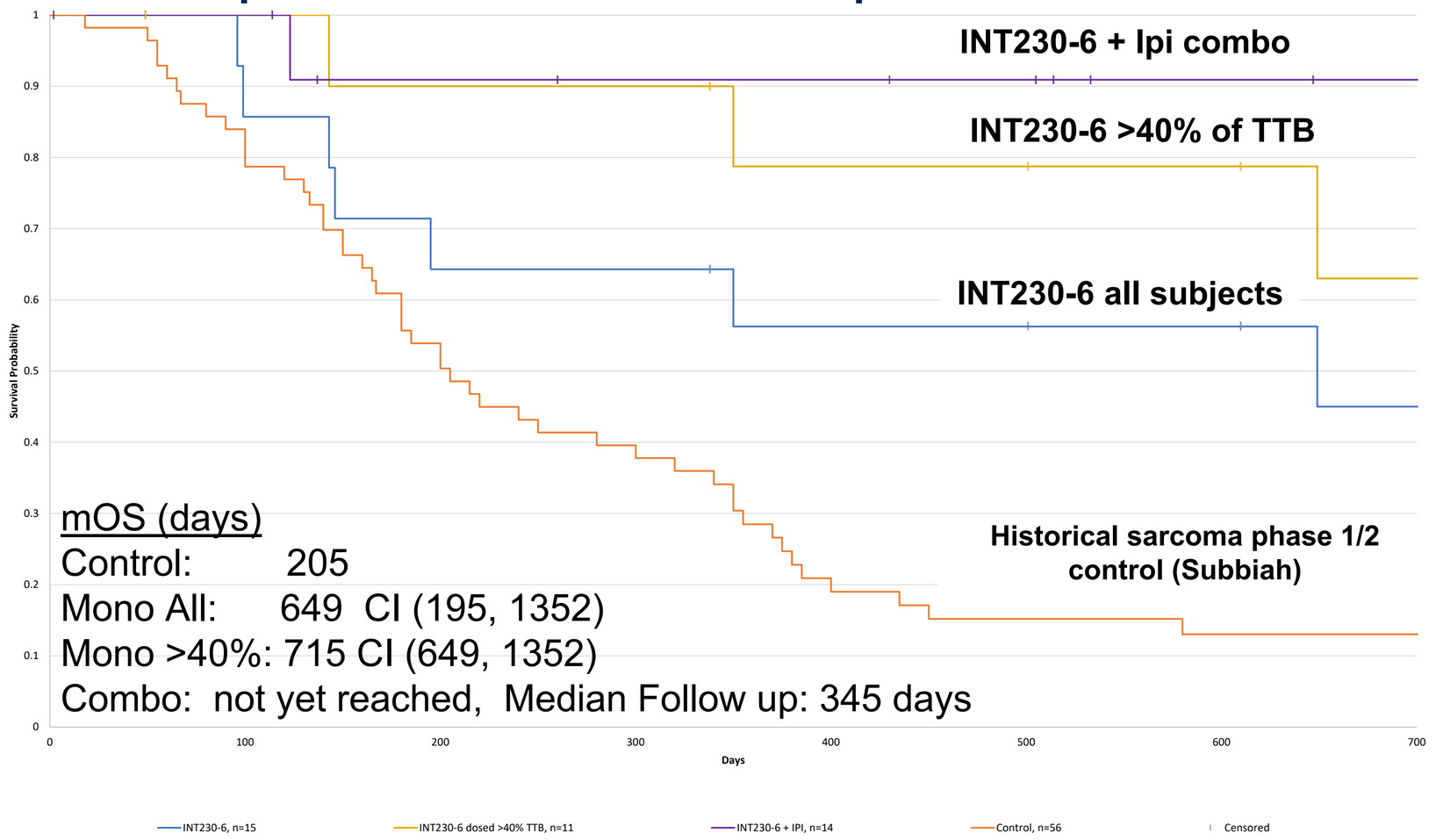
Overall Survival Increased Compared to Historical Results INT230-6 Alone or with Ipilimumab in Sarcoma

Kaplan Meier estimates sarcoma patients



mOS (days)
Control: 205
Mono All: 649 CI (195, 1352)
Mono >40%: 715 CI (649, 1352)
Combo: not yet reached, Median Follow up: 345 days

Dose relative to incoming total tumor burden (TTB) show increased survival with higher drug ratio

Favorable hazard ratios (HR)

Abscopal responses seen

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Phase 3 Trial Design for INT230-6 in Soft Tissue Sarcoma (STS) Schema
2nd or 3rd Line

HR: 0.65

Overall survival:
14.0 months Control
21.5 months INT230-6

- ≥ 18 years
- ECOG PS ≤ 2
- Locally recurrent, inoperable or metastatic Soft Tissue Sarcomas
- **2L/3L**
- measurable disease by RECIST 1.1
- at least one target tumor for injection

Must have had doxorubicin

2:1

n = up to 332

INT230-6

- INT230-6 q2 weeks x 5 doses
- Maintenance q9 weeks x 22 months

SOC

- Pazopanib: 800 mg PO qD
- Trabectedin: 1.5 mg/m2 BSA as a 24-hour IV infusion q3 weeks
- Eribulin: 1.4 mg/m2 BSA IV on Days 1 and 8 q3 weeks

Primary Endpoint:
- OS

Secondary Endpoints:
- Safety
- QoL
- OS for leiomyosarcoma
- OS for liposarcoma

Data readout at 80% of events

Two interim looks at 50% and 75% of events: test for futility and endpoint

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Conclusions

- INT230-6 is well tolerated with favorable safety as monotherapy and in combination with Ipilimumab
- PK data indicates drug stays in the tumor
- INT230-6 demonstrates direct tumor killing.
- Biopsies and resected tumors indicate substantial tumor necrosis can be achieved
- Data shows increased TILs (infiltration with CD4 and CD8 T-cells) into the tumor.
- An exploratory analysis suggests promising survival for subjects receiving an INT230-6 dose ≥40% of their tumor burden compared to historic survival [1,2]
- A randomized Phase III study with INT230-6 in subjects with soft tissue sarcoma is planned in 2023.

1. Laguna-Garrido **et al.** Cancer 3/2012 **2**. Chau et al. BMC Cancer 10/2011

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Conclusions

- The study teams would like to thank the patients and their families who participated in the trial

- The study teams coordinators and nurses

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Tasnia Hasan	Xiomara Menendez	Ravi Louis	Dawn Pepka-Jones
Maryia Yanekina	Negeen Izadian	John Ojo	Yasmin Haider
Jessica Levano	Cristina Deleon	Saisi (Elaine) Omingo	Jacqueline Wheeler
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