SAFETY AND EFFICACY FROM A PHASE 1/2 STUDY OF INTRATUMORAL INT230-6 ALONE OR IN COMBINATION WITH IPILIMUMAB [INTENSITY# IT-01; BMS# CA184-592] IN ADULT SUBJECTS WITH METASTATIC SARCOMAS (NCT 03058289)

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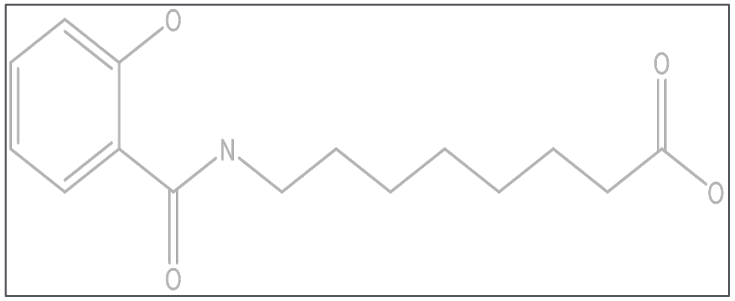
INT230-6 is a novel intratumoral agent consisting of cisplatin, vinblastine and SHAO

Cisplatin & Vinblastine is 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.

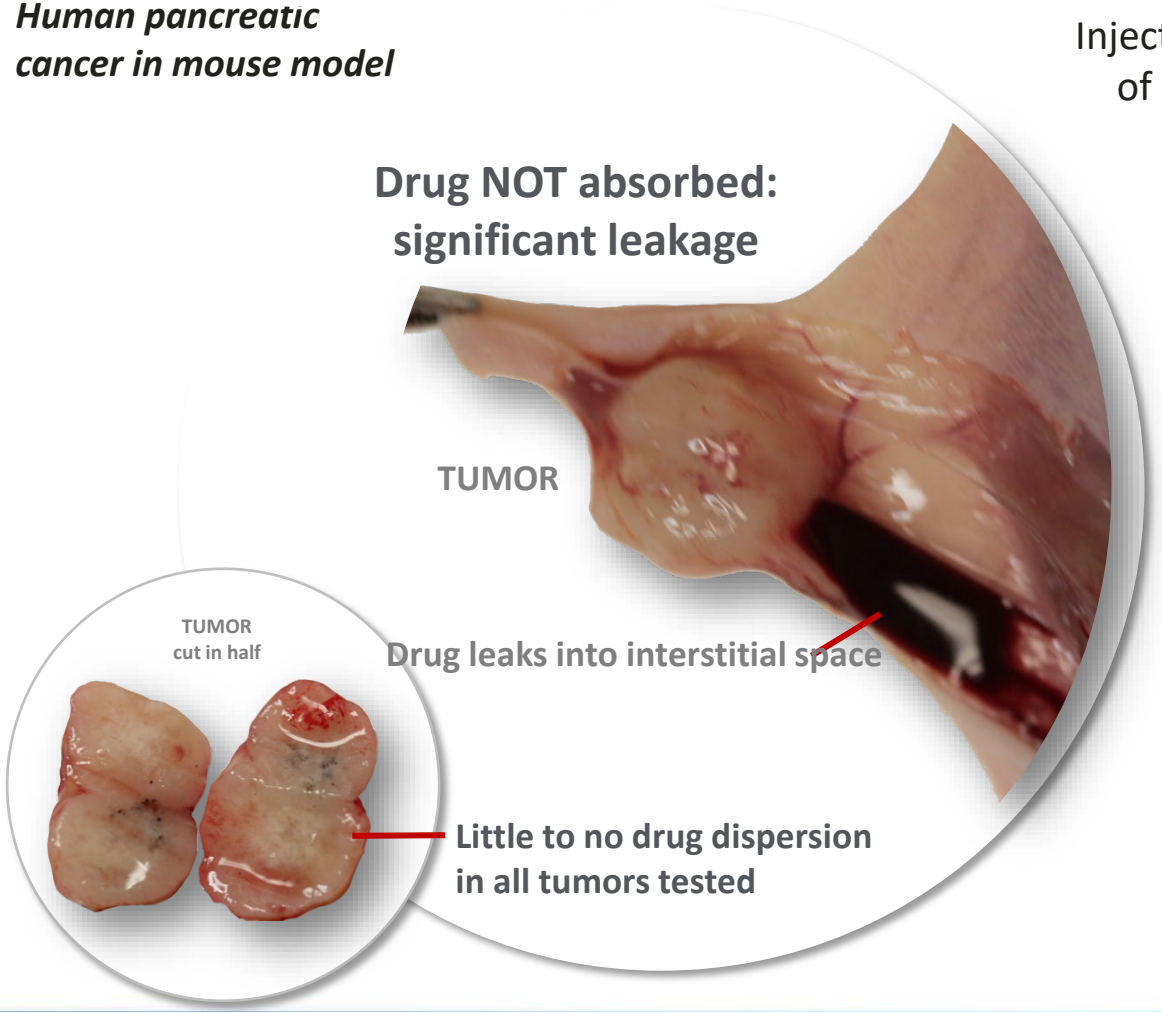
Cancer Res; 2009 Sept 1: 69(17): 6987-6994

Intratumoral INT230-6 diffuses in and is absorbed in tumors

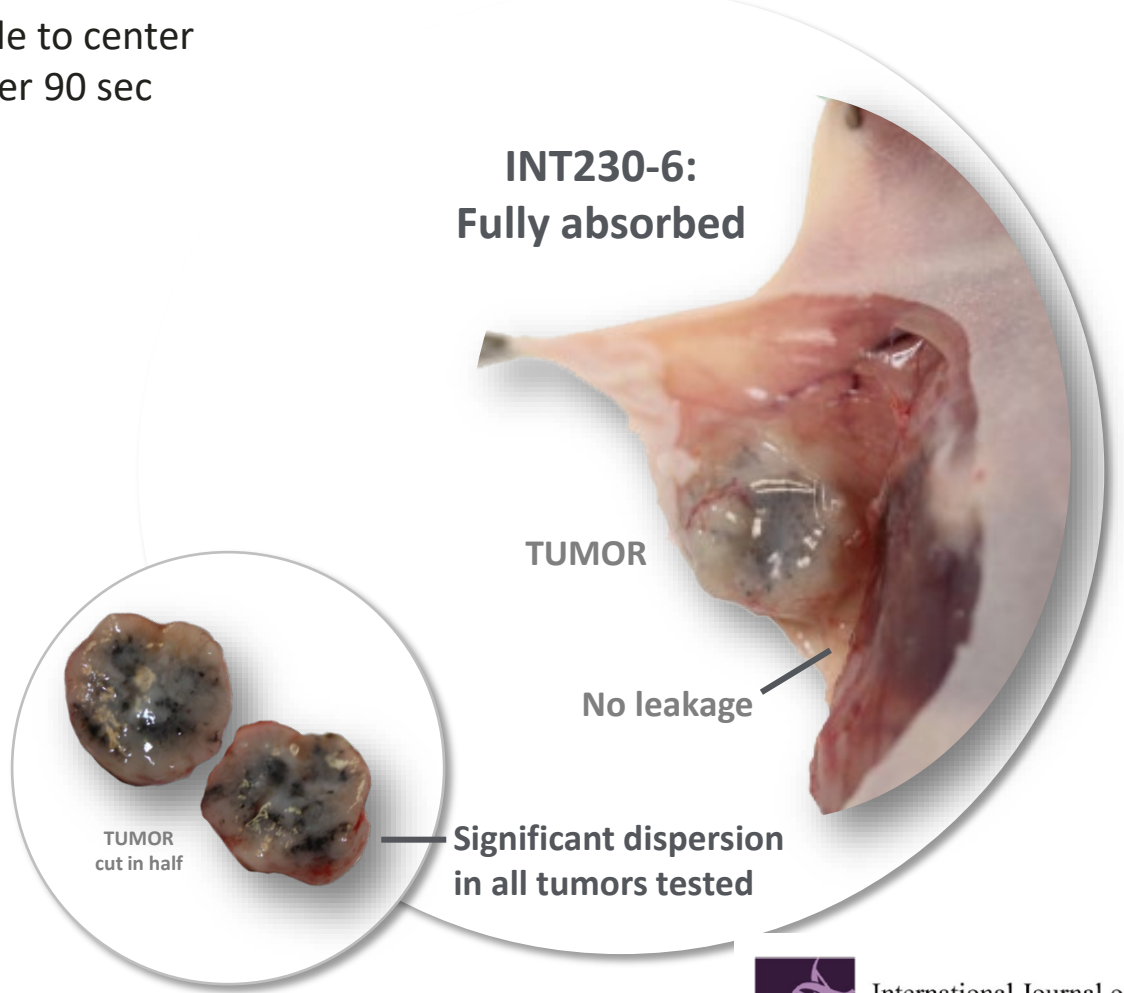
Human pancreatic cancer in mouse model

CYTOTOXICS *+ dye in H_2O*

Injections made to center of tumor over 90 sec

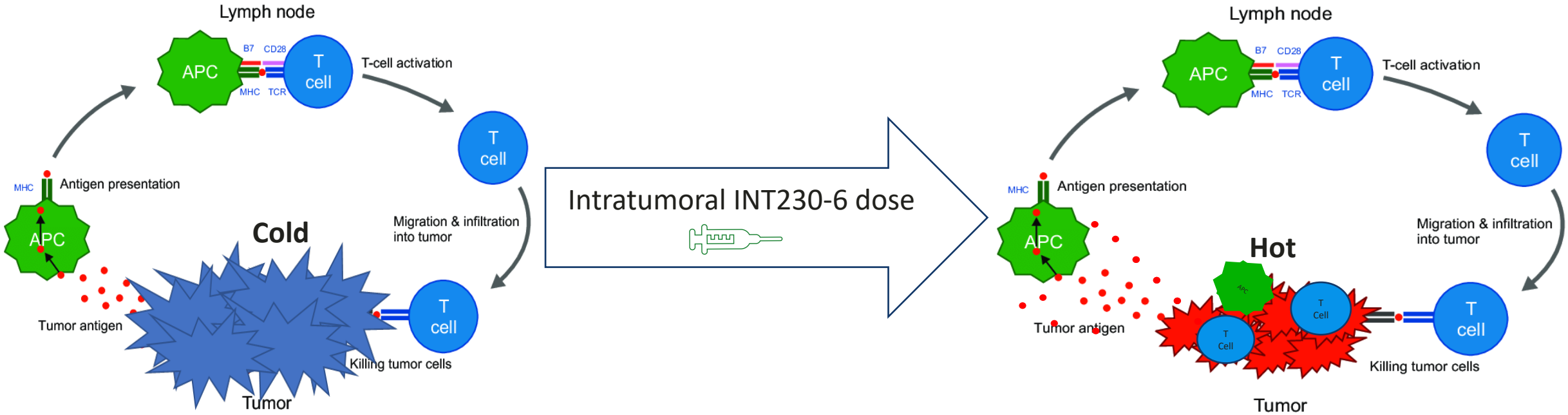


INT230-6 *+ dye in H_2O*



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

INT230-6 overcomes problems of current therapies to treat cancer and alter tumors



Tumor microenvironment is unfavorable to treatment

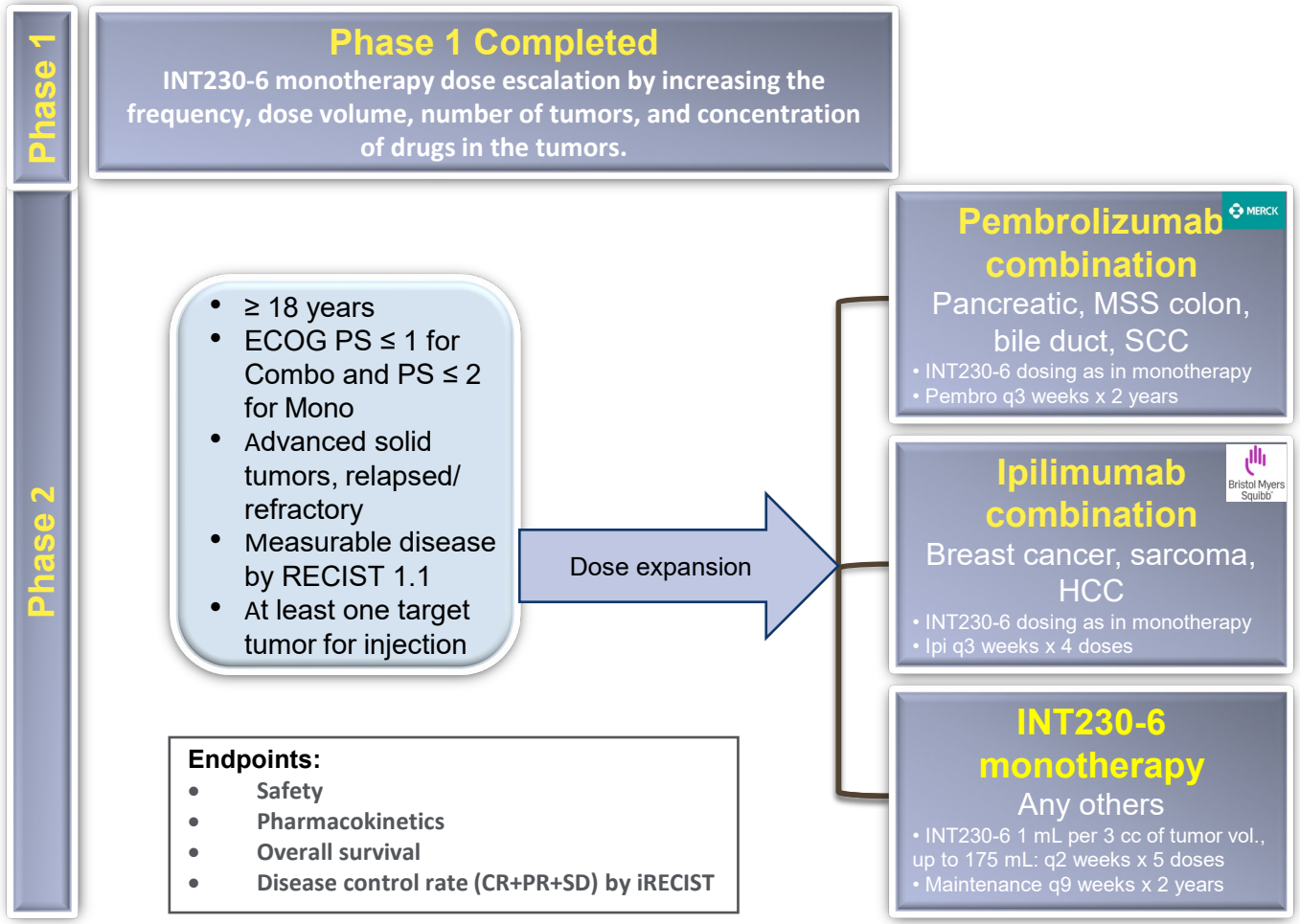
- Systemic delivered drugs can not reach hypoxic areas
- Tumor microenvironment can inhibit T-cells.
- Cytokines produced by cancer cells prevent Antigen Preventing Cell recognition.

Post-INT2306 Injection: Necrotic tumor

- INT230-6 saturates tumor with killing agents – cancer dies, including hypoxic areas.
- Larger quantities of quality antigen are released.
- Tumor microenvironment now favorable to T-cell and APC influx.

Modified Image originally from Tumor Immunology and Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer; January 2018 Tuberculosis and Respiratory Diseases 81(1):29.

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



- INT230-6 dosing is proportional to the injected tumor's volume.
- Up to 175 mL (86mg cis, 17.2 mg vin) injected in 1 up to 5 lesions at one session.
- Injections performed into superficial and 390+ deep tissues, including liver, lung, pancreas and other deep tissues.
- INT230-6 is administered IT every 2 weeks for 5 doses as monotherapy or on the same schedule in combination with Ipilimumab which was dosed at 3mg/kg IV every 3 weeks for a total of 4 doses.
- Retreatment or maintenance therapy with INT230-6 was allowed.

ClinicalTrials.gov Identifier: NCT03058289

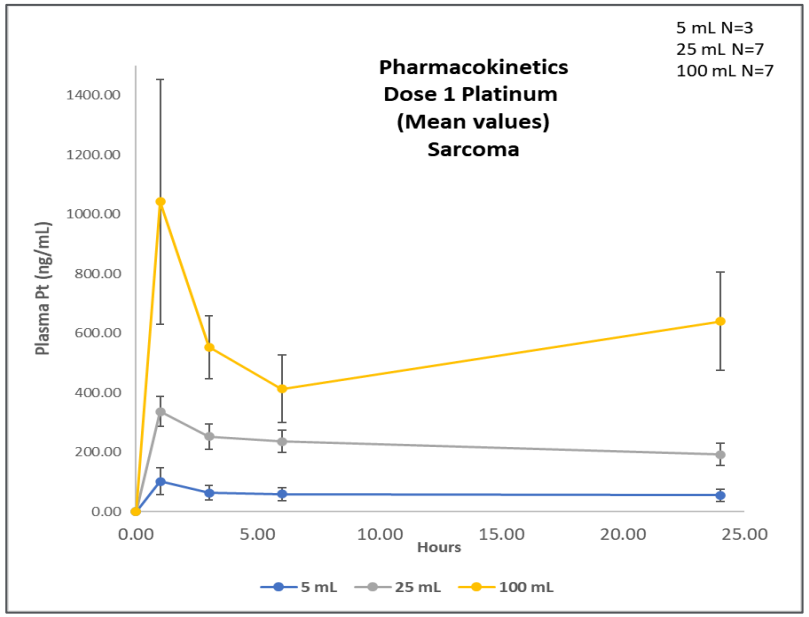
Demographics as of July 31, 2021

DEMOGRAPHICS	
Age	Median 64 (33-82)
Gender	11 male, 8 female
ECOG	32% ECOG 0 63% ECOG 1 5% ECOG 2
Median number of prior therapies (range)	3 (0-9)
Tumor types	4 Leiomyosarcoma, 3 Liposarcoma, 3 Pleomorphic sarcomas, 3 Chondrosarcomas, and 1 each of myofibroblastic sarcoma, chondroid syringoma, desmoid type, myxofibrosarcoma, malignant solitary fibrous tumor, and Kaposi sarcoma

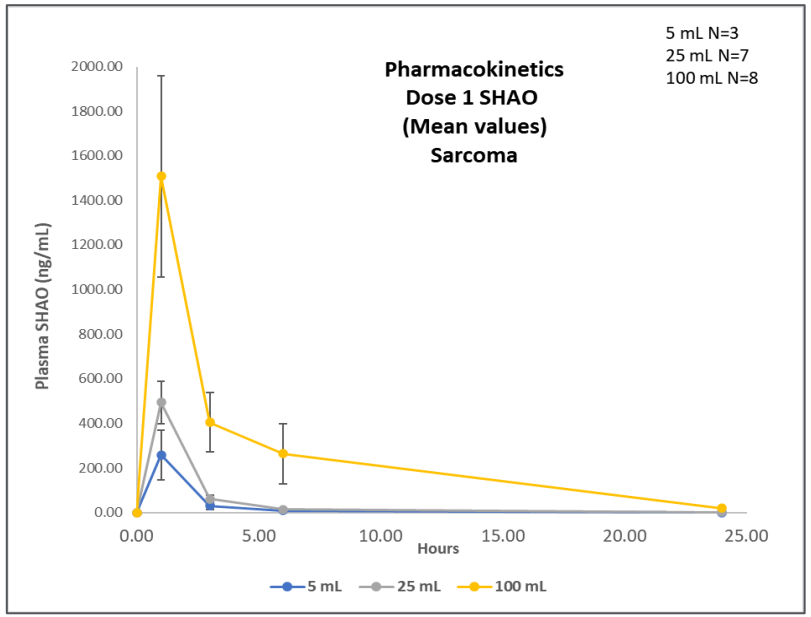
- 19 soft tissue sarcoma (STS) subjects (10 monotherapy, 8 combination with ipilimumab, and 1 other checkpoint combination).
- Demographics were similar in subjects enrolled in monotherapy and checkpoint inhibitor combination arms.
- INT230-6 doses: Cumulative dose of INT230-6 IT injections ranged from 20 to 530mL (265mg cisplatin, 53mg vinblastine), with repeated intratumoral injections in multiple tumors.
- Since there were few evaluable subjects in the ipilimumab combination, the safety dataset was evaluated for all sarcoma subjects.
- Pharmacokinetic (PK) profile analysis from 18 STS subjects in IT-01 Phase 1 and 2 cohorts were analyzed for cisplatin, SHAO and vinblastine as of August 5, 2021.

Pharmacokinetics

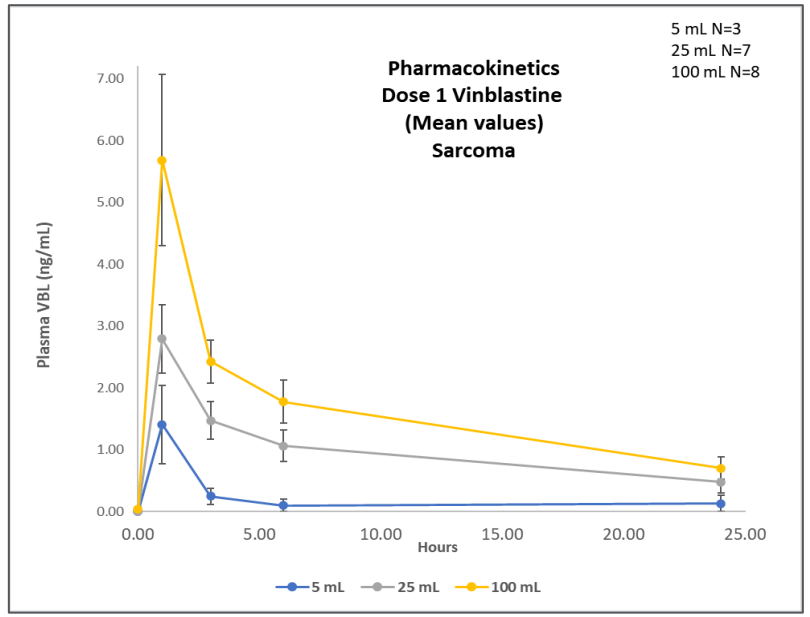
Pharmacokinetic profiles for retained platinum for the first 24 hours following the first INT230-6 dose for 17 samples by dose.



Pharmacokinetic profiles for SHAO for the first 24 hours following the first INT230-6 dose for 18 samples by dose.



Pharmacokinetic profiles for vinblastine for the first 24 hours following the first INT230-6 dose for 18 samples by dose.



Related AEs in INT230-6 alone or checkpoint inhibitor combination by max severity in >1 STS subject (n=19)

	Grades					
Preferred Term	1	2	3	4	5	Total
No. of subjects with least 1 AE	4 (21.1%)	10 (52.6%)	4 (21.1%)	0	0	18 (94.7%)
Localized tumor-related pain	6 (31.6%)	6 (31.6%)	1 (5.3%)	0	0	13 (68.4%)
Nausea	6 (31.6%)	2 (10.5%)	0	0	0	8 (42.1%)
Decreased appetite	1 (5.3%)	6 (31.6%)	0	0	0	7 (36.8%)
Fatigue	3 (15.8%)	3 (15.8%)	1 (5.3%)	0	0	7 (36.8%)
Vomiting	4 (21.1%)	2 (10.5%)	0	0	0	6 (31.6%)
Anaemia	0	1 (5.3%)	2 (10.5%)	0	0	3 (15.8%)
Pruritus	3 (15.8%)	0	0	0	0	3 (15.8%)
Rash maculo-papular	3 (15.8%)	0	0	0	0	3 (15.8%)
Blood creatinine increased	2 (10.5%)	0	0	0	0	2 (10.5%)
Chills	1 (5.3%)	1 (5.3%)	0	0	0	2 (10.5%)
Dizziness	1 (5.3%)	1 (5.3%)	0	0	0	2 (10.5%)
Headache	1 (5.3%)	1 (5.3%)	0	0	0	2 (10.5%)
Hypomagnesaemia	1 (5.3%)	1 (5.3%)	0	0	0	2 (10.5%)
Hyponatraemia	1 (5.3%)	0	1 (5.3%)	0	0	2 (10.5%)
Injection site reaction	0	2 (10.5%)	0	0	0	2 (10.5%)
Pyrexia	2 (10.5%)	0	0	0	0	2 (10.5%)

Hematoxylin and Eosin (H&E) from matched pair biopsies from a STS subject pre and post two INT230-6 injections

- H&E assessments demonstrated substantial reductions of cancer cells in biopsies from INT230-6 monotherapy subjects after two injections of INT230-6, when compared to baseline.

Image A: Pre-dose Day 0

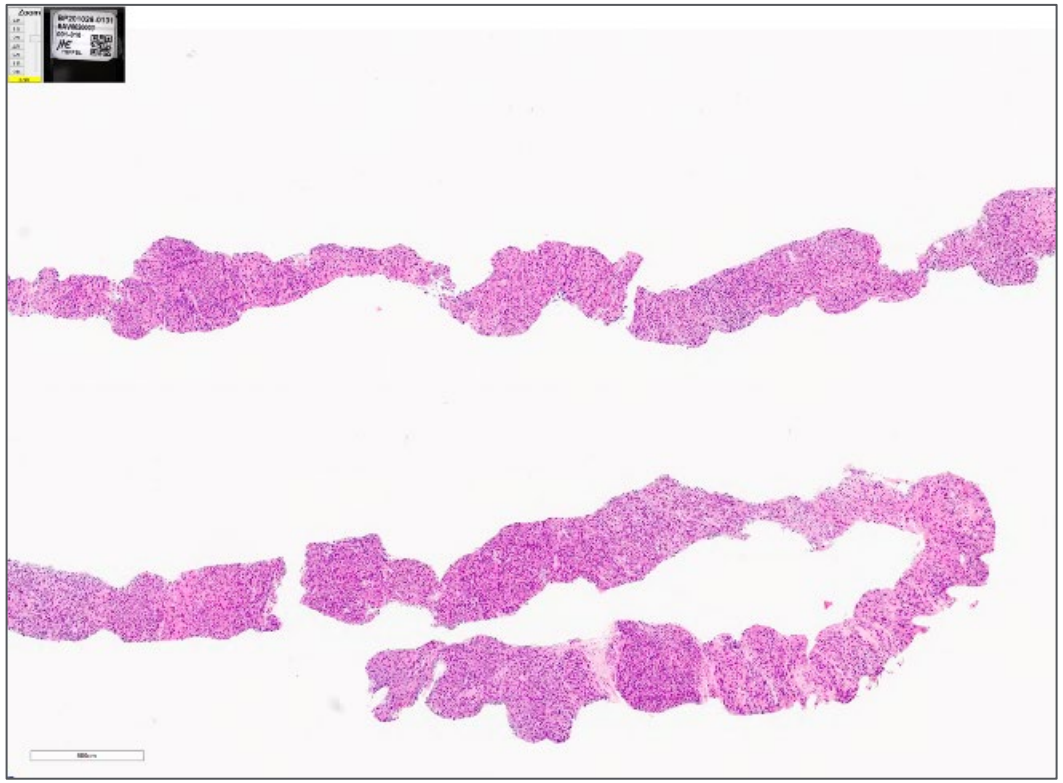


Image B: Post 2 doses Day 28

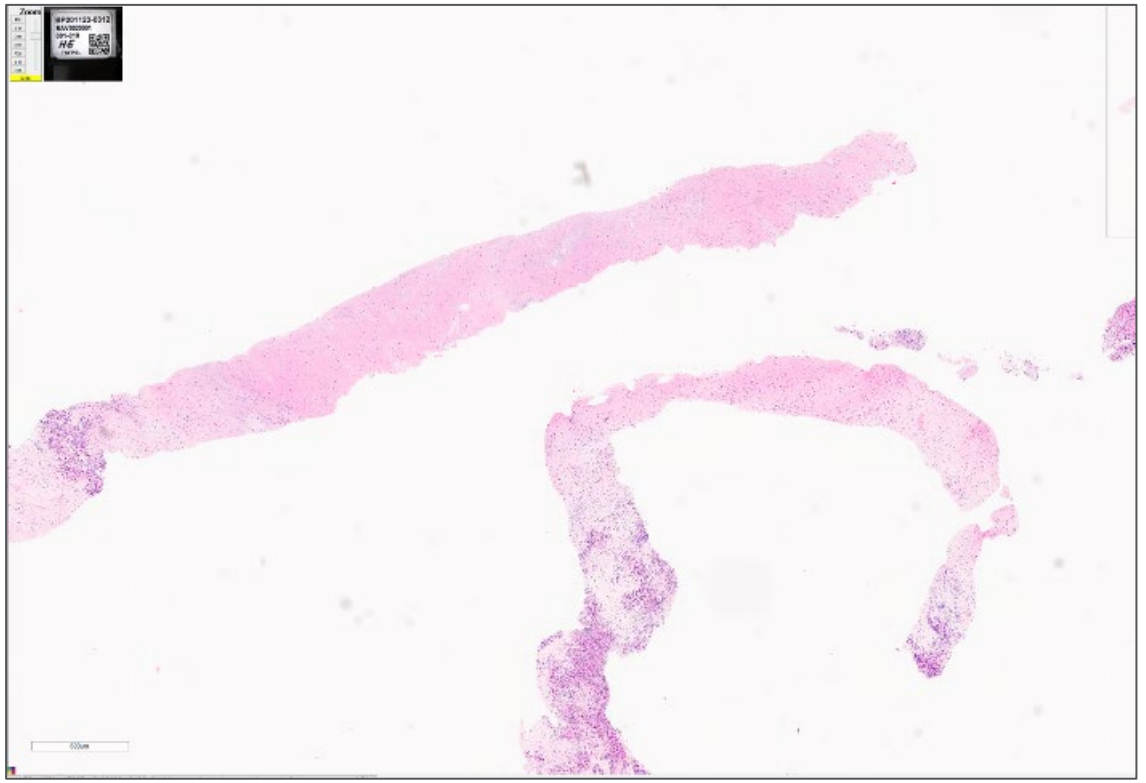
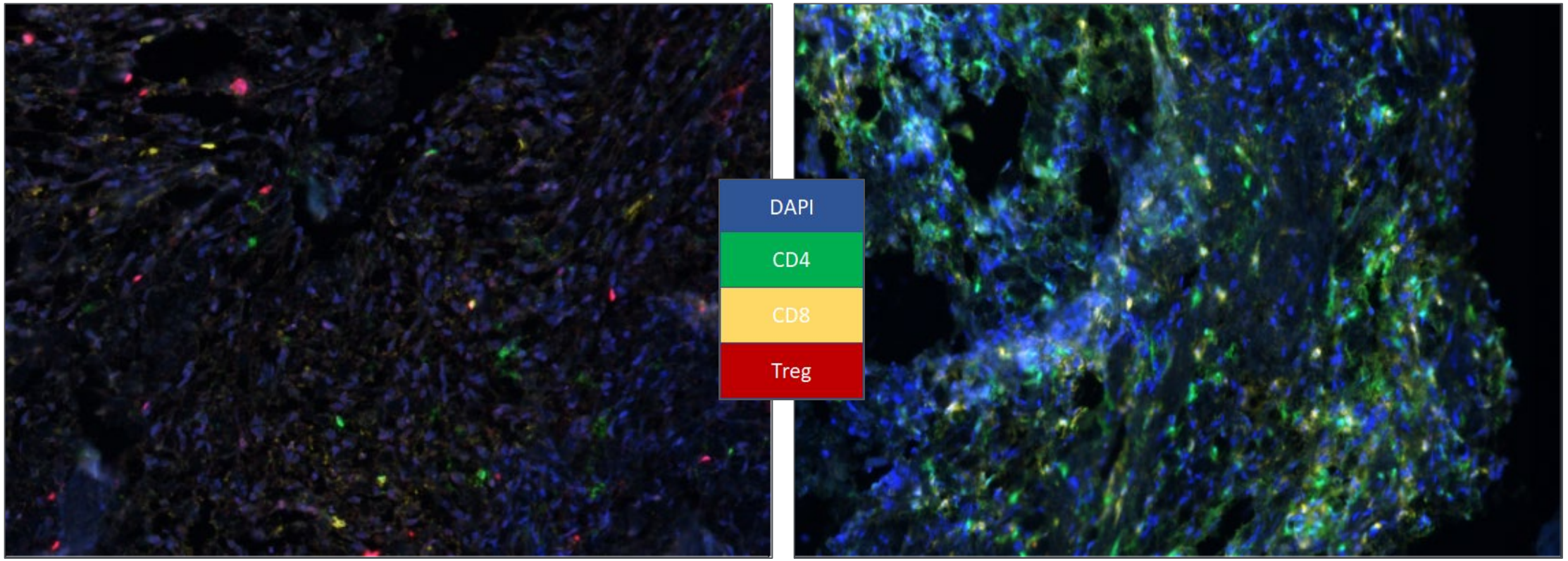


Image A sample pre-dose shows significant cancer. Image B sample taken on day 28 post two doses (day 0 and day 14) shows significant reduction in cancer cells. (Magnification 3.7x)

Multiplex IHC staining from matched pair biopsies from an INT230-6 monotherapy STS subject pre and post two INT230-6 injections

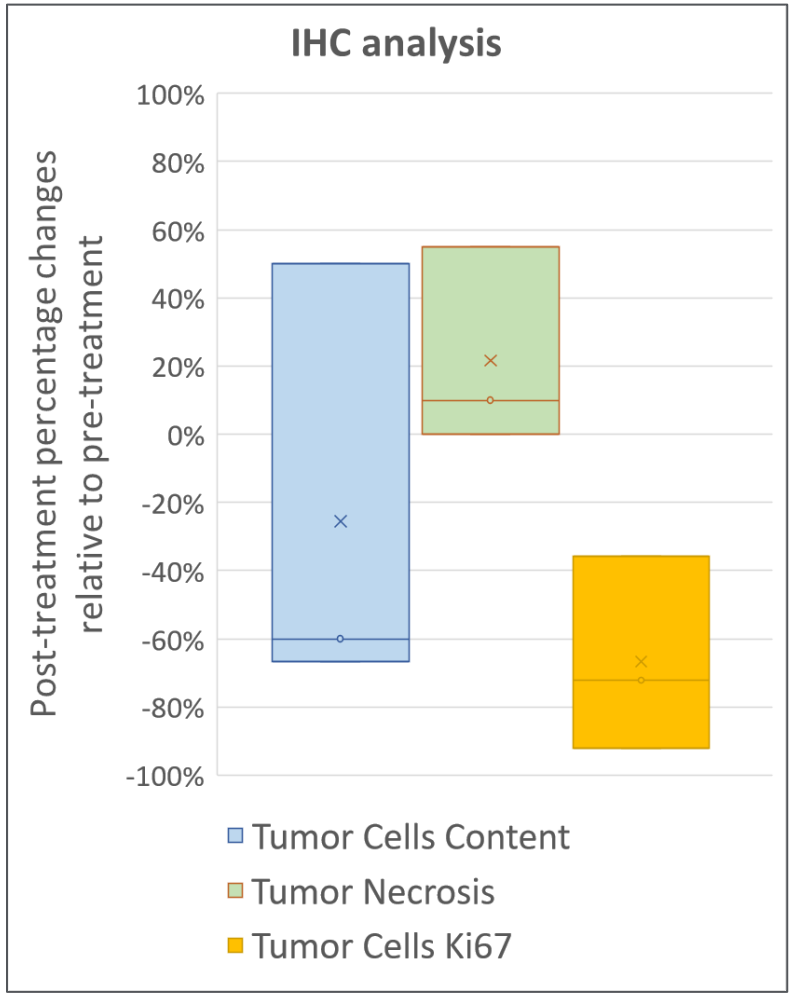
Image A: Pre-dose Day 0

Image B: Post 2 doses Day 28



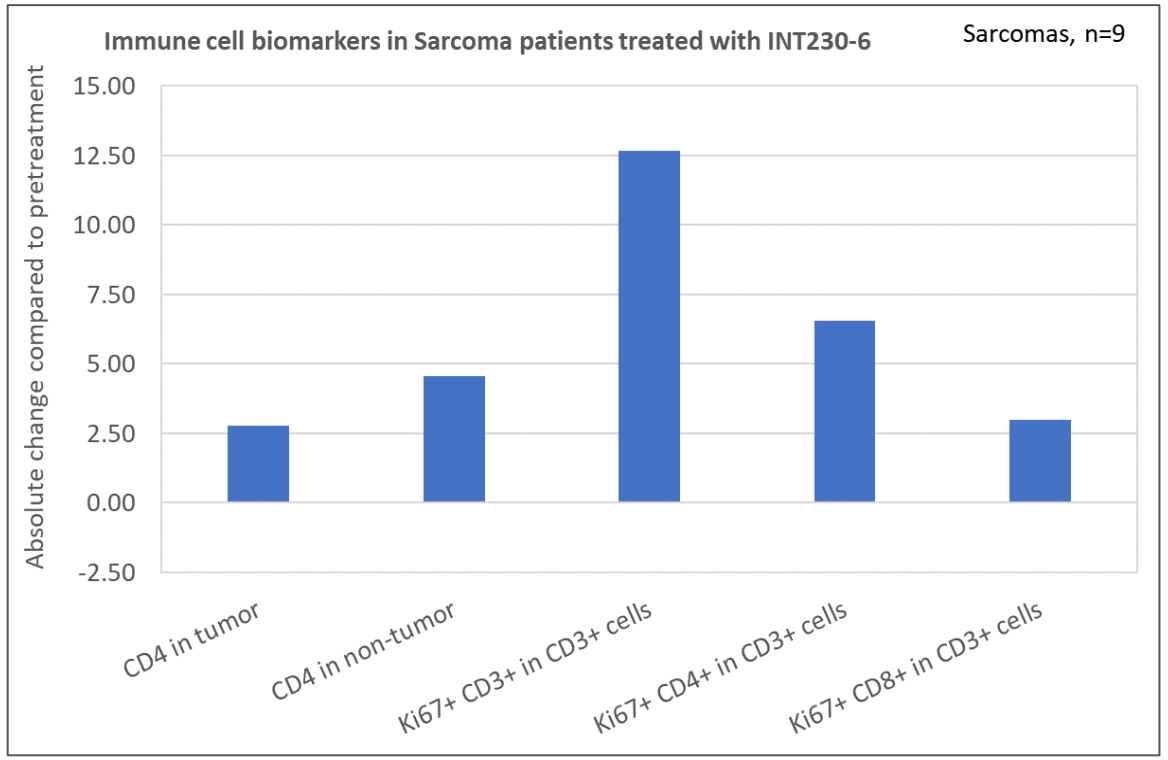
Post dose, there is a decrease in Treg cells (red), and an increased presence of T-cells, representing an influx of CD4 and CD8 T-cells (green, yellow stains). Monotherapy liposarcoma subject.

Immunohistochemistry & Immunofluorescence Biomarker analysis of tumor and microenvironment from STS subjects

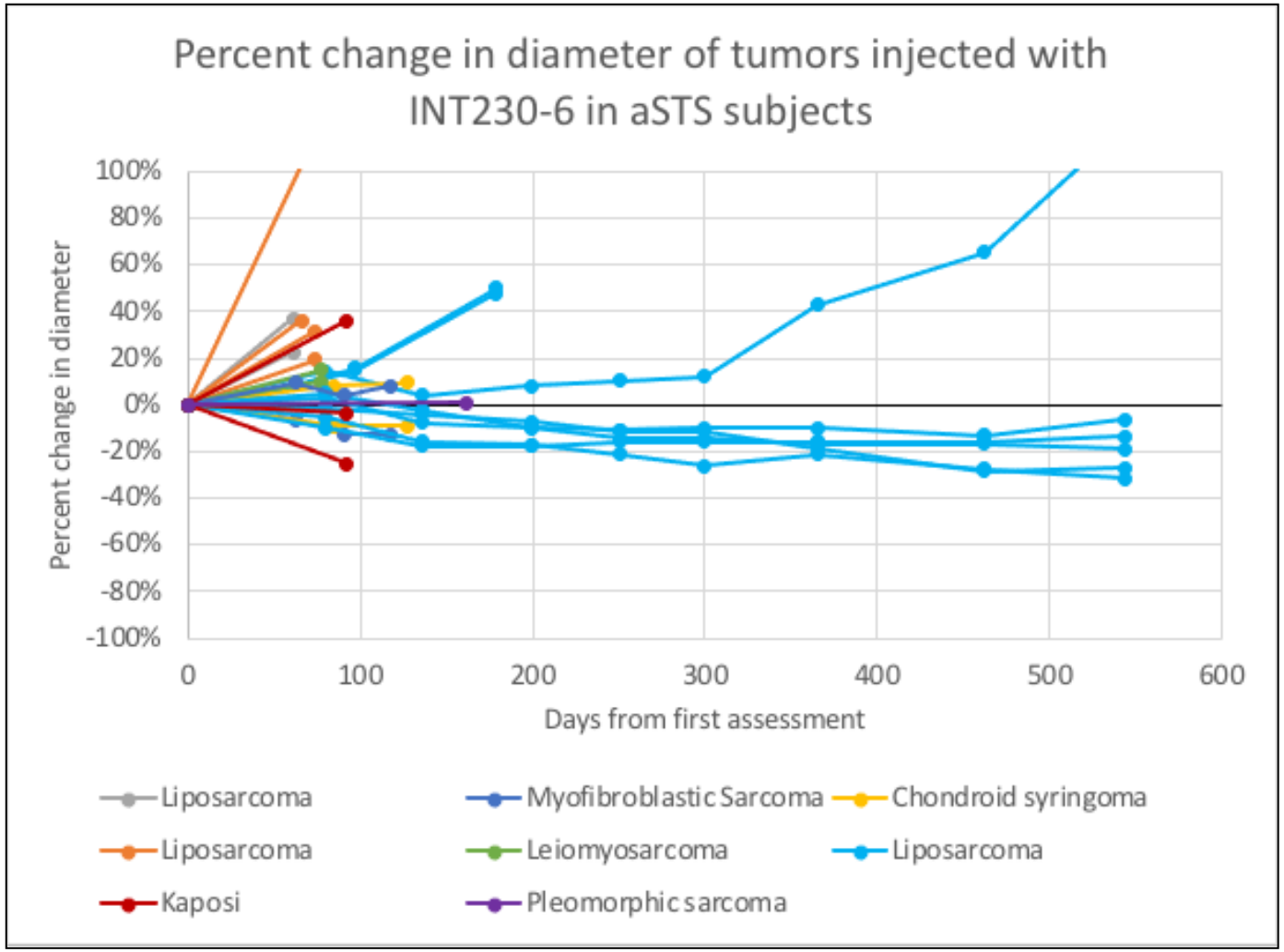


Immunohistochemistry analysis of paired (pre- and 28 days post-dose) biopsy from 3 INT230-6 monotherapy STS subjects.

Immunofluorescence analysis of immune cells biomarkers conducted from biopsies of 9 sarcoma subjects (5 INT230-6 monotherapy and 4 INT230-6 + Ipilimumab combination).



Spider plot showing long term stabilization of individual lesions in 8 INT230-6 monotherapy STS subjects



- Abscopal effects were seen in visceral lesions in 2 INT230-6 monotherapy STS subjects.

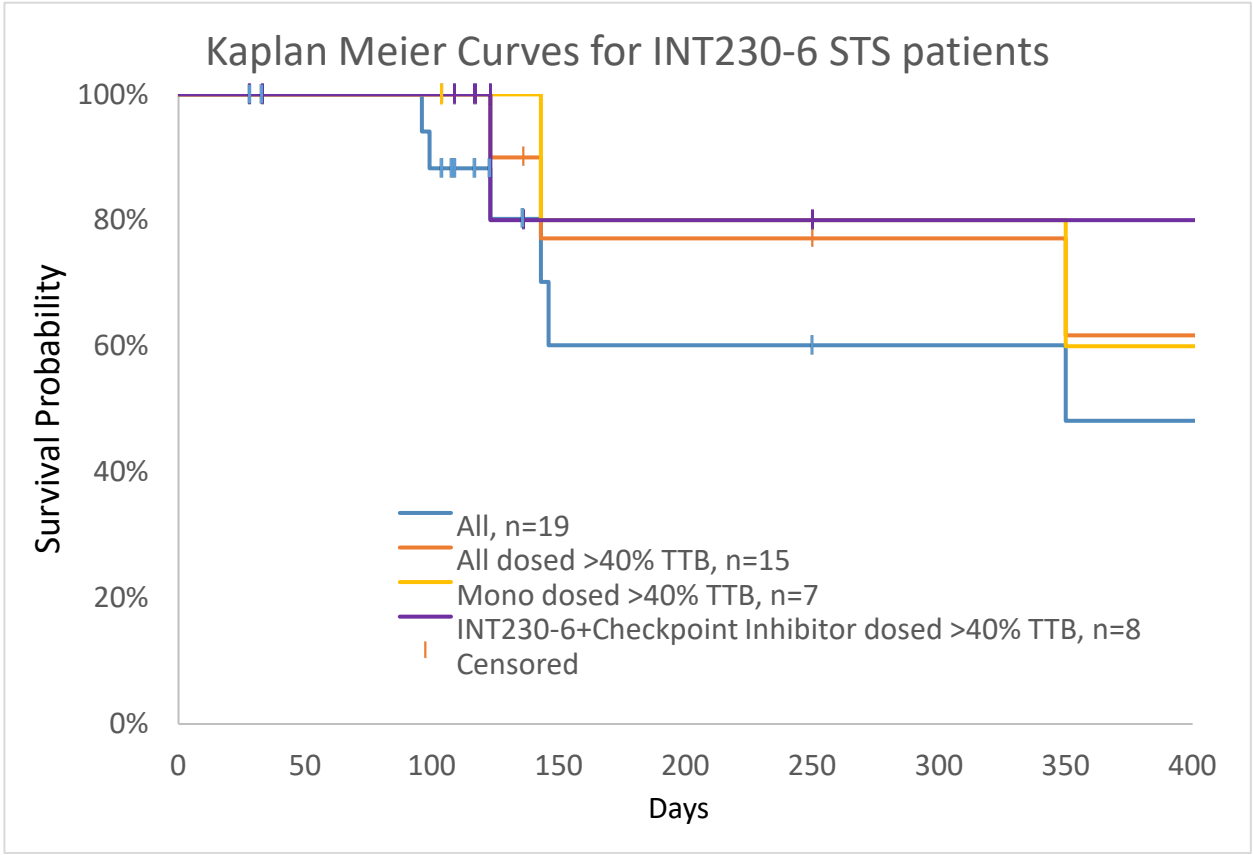
Overall Survival for STS subjects

- For all sarcoma subjects enrolled in IT-01 study, ~50% of subjects will be alive at 1 year. Blue curve (n=19)
- In a retrospective exploratory analysis, subjects were assessed by comparing INT230-6 dosed to ≥ 40% total tumor burden (TTB) vs. < 40% TTB.
- For sarcoma subjects dosed to ≥40% of their TTB, ~60% of subjects will be alive at 1 year. Orange curve (n=15)
- For subjects receiving INT230-6 monotherapy dosed to ≥40% of their TTB, ~60% of subjects will be alive at 1 year. Yellow curve (n=7)
- These results compare favorably to those seen in Phase 1 / 2 basket studies of sarcoma subjects with similar where ~50% of subjects are deceased at 3 to 8 months depending on prognostic factors scores (ECOG, LDH, # of metastatic sites) [1]

Note: Data for INT230-6 with Checkpoints is immature as many subjects were recently enrolled.

1. Subbiah, V Scientific Reports | 6:35448 | DOI: 10.1038/srep35448

Kaplan Meier estimates of sarcoma subjects, exploratory analysis by dose, for INT230-6 monotherapy patients dosed to ≥40% TTB



*3 subjects with reported total tumor burdens >2 cc and <700 cc were excluded.

Conclusions

- INT230-6 is well tolerated as monotherapy and preliminary data suggests that INT230-6 is well tolerated in combination with ipilimumab in a heterogenous group of soft tissue sarcoma subjects.
- INT230-6 demonstrates direct tumor killing and abscopal effects.
- Biopsies showed substantial tumor necrosis, reduction of viable cancer, a decreased cancer proliferation as measured by Ki67, and increased TILs (infiltration with CD4 and CD8 T-cells).
- An exploratory analysis suggests promising survival for subjects receiving an INT230-6 dose ≥40% of their tumor burden compared to historic survival from Phase 1 basket studies accounting for prognostic factors (ECOG, LDH, # of metastatic sites). [1,2]
- A randomized Phase III study with INT230-6 in subjects with soft tissue sarcoma is planned in 2022.

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