Intratumoral INT230-6 shows a favorable safety profile and early signs of efficacy in advanced soft tissue sarcoma with monotherapy and in combination with Ipilimumab [Intensity IT-01; BMS#CA184-592]

Matthew Ingham[1], James S. Hu[2], Giles Whalen[3], Jacob Thomas[2], Anthony B. El-Khoueiry[2], Diana Hanna[2], Anthony J. Olszanski[4], Christian Meyer[5], Nilofer Saba Azad[5], Syed Mahmood[6], Lewis H. Bender[6], Ian B Walters[6]*, Lillian L. Siu[7], Albiruni R Abdul Razak[7]

1. Columbia University College of Physicians and Surgeons, New York, NY. 2. University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA. 3. University of Massachusetts Memorial Cancer Center, Worchester, MA. 4. Fox Chase Cancer Center, Philadelphia, PA. 5. The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD. 6. Intensity Therapeutics, Inc., Westport, CT. 7. Princess Margaret Cancer Centre, University Health Network, Toronto, ON.

NCT:03058289 **Abstract Number: 16284**

BACKGROUND

INT230-6 is a novel intratumoral agent consisting of cisplatin (CIS), vinblastine (VIN) and an amphiphilic cell penetration enhancer (SHAO) that enables tumor dispersion and diffusion into cancer cells.

Preclinical data indicates INT230-6 increases influx of antigen presenting cells (APCs) to the tumor microenvironment and increases the amount and quality of expressed antigens. On pre- and post- first INT230-6 dose biopsies in humans, we have previously reported a reduction in Ki67+ cells, FoxP3 and viable tumor cells, with increases in CD4 and CD8 T-cells in the tumor micro-environment using whole section image analysis of paired samples for assessment. Previously we reported that INT230-6 has demonstrated the ability to substantially reduce the cancer in large tumors and induce an adaptive (T-cell mediated) immune response that attacks not only the injected tumor, but also non-injected tumors and unseen micro-metastases. [i, ii]

INT230-6 is designed to improve cancer treatment by more efficiently killing tumors, presenting antigen to activate immune system, and reducing the side effects associated with systemic therapies. IT-01 (BMS # CA184-592) is an open-label phase 1/2 study, currently enrolling adult subjects with solid tumors in phase 2 cohorts. This poster describes the safety and efficacy of intratumoral (IT) INT230-6 alone and in combination with Ipilimumab in subjects with sarcoma.

Sarcomas are a rare and heterogeneous group of solid tumors derived from mesenchymal origin. Although single agent or combination anthracycline-based chemotherapy provides some benefit for the treatment of advanced sarcomas, prognosis is still unfavorable with median overall survival of 15–18 months and there is significant unmet medical need. By the time subjects fail approved therapies, their mOS is typically 4-6 months. [iii, iv]

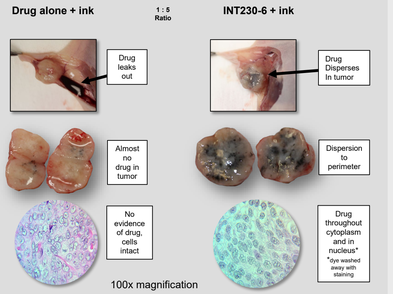
* Intensity Therapeutics, Inc.
Email: iwalters@intensitytherapeutics.com
Phone: (203) 221-7378
61 Wilton Road
Westport, CT 06880
Twitter @IntensityInc
Website: www.Intensitytherapeutics.com

A collaboration with Bristol Myers Squibb, Lawrenceville, NJ

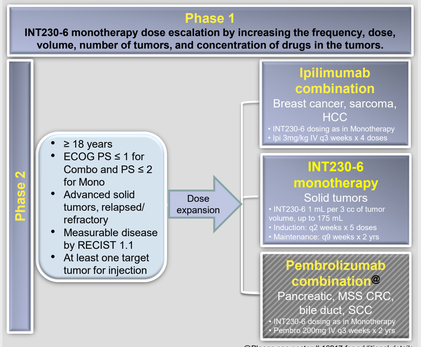
PRECLINICAL STUDY

- INT230-6 or control (aqueous cisplatin solution) was injected with India ink into the center of a murine pancreatic tumor (BxPc3 ~1.2 cm^3). (Figure 1)
- Tumors were immediately imaged and excised for sectioning.
- Results indicated enhanced INT230-6 dispersion throughout the tumor. In contrast, the control did not disperse or enter cancer cells and mostly leaked out of the tumor. [v]

Figure 1



CLINICAL STUDY



@Please see poster # 16217 for additional details.

IT-01 is an open-label, multi-arm Phase 1/2 clinical study in heavily pre-treated adult subjects with solid tumors.

Primary Outcome Measures for Phase 2:
- Assess the preliminary efficacy of INT230-6 alone or in combination with immunotherapy as measured by disease control rate utilizing iRECIST.

Additional Outcome Measures for Phase 2:
- Characterize the overall safety of INT230-6 alone or in combination with immunotherapy by the rate of grade 3 or higher adverse events (AEs) attributed to the combination.
- Assess the injected tumor response.
- Characterize the pharmacokinetic (PK) profile of multiple doses of the three INT230-6 components (CIS, VBL, and SHAO) after single and then multiple IT tumor site injections.

DEMOGRAPHICS & EXPOSURE

19 soft tissue sarcoma (STS) subjects (10 monotherapy, 8 combination with ipilimumab, and 1 other checkpoint combination) treated as of July 31, 2021. PK data reflects analysis as of August 5, 2021.

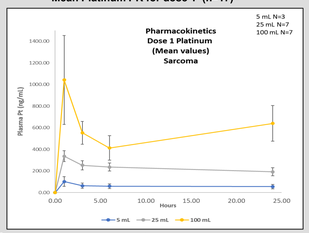
DEMOGRAPHICS	
Age	Median 64 (33-82)
Gender	11 male, 8 female
ECOG	32% ECOG 0 63% ECOG 1 5% ECOG 2
Median number of prior therapies (range)	3 (0-9)
Tumor types	4 Leiomyosarcoma, 3 Liposarcoma, 3 Pleomorphic sarcomas, 3 Chondrosarcomas, and 1 each of myofibroblastic sarcoma, chondroid syringoma, desmoid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

- Demographics were similar in subjects enrolled in monotherapy and checkpoint 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 checkpoint inhibitor combination, the safety dataset was evaluated for all sarcoma subjects.

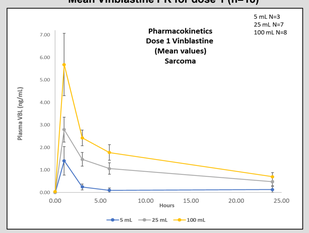
PK data from phase 1 and 2 sarcoma subjects (n=18, including 1 retreatment) are listed below. (Figure 2)
- Dose response proportionality observed in PK profile.
- Most of the drug is cleared by 24 hours.
- Cisplatin is reduced rapidly to metal and released at low levels from tissue over an extended period of time. Peak plasma concentrations of vinblastine are ~5% of predicted based on historical IV kinetics, indicating most of the drug remains in the tumor. [vi]

Figure 2

Mean Platinum PK for dose 1 (n=17) [§]



Mean Vinblastine PK for dose 1 (n=18)



§ 1 subject pending analysis for platinum.

SAFETY

Related Treatment emergent AEs in INT230-6 alone or checkpoint inhibitor combination by max severity in >1 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%)

- Most adverse events were low grade and transient. There were no related grade 4 or 5 TEAEs.
- There were no events that were dose limiting.
- There was 1 subject with INT230-6 monotherapy related SAE of localized tumor-related pain; and 1 subject with Ipi-related SAE of colitis and headache.

BIOMARKERS

Haemotoxylin and Eosin (H&E) assessments were conducted to determine the percentage of viable tumor cells and necrotic cells. There were substantial reductions of cancer cells in biopsies of injected lesions from INT230-6 monotherapy subjects after two injections of INT230-6, when compared to baseline. Images from matched pair biopsies from a STS subject pre and post two INT230-6 injections is shown in Figure 3.

Figure 3

Image A: Pre-dose Day 0 Image B: Post 2 doses Day 28

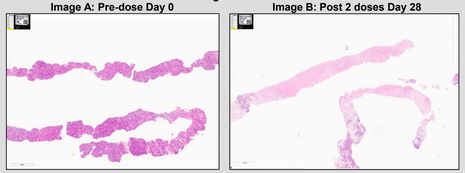
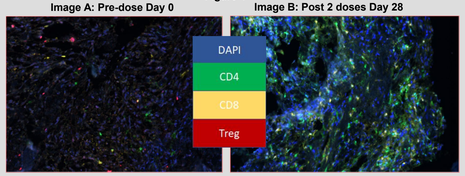


Image A sample pre-dose shows significant cancer. Image B sample taken on day 28 post two doses (day 0 and day 14) shows significant reduction in cancer cells. (Magnification 3.7x)

Multiplex immunohistochemistry staining of biopsies of injected lesions from an INT230-6 monotherapy STS subject pre dose (day 0) and T= 28 days post 2 doses of INT230-6 monotherapy (days 0 and 14) is shown in Figure 4.

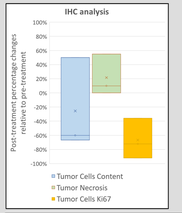
Figure 4

Image A: Pre-dose Day 0 Image B: Post 2 doses Day 28



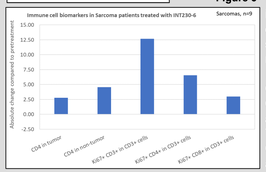
Post dose, there is a decrease in Treg cells (red), and an increased presence of T-cells, representing an influx of CD4 and CD8 T-cells (green, yellow stains). Monotherapy liposarcoma subject.

Figure 5



Immunohistochemistry analysis of INT230-6 monotherapy paired (pre- and 28 days post-dose) biopsy of injected lesions from 3 INT230-6 monotherapy STS subjects showed a median of 60% reduction in tumor cell content, a 10 % increase in tumor necrosis and a 72% reduction in Ki67 staining (proliferation marker). (Figure 5)

Figure 6

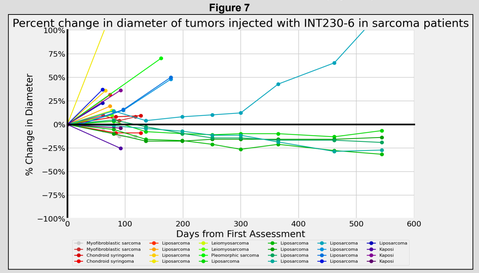


Immunofluorescence analysis of immune cells biomarkers were conducted from biopsies of 9 sarcoma subjects (5 INT230-6 monotherapy and 4 INT230-6 + Ipilimumab combination). Overall, the data suggest higher CD4+ T-cell infiltration in the tumor and in its periphery. Within the CD3+ T-cell population, infiltration with both CD4+ and CD8+ cells were seen after treatment. (Figure 6)

EFFICACY

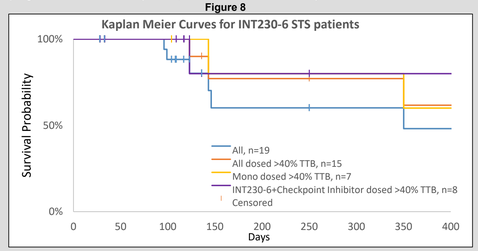
INT230-6 monotherapy and/or checkpoint inhibitor combination subjects:
- Individual tumor lesion diameters in 8 STS subjects that received INT230-6 monotherapy demonstrate that several tumors have prolonged stabilization. (Figure 7)

Figure 7



- Abscopal effects were seen in visceral lesions in 2 INT230-6 monotherapy STS subjects. This estimate of an abscopal effects may be underestimated as tumors under 1 cm and not all tumor lesions were followed.
- For the overall sarcoma population (INT230-6 with checkpoints and INT230-6 mono subjects), the Kaplan Meier estimate indicates that 50% of subjects will have a probability of being alive at 1 year. Blue curve (Figure 8)
- In a retrospective exploratory analysis, subjects were assessed by comparing INT230-6 dosed to ≥ 40% total tumor burden (TTB) vs. < 40% TTB. For overall sarcoma subjects dosed to ≥40% of their TTB, ~60% of subjects will be alive at 1 year. Orange curve
- These results compare favorably to those seen in basket studies of patients with similar prognostic factors scores (ECOG, LDH, # of metastatic sites). [iii, iv]

Figure 8



*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). [iii, iv]
- A randomized Phase III study with INT230-6 in subjects with soft tissue sarcoma is planned in 2022.

i. Bloom et al. Oncoimmunology 7/2019 ii. El-Khoueiry et al. JITC 11/2020. iii. Laguna-Garrido et al. Cancer 3/2012 iv. Chau et al. BMC Cancer 10/2011 v. Bender et al. Int J Mol Sci 6/2020 vi. historical PK data from IV administration: Owelien J. Cancer Res 8/1977