INT230-6 Demonstrates Activity as Monotherapy and in Combination with Ipilimumab (IPI) Across a Broad Spectrum of Refractory Soft Tissue Sarcomas (STS) [Intensity IT-01; BMS#CA184-592]

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BACKGROUND

INT230-6 is a novel product with a unique dual anti-cancer mechanism. 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.

The drug is comprised of cisplatin (CIS) and vinblastine (VIN) co-formulated with a cell penetration and unique tissue dispersing enhancing molecule, 8-((2-hydroxybenzoyl)amino) octanoate (SHAO), that enables drug movement throughout a tumor (including to hypoxic regions) and passive diffusion into cancer cells following intratumoral (IT) delivery. A neoadjuvant study in breast cancer confirms that a single injection can kill up to 95% of an injected tumor and recruit TILs.[1]

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-biopsies following two INT230-6 treatments 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]

The role of cytotoxic agents in augmenting the response of checkpoint inhibitors was established based on the KEYNOTE-189 trial in NSCLC.[i] Cisplatin immune effects include modulation of STAT signaling; induction of an immunogenic type of cancer cell death through exposure of calreticulin and release of ATP and high-mobility group protein box-1 (HMGB-1)ii resulting in binding to T-cells via TLR. The vinca compound vinblastine, in addition to cytotoxic effects, is capable of inducing dendritic cell maturation. IT-01 is an open-label phase 1/2 study, currently enrolling adult subjects with solid tumors in phase 2 cohorts. The study seeks to assess the safety and efficacy of intratumoral (IT) INT230-6 alone and in combination with Pembrolizumab or Ipilimumab.

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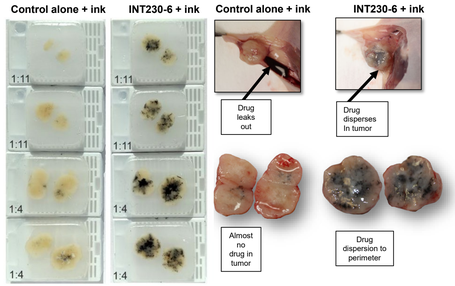
DRUG DISPERSION IN TUMORS

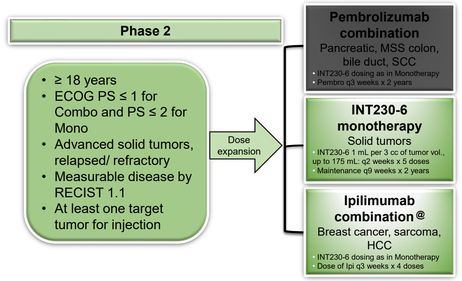
- Control, an aqueous cisplatin solution, (Figures 1A, 1C) or INT230-6 (Figures 1B, ID) were injected with India ink into the center of a murine pancreatic tumors (BxPc3 ~1.2 cm^3). Tumors were immediately imaged and excised for sectioning.
- Results indicated enhanced INT230-6 dispersion throughout the tumor (1B and 1D) compared to controls. The control formulation did not disperse, was not retained by the cancer cells and mostly leaked out of the tumors (1A and 1C).[ii]

Figure 1A Figure 1B Figure 1C Figure 1D



CLINICAL STUDY

subjects enrolled with varying numbers and sizes of tumors. Dose per tumor was set by its volume with the total dose per visit being the sum of the doses for each tumor. INT230-6 dose per session was escalated in the phase 1 portion from 5 mL every 28 days to a maximum dose of 175 mL given every 14 days. Checkpoint drugs were given per label. Several biomarkers are being evaluated using collected blood and tumor tissue.



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

Additional Outcome Measures for Phase 2:

1. 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 study treatments.
2. 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.

SARCOMA DEMOGRAPHICS

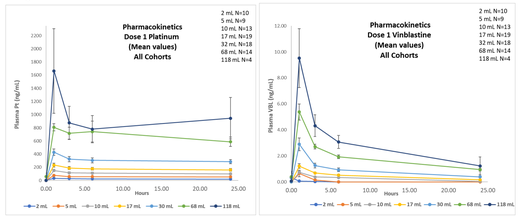
As of April 1, 2022, there were 26 subjects in the safety database (15 mono, 11 combined with ipilimumab. The types of sarcomas enrolled in IT-01 mono therapy were; leiomyosarcoma, liposarcoma 3, pleomorphic 2, chondrosarcoma, sacral chordoma 3, undifferentiated, connective tissue, osteosarcoma (chondroid syringoma), myofibroblastic, Kaposi. In the ipi combo: leiomyosarcoma 3, liposarcoma, pleomorphic, chondrosarcoma 2, sacral chordoma, myxoid spindle cell, fibrosarcoma, Langerhans cell.

Demographics (1April22)	INT230-6 (n=15)	INT230-6 + IPI (n=11)
Age (median, range)	64 (41.9-76.1)	63.3 (33-82.1)
Gender	73.3% male	45.5% male
ECOG	0 (13%), 1 (80%) 2 (6.7%)	0 (45.5%) 1 (54.5%)
Median # of prior therapies,	3 (0-8)	5 (0-9)
Overall # of tumors injected (% deep)	120 (49.1)	127 (71%)

PHARMACOKINECTICS & EXPOSURE

The pharmacokinetic data is from 87[§] subjects. Dose response proportionality is observed in the PK profile for doses ranging from 2 to 118 mL of INT230-6 (Figure 2). At 7 days post dose, no accumulation of vinblastine is seen. Cisplatin when dosed is rapidly reduced to platinum (Pt) metal, which has no known toxicities. SHAO is Generally Regarded As Safe (GRAS) and considered an excipient. Peak plasma concentrations of vinblastine are ~ 1 to 5% of predicted based on historical IV kinetics, indicating most of the drug remains in the tumor.[iii] Some subjects received 3X the typical systemic IV dose of VIN. Further analysis showed that there are no differences in INT230-6 PK due to age (< or ≥ 65), ECOG, or gender.

Figure 2 [§] reflects analysis as of April 1, 2022



SAFETY

As of April 1, 2022

Related Treatment emergent AEs by max severity in >10% subjects (n=15) INT230-6 mono

INT230-6 Monotherapy	Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	Any	2 (13.3%)	9 (60.0%)	3 (20.0%)	0	0	14 (93.3%)
	Localized tumor-related pain	7 (46.7%)	4 (26.7%)	1 (6.7%)	0	0	12 (80.0%)
	Nausea	4 (26.7%)	3 (20.0%)	0	0	0	7 (46.7%)
	Fatigue	0	5 (33.3%)	1 (6.7%)	0	0	6 (40.0%)
	Decreased appetite	0	5 (33.3%)	0	0	0	5 (33.3%)
	Vomiting	3 (20.0%)	1 (6.7%)	0	0	0	4 (26.7%)
	Anaemia	0	2 (13.3%)	1 (6.7%)	0	0	3 (20.0%)
	Injection site reaction	0	2 (20.0%)	0	0	0	2 (20.0%)
	Hypomagnesaemia	1 (6.7%)	1 (6.7%)	0	0	0	2 (13.3%)
	Hyponatraemia	1 (6.7%)	0	1 (6.7%)	0	0	2 (13.3%)
	Injection site reaction	0	2 (13.3%)	0	0	0	2 (13.3%)
	Blood creatinine increased	2 (13.3%)	0	0	0	0	2 (13.3%)

Related Treatment emergent AEs by max severity in >10% of subjects (n=11) IPI + INT230-6

Ipilimumab + INT230-6	Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	Any	5 (45.5%)	5 (45.5%)	1 (9.1%)	0	0	11 (100%)
	Fatigue	4 (36.4%)	1 (9.1%)	0	0	0	5 (45.5%)
	Localized tumor-related pain	2 (18.2%)	2 (18.2%)	0	0	0	4 (36.4%)
	Nausea	4 (36.4%)	0	0	0	0	4 (36.4%)
	Vomiting	2 (18.2%)	1 (9.1%)	0	0	0	3 (27.3%)
	Pruritus	3 (27.3%)	0	0	0	0	3 (27.3%)
	Rash maculo-papular	3 (27.3%)	0	0	0	0	3 (27.3%)
	Headache	2 (18.2%)	0	0	0	0	2 (18.2%)
	Anaemia	0	1 (9.1%)	1 (9.1%)	0	0	2 (18.2%)
	Decreased appetite	1 (9.1%)	1 (9.1%)	0	0	0	2 (18.2%)

EFFICACY

INT230-6 monotherapy and combination showed preliminary efficacy in a population of aggressive and heavily pre-treated sarcomas. The DCR (CR + PD + SD per RECIST) for sarcoma patients at 50 days was 56% for monotherapy and 57% for combination. However, RECIST metrics (sum of longest diameters) to gauge efficacy are validated for use with systemically delivered therapies. RECIST is not ideal for use with intratumorally administered therapies. In this study, RECIST response is complicated by the amount of INT230-6 repeatedly injected and retained in the tumors prior to the first scan. Immune infiltration could increase tumor size. Results in a neoadjuvant setting (ASCO 2022 Abstract Number: 605, Poster: 376) show a single injection of INT230-6 can cause near complete necrosis of the tumor. A scan of a monotherapy chordoma tumor highlights this issue (Figure 3). Longest diameter declines 15%, whereas 2nd longest diameter declines 42%

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

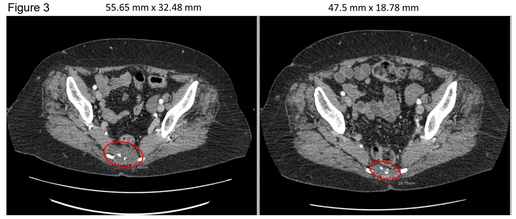
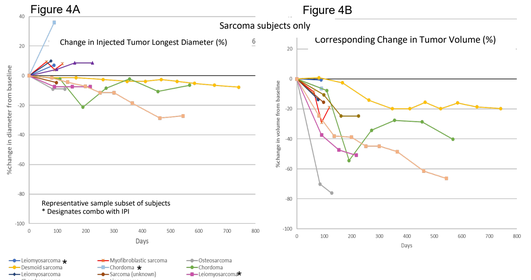


Figure 4 highlights the observation that evaluating tumors by RECIST criteria (longest diameter (LD)) may not correspond to changes in tumor volume. Panel A reports changes in a tumor longest diameter over time. Figure 4B shows the tumor's corresponding volume change calculated from 3 dimensions using the modified ellipsoid formula. Each line represents an injected tumor from a sarcoma subject receiving either INT230-6 with or without IPI. Tumors diameters with a size increase or that were stable often shown a decrease in volume with considerable variability. The lack of correlation between LD and volume indicates that RECIST may be unreliable for IT INT230-6 as a metric of efficacy in sarcoma.

Figure 4A Figure 4B



IT-01 is a single arm study. Published clinical phase 1/2 basket trials in sarcoma that report median overall survival (mOS), ranging from 7.6 to 9.6 months [iv, v, vi] and that OS can be predicted based on a validated index of 3 factors (# of metastatic sites, albumin and LDH levels) developed by the Royal Marsden Hospital (RMH). To understand survival results, we created a KM survival control group derived from the Subbiah basket trial[vi] data matched to our enrolled sarcoma subjects incoming RMH Index scores.

i. Ghandiet al. NEJM 4/2018; ii. Bender et al. Int J Mol Sci 6/2020 ; iii. Historical PK data from IV administration: OwelienJ. Cancer Res 8/1977; iv. Jones Cancer Chemother Pharmacol (2011) 68:423–429; v. Cassier et. al., Annals of Oncology 25: 1222–1228, 201; vi. Subbiah et. al., Scientific Reports | 6:35448 2016,

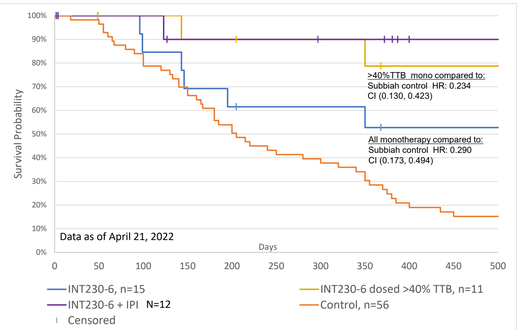
MedDRA = Medical Dictionary for Regulatory Activities; SOC = System Organ Class; PT = Preferred Term.
Version 19.1 of MedDRA was used to code AE. NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe; Grade 4: Life-threatening or disabling; Grade 5: Death related to AE

EFFICACY

During our dose escalation several subjects were well under-dosed relative to their total tumor burden (TTB). We conducted an exploratory analysis of cumulative dose relative to a subject's incoming reported TTB. The survival curves are shown in figure 5 below. The favorable hazard ratios (HR) for STS subjects administered solely INT230-6 is reported below. Abscopal responses seen were primarily in subjects dosed to ≥ 40% total tumor burden (data previously presented).

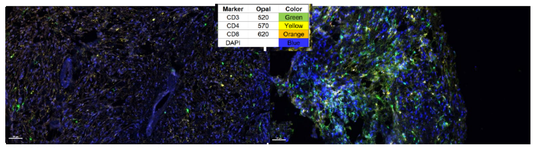
	Control (Subbiah data)	INT230-6 all	INT2306 >40% TTB	INT230-6 + IPI
mOS , CI	205 days	649 (146, 1219)	715 (649, 1219)	**Not reached median follow-up: 297 days**

Figure 5 Kaplan Meier estimates sarcoma subjects



BIOMARKERS

Figure 6



C1D0 brightness was adjusted in photoshop for easier viewing

Biopsies from injected tumors were taken pretreatment cycle 1 day 0 (C1D0) and Day 28 (C2D0) for immunohistochemistry (IHC) analysis. Dosing was conducted immediate post the first biopsy and C1D14. IHC analysis included evaluation of CD3+, CD4+, CD8+ T-cells, DAPI (cancer). There was a notable reduction in cancer cells in the post dose biopsies and an increase in all T-cells types. The above representative figure 6 shows a significant influx of T-cells from a biopsies from a refractory, monotherapy liposarcoma cancer patient who prior to enrollment progressed on multiple standard chemo agents.

CONCLUSIONS

- INT230-6 is well tolerated as monotherapy and in combination with ipilimumab.
- INT230-6 is retained in the tumor and demonstrates direct tumor killing in injected lesions.
- IHC results in injected lesions indicate dosing INT230-6 activates a T-cell mediated immune response. Uninjected tumor regression previously reported (SITC 2021 abstract 501 support a potential immune response.
- Data suggests that RECIST criteria have limitations in evaluating efficacy for IT therapies. Preliminary data suggests that INT230-6 may extend survival compared to historical data from published basket phase 1/2 studies in sarcoma subjects.
- An exploratory analysis suggests survival for monotherapy subjects receiving INT230-6 dosed to ≥40% of their total tumor burden compares favorably to the <40% group
- Data is encouraging though the sample size is small, sarcoma subtypes may differ between groups and data is still early. Randomized controlled studies would be needed to assess efficacy for the combination of INT230-6 with ipilimumab or as monotherapy