Early Results of Intratumoral INT230-6 Alone or in Combination with Ipilimumab in Subjects with Advanced Sarcomas

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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 improves APCs' ability to recognize expressed antigens. On pre- and post-first INT230-6 dose biopsies in humans, we have previously reported a reduction in Ki67+ cells, viable cells and FoxP3, 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]

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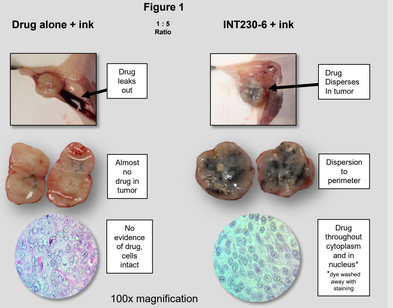
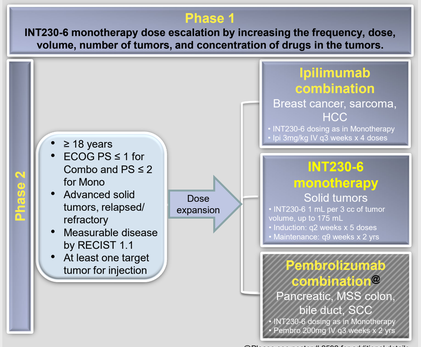
PRECLINICAL STUDY

- 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 # 2592 for additional details.

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

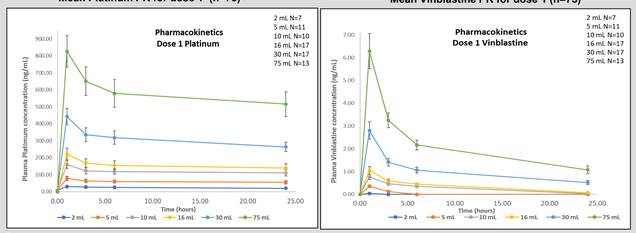
18 heterogenous sarcoma subjects (13 mono, 5 combination with Ipilimumab) were enrolled as of April 1 2021.

DEMOGRAPHICS	
Age	Median 63 (32-77)
Gender	12 male, 6 female
ECOG	17% ECOG 0
	72% ECOG 1
	11% ECOG 2
Median number of prior therapies (range)	3 (0-9)
Tumor types	5 Chordomas, 3 Leiomyosarcoma, 3 Liposarcoma, and 1 each of myofibroblastic sarcoma, pleomorphic sarcoma, chondrosarcoma, osteosarcoma, mesenchymal chondrosarcoma, Kaposi sarcoma and an unspecified sarcoma

- Demographics were similar in subjects enrolled in monotherapy and Ipilimumab combination arms.
- INT230-6 doses: INT230-6 IT injections were given at doses of 0.3 to 145mL (72.5mg cisplatin, 14.5mg vinblastine) in a single session, which are higher amounts than typical IV doses, with repeated intratumoral injections in multiple tumors.
- Since there were only 4 evaluable subjects in the Ipilimumab combination, the safety and efficacy was combined with Monotherapy.

PK data from all phase 1 and 2 cohorts (n=75, including 6 retreatments) are listed below for reference. Data cut off: January 31 2021.
- Dose response proportionality observed in PK profile: most of the drug cleared by 24 hours. (Figure 2)
- 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



§ includes 2 subjects who were retreated multiple times.

SAFETY

Related Treatment emergent AEs by max severity in >1 subject (n=17)[y]

	Grades					
Preferred Term	**1**	**2**	**3**	**4**	**5**	**Total**
No. of subjects with least 1 AE	15 (88.2%)	11 (64.7%)	4 (23.5%)	0	0	15 (88.2%)
Localized tumor-related pain	6 (35.3%)	4 (23.5%)	1 (5.9%)	0	0	11 (64.7%)
Fatigue	1 (5.9%)	5 (29.4%)	1 (5.9%)	0	0	7 (41.2%)
Decreased appetite	0	6 (35.3%)	0	0	0	6 (35.3%)
Nausea	4 (23.5%)	2 (11.8%)	0	0	0	6 (35.3%)
Vomiting	3 (17.6%)	2 (11.8%)	0	0	0	5 (29.4%)
Anaemia	0	1 (5.9%)	2 (11.8%)	0	0	3 (17.6%)
Blood creatinine increased	2 (11.8%)	0	0	0	0	2 (11.8%)
Dizziness	1 (5.9%)	1 (5.9%)	0	0	0	2 (11.8%)
Hypomagnesaemia	1 (5.9%)	1 (5.9%)	0	0	0	2 (11.8%)
Hyponatraemia	1 (5.9%)	0	1 (5.9%)	0	0	2 (11.8%)
Injection site reaction	0	2 (11.8%)	0	0	0	2 (11.8%)
Pruritus	2 (11.8%)	0	0	0	0	2 (11.8%)
Rash maculo-papular	2 (11.8%)	0	0	0	0	2 (11.8%)

[y] 1 subject did not have data entered by the data cutoff date.
- 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 were 3 subjects with related SAEs (colitis (occurred on day 26 was attributed to Ipilimumab, and is consistent with past experience with Ipilimumab), headache, and localized tumor-related pain).

EFFICACY

RECIST methodology may not be a good measure of clinical benefit with INT230-6 when dosing based on tumor volume. Evaluation of tumor enlargement is complicated by the amount of INT230-6 that is injected and retained in the tumor and/or the potential for immune infiltration. As a result, longer term outcomes such as overall survival may be a more appropriate endpoint to assess efficacy.

INT230-6 monotherapy and/or Ipilimumab combination sarcoma and chordoma subjects (n=15)[1]:
- **Disease control rate (DCR) for the overall population at ≥ 50 days (approximate 2 months assessment) was 60%.**
- Pilot immunohistochemistry analysis of 5 monotherapy paired (pre- and 28 days post-dose) biopsy samples showed substantial tumor necrosis, reduction of viable cancer, a decreased cancer proliferation as measured by Ki67, and increased TILs.
- In an exploratory preliminary analysis, subjects were grouped with INT230-6 dosed to ≥ 50% total tumor burden vs. < 50% total tumor burden.[1] (Figures 3,4)

Subjects dosed to ≥50%:	Subjects dosed to <50%:
• 6 of 11 subjects alive (4 deaths; 1 lost to follow up)	• 0 of 4 subjects alive (4 deaths)
• Tumor burden: mean (311 cm^3) & median (286cm^3)	• Tumor burden: mean (2080cm^3) & median (1210cm^3)

Figure 3

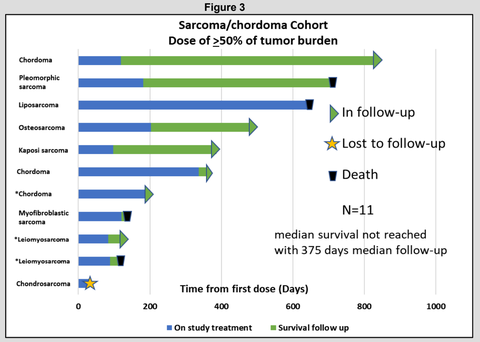
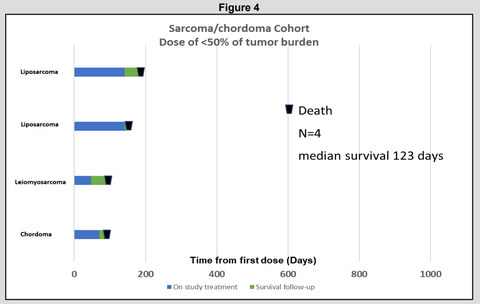


Figure 4

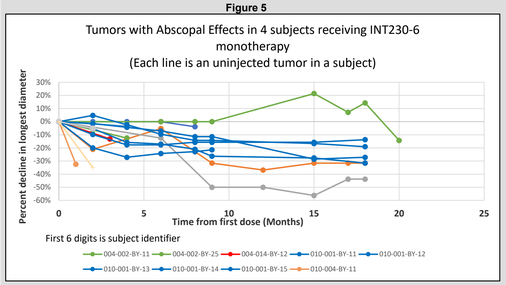


[1]3 subjects were excluded from ≥50% tumor burden group because 1 was also treated in another combination arm of the study, and 2 FEC subjects did not have tumor burden reported as of the data cut off date.
* Ipilimumab combination subjects.

EFFICACY continued

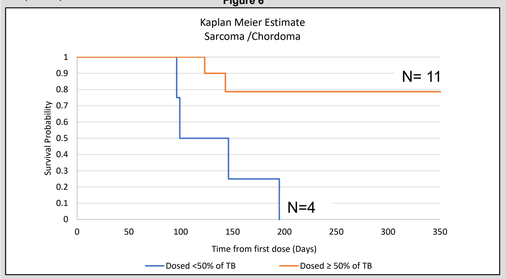
- **Abscopal effects were seen in non-injected lung, liver and lymph node lesions in 4 monotherapy subjects. (Figure 5)**

Figure 5



- In the overall population, median overall survival (mOS) in monotherapy subjects was 23.6 months with 75% of monotherapy subjects with a Royal Marsden Hospital index (RMHI) score of 2. [iii, iv]

Figure 6



- The exploratory analysis of dose relative to tumor burden showed (monotherapy and/or Ipilimumab combination) sarcoma subjects receiving a dose of INT230-6 <50% of their reported tumor burden had a mOS of ~100 days. While subjects receiving a dose of INT230-6 to ≥50% of tumor burden, mOS has not yet been reached after a median follow up of 365 days. (Figure 6)
- Basket studies of sarcomas, including chordoma, with RMHI scores of 2 or higher, report mOS of 4-6 months. [iii, iv]

CONCLUSIONS

- INT230-6 is well tolerated as monotherapy and in combination with Ipilimumab in a heterogenous group of sarcoma subjects.
- INT230-6 demonstrates direct tumor killing and abscopal effects.
- RECIST methodology may not be a good measure of clinical benefit with INT230-6. Overall survival may be a more appropriate endpoint to assess efficacy in subjects that receive INT230-6.
- An exploratory analysis suggests promising survival for subjects receiving an INT230-6 dose ≥50% of their tumor burden compared to historic survival from Phase 1 basket studies accounting for prognostic factors (ECOG, LDH, # of metastatic sites). [iii, iv]
- Ipilimumab + INT230-6 combination continues to accrue and with further follow up, we will do a more robust analysis of monotherapy vs combination.

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