A Phase 1/2 study of Intratumoral INT230-6 Alone (IT-01) or in Combination with Pembrolizumab [KEYNOTE-A10] in Adult Subjects with Locally Advanced, Unresectable and Metastatic Solid Tumors Refractory to Therapy

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BACKGROUND

INT230-6 is a novel intratumoral agent consisting of cisplatin (CIS), vinblastine (VIN) and an amphiphilc 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, 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.

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]; Vinblastine, in addition to cytotoxic effects, is capable of inducing dendritic cell maturation. 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 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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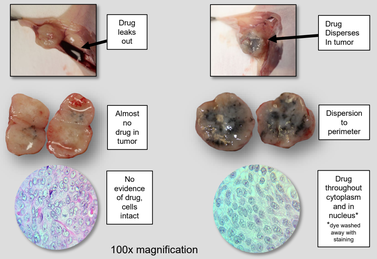
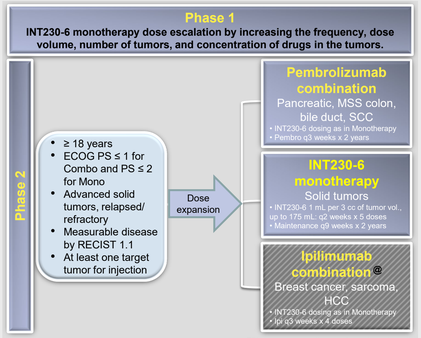
PRECLINICAL STUDY

- 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. While the control formulation did not disperse or enter the cancer cells and mostly leaked out of the tumor.[iii]

Figure 1



CLINICAL STUDY



@Please see poster # 11557 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.

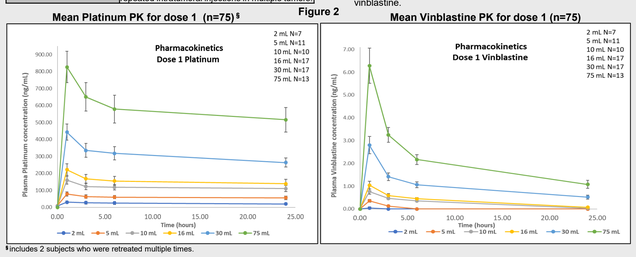
DEMOGRAPHICS & EXPOSURE

72 subjects (58 mono, 14 combo with Pembro) have been treated as of April 1 2021.
PK data reflects analysis as of January 31 2021.

DEMOGRAPHICS	
Age	Median 62 (42-85)
Gender	37 male, 35 female
ECOG	25% ECOG 0
	68% ECOG 1
	7S% ECOG 2
Median number of prior therapies (range)	3 (0-10)
Tumor types	20+ cancer types were accrued; breast cancer and sarcoma were the most frequent.
Sites of injection	Over 500 INT230-6 IT injections were given (267 to deep tumors, including liver, lung, pancreas, lymph nodes) at doses of 0.3 to 172mL (86 mg CIS, 17.2 mg VIN) in a single session, which are higher amounts than typical IV doses, with repeated intratumoral injections in multiple tumors.

- Demographics were similar in subjects enrolled in monotherapy and PD-1 combination arms; and for subjects dosed to ≥ 50% tumor burden vs. < 50% tumor burden.
- Dose response proportionality is observed in the PK profile, with most of the drug cleared by 24 hours. (Figure 2)
- At 7 days post dose, no accumulation of vinblastine is seen. Cisplatin when dosed is rapidly degraded to platinum (Pt) metal. When dosing cisplatin IV, a slow release of the metal is observed for several months. However, the metal has no known toxicities and no appreciable accumulation is observed. In patients previously dosed with platinum agents, Pt metal is detected predose. There is no observed difference on the plasma measurement of the INT230-6 components in the presence of Pembrolizumab.
- Peak plasma concentrations of vinblastine are ~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 vinblastine.

Figure 2



§ includes 2 subjects who were retreated multiple times.

SAFETY

Related Treatment emergent AEs by max severity in >2 subjects (n=58 §)

Monotherapy	Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	No. of subjects with least 1 AE	**49 (89.4%)**	**29 (50.0%)**	**7 (12.1%)**	**0**	**0**	**50 (86.2%)**
	Localized tumor-related pain	21 (36.2%)	11 (19.0%)	2 (3.4%)	0	0	34 (58.6%)
	Nausea	17 (29.3%)	4 (6.9%)	0	0	0	21 (36.2%)
	Fatigue	5 (8.6%)	11 (19.0%)	1 (1.7%)	0	0	17 (29.3%)
	Vomiting	11 (19.0%)	3 (5.2%)	0	0	0	14 (24.1%)
	Decreased appetite	4 (6.9%)	7 (12.1%)	0	0	0	11 (19.0%)
	Anaemia	1 (1.7%)	4 (6.9%)	2 (3.4%)	0	0	7 (12.1%)
	Abdominal pain	2 (3.4%)	1 (1.7%)	1 (1.7%)	0	0	4 (6.9%)
	Back pain	3 (5.2%)	1 (1.7%)	0	0	0	4 (6.9%)
	Dizziness	3 (5.2%)	1 (1.7%)	0	0	0	4 (6.9%)
	Chills	3 (5.2%)	0	0	0	0	3 (5.2%)
	Dry mouth	2 (3.4%)	1 (1.7%)	0	0	0	3 (5.2%)
	Dysgeusia	2 (3.4%)	1 (1.7%)	0	0	0	3 (5.2%)
	Groin pain	2 (3.4%)	1 (1.7%)	0	0	0	3 (5.2%)
	Myalgia	2 (3.4%)	1 (1.7%)	0	0	0	3 (5.2%)

Related Treatment emergent AEs by max severity in >1 subject (n=14)

PD1 Combo	Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	No. of subjects with least 1 AE	**9 (64.3%)**	**7 (50.0%)**	**3 (21.4%)**	**0**	**0**	**11 (78.6%)**
	Localized tumor-related pain	4 (28.6%)	4 (28.6%)	0	0	0	8 (57.1%)
	Nausea	4 (28.6%)	0	0	0	0	4 (28.6%)
	Decreased appetite	1 (7.1%)	2 (14.3%)	0	0	0	3 (21.4%)
	Vomiting	2 (14.3%)	0	1 (7.1%)	0	0	3 (21.4%)
	Anaemia	1 (7.1%)	0	1 (7.1%)	0	0	2 (14.3%)
	Neck pain	1 (7.1%)	1 (7.1%)	0	0	0	2 (14.3%)

§ 2 subjects were re-enrolled in subsequent arms of the study, and safety was assessed for each arm.
Additional related grade 3 AEs reported in 3 subjects of dehydration, dyspnoea, hypokalemia, pneumothorax, and pyrexia.

- 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.
- Although data are early, the preliminary safety profile of Pembrolizumab combo is similar to monotherapy.

Monotherapy: 2 related SAEs (localized tumor-related pain, and procedural pain).
Pembrolizumab Combination: 4 related SAEs (headache, pneumothorax, pyrexia, vomiting).

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, overall survival may be a more appropriate endpoint to assess efficacy.

Monotherapy (n=53)[1]: Disease control rate (DCR) at > 50 days (approximate 2 months assessment) was 40% in evaluable subjects.
Subjects were assessed by comparing INT230-6 dosed to ≥ 50% total tumor burden vs. < 50% total tumor burden for a retrospective exploratory analysis.
These groups were reasonably balanced with respect to age, gender, ethnicity, tumor types, mean baseline tumor burden (p =0.25), and Royal Marsden Hospital index (RMHI)

Subjects dosed to ≥50%:	Subjects dosed to <50%:
• 19 of 36 subjects alive (17 deaths)	• 7 of 17 subjects alive (10 deaths)
• Tumor burden: mean (173 cm^3) & median (105 cm^3)	• Tumor burden: mean (234 cm^3) & median (196 cm^3)

Figure 3

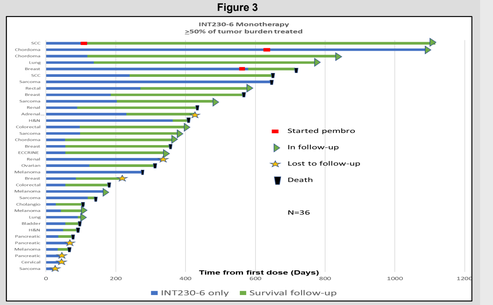
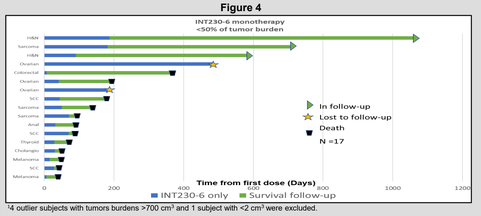


Figure 4

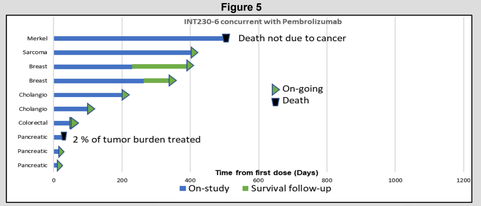


[4] outlier subjects with tumors burdens >700 cm^3 and 1 subject with <2 cm^3 were excluded.

- DCR was 47% in subjects dosed to ≥50% vs. 19% for subjects dosed to <50%.

Pembrolizumab Combination (n=10)[2]: 8 of 10 subjects alive (2 deaths). Mean and median tumor burden were similar to the monotherapy cohort.

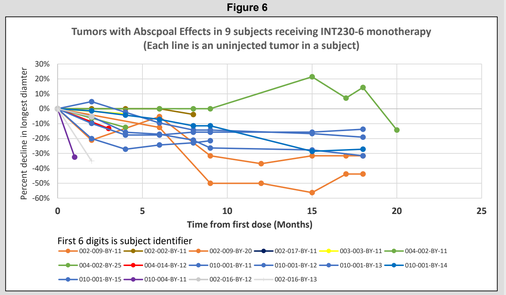
Figure 5



[2]4 subjects were excluded in this analysis: 2 were initially enrolled in the monotherapy cohort and crossed over to the Pembrolizumab combination, 1 had very bulky disease (>3000), and 1 had received a very small tumor (<2cm).

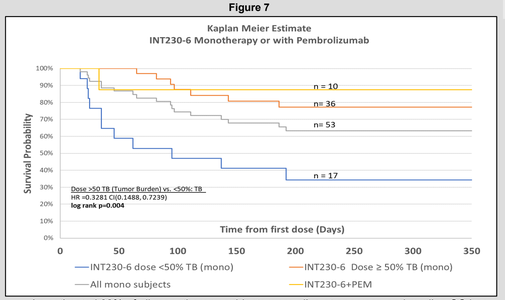
EFFICACY continued

Figure 6



- Abscopal effects seen in non-injected lung, liver and lymph node lesions in 9 monotherapy subjects; 8 of these 9 subjects had INT230-6 dosed to ≥ 50% total tumor burden. (Figure 6)

Figure 7



- An estimated 62% of all monotherapy subjects were alive at one year, and median OS has not been reached with 221 days of median follow up. (Figure 7)
- An exploratory analysis of dose relative to tumor burden (TB) showed that subjects receiving a dose of INT230-6 <50% of their reported TB had a mOS of 95 days. While in subjects receiving a dose of INT230-6 to ≥50% of TB, mOS has not yet been reached after a median follow up of 342 days (HR: 0.33 (0.15,0.72)).
- Preliminary estimate of survival of the Pembrolizumab combination is 88% at one year. Data is immature.
- In basket studies with similar Phase 1 solid tumor populations, the mOS is 90-160 days.[iv, v]

CONCLUSIONS

- INT230-6 is well tolerated as monotherapy and in combination with Pembrolizumab.
- INT230-6 demonstrates direct tumor killing and abscopal effects.
- RECIST methodology may not be a good measure of clinical benefit with INT230-6 and overall survival may be a more appropriate endpoint to assess efficacy.
- An exploratory analysis suggests survival for monotherapy subjects receiving INT230-6 dose to ≥50% of their tumor burden compares favorably to the <50% group and to historical survival from Phase 1 solid tumor basket studies with similar prognostic indicators (ECOG, LDH, # of metastatic sites).[iv, v]
- Further enrollment and follow up in the Pembrolizumab + INT230-6 combination group will be needed to confirm if there is benefit of the combination.

i. Ghandi et al. NEJM 4/2018 ii. Bender et al. Int J Mol Sci 6/2020 iii. historical PK data from IV administration: Owelien J. Cancer Res 8/1977
iv. Laguna-Garrido et al. Cancer 3/2012 v. Chau et al. BMC Cancer 10/2011