Intratumoral INT230-6 increases tumor T cell infiltration and results in durable benefit as monotherapy and in combination with pembrolizumab in refractory patients.

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BACKGROUND

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

INT230-6 has demonstrated the ability to kill 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 in animal models. Preclinical data indicates INT230-6 increases influx of antigen presenting cells (APCs) to the tumor microenvironment and improves APCs' ability to recognize expressed antigens.

The role of cytotoxic agents in augmenting the response of checkpoint inhibitors was established based on the KEYNOTE-189 trial in NSCLC.[i] It is our aim to improve cancer treatment, reduce the side effects associated with systemic therapies and improve patient outcomes using intratumoral INT230-6. In addition, the direct intratumoral injection approach has the potential to debulk the cancer and release greater quality and amounts of tumor specific antigens to prime the immune system. In animal models, systemic chemotherapy inhibits the immune response induced by a PD-1 antibody while local delivery of potent agents potentiates activity.[ii]

We report updated safety, efficacy and biomarker data from an ongoing Phase 1/2 clinical study at 7 major academic centers the US and Canada, IT-01/KEYNOTE A10.

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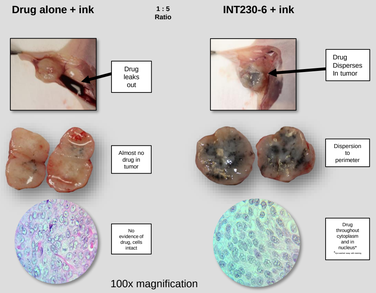
PRECLINICAL DATA

- 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).
- 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]



CLINICAL STUDY

Phase 1

INT230-6 monotherapy dose escalation by increasing the frequency, dose volume, number of tumors, and concentration of drugs in the tumors.

Phase 2

- ≥ 18 years
- ECOG PS ≤ 1 for Combo and PS ≤ 2 for Mono
- Advanced solid tumors, relapsed/ refractory
- Measurable disease by RECIST 1.1
- At least one target tumor for injection

Dose expansion

Pembrolizumab combination
Pancreatic, MSS colon, bile duct, SCC
- INT230-6 dosing as in EC3
- Pembro q3 weeks x 2 years

Ipilimumab combination
Breast cancer, sarcoma, HCC
- INT230-6 dosing as in EC3
- Ipi q3 weeks x 4 doses

INT230-6 monotherapy
Any others
- INT230-6 1 mL per 3 cc of tumor vol., up to 175 mL, q2 weeks x 5 doses
- Maintenance q9 weeks x 2 years

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 (SAEs) 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

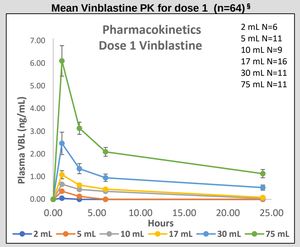
DEMOGRAPHICS & EXPOSURE

DEMOGRAPHICS	
Age	Median 61 (42-85)
Gender	30 male, 30 female
Race	83% Caucasian
	5% African American
	12% Asian
ECOG	27% ECOG 0
	65% ECOG 1
	8% ECOG 2
Tumor types	9 Sarcoma
	7 Breast
	6 Squamous cell carcinoma
	5 Chordoma
	5 Melanoma
	4 Colorectal
	4 Head and Neck
	4 Ovarian
	3 Pancreatic
	2 Cholangiocarcinoma
	2 Renal
	9 Others, one tumor type each
Median number of prior therapies (range)	3 (0-10)
# with prior Platinum	43%
# with prior PD1	43%

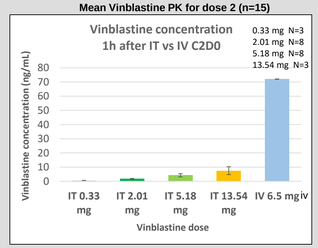
60 subjects (53 mono, 7 combo with PD1) have been treated as of September 29 2020. PK data reflects analysis as of May 31 2020.

- 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.
- Doses from 0.3 ml up to-172 ml of INT230-6 (86 mg CIS and 17mg of VIN) were injected (INT230-6 was dosed by tumor volume) with repeated intratumoral injection and multiple tumors injected.
- **225 deep tumor injections given** (including liver, lung, pancreas, lymph nodes) with minimal leakage.
- Dose response proportionality observed in PK profile, all drug cleared by 2 weeks.
- Peak plasma concentrations of vinblastine are ~5% of predicted based on historical IV kinetics, indicating drug remains in the tumor.
  - Some subjects received 3X the typical systemic IV dose of vinblastine.[iv]

Mean Vinblastine PK for dose 1 (n=64) §



Mean Vinblastine PK for dose 2 (n=15)



§ includes 2 patients who were retreated multiple times.

SAFETY

Treatment emergent AEs by max severity in >2 patients (n=55 §)

	Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4 or 5	Total
Monotherapy	Any	19 (34.5%)	22 (40.0%)	7 (12.7%)	0	48 (87.3%)
	Localized tumor-related pain	20 (36.4%)	9 (16.4%)	3 (5.5%)	0	32 (58.2%)
	Nausea	16 (29.1%)	4 (7.3%)	0	0	20 (36.4%)
	Fatigue	5 (9.1%)	12 (21.8%)	1 (1.8%)	0	18 (32.7%)
	Vomiting	12 (21.8%)	3 (5.5%)	0	0	15 (27.3%)
	Decreased appetite	4 (7.3%)	8 (14.5%)	0	0	12 (21.8%)
	Anemia	1 (1.8%)	5 (9.1%)	2 (3.6%)	0	8 (14.5%)
	Myalgia	3 (5.5%)	2 (3.6%)	0	0	5 (9.1%)
	Abdominal pain	2 (3.6%)	1 (1.8%)	1 (1.8%)	0	4 (7.3%)
	Back pain	3 (5.5%)	1 (1.8%)	0	0	4 (7.3%)
	Chills	4 (7.3%)	0	0	0	4 (7.3%)
	Dizziness	3 (5.5%)	1 (1.8%)	0	0	4 (7.3%)
	Dry mouth	2 (3.6%)	1 (1.8%)	0	0	3 (5.5%)
	Dysgeusia	2 (3.6%)	1 (1.8%)	0	0	3 (5.5%)
	Groin pain	2 (3.6%)	1 (1.8%)	0	0	3 (5.5%)

Treatment emergent AEs by max severity in >1 patient (n=7)

	Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4 or 5	Total
PD1 Combo	Any	2 (28.6%)	3 (42.9%)	1 (14.3%)	0	5 (71.4%)
	Localized tumor-related pain	2 (28.6%)	3 (42.9%)	0	0	5 (71.4%)
	Vomiting	2 (28.6%)	0	1 (14.3%)	0	3 (42.9%)
	Nausea	2 (28.6%)	0	0	0	2 (28.6%)

§ 2 patients were re-enrolled in subsequent arms of the study, and safety was assessed for each arm.

SAFETY continued

- Most adverse events were low grade and transient.
- There were no events that were dose limiting.
- Safety profile of Pembrolizumab combo is similar to monotherapy.

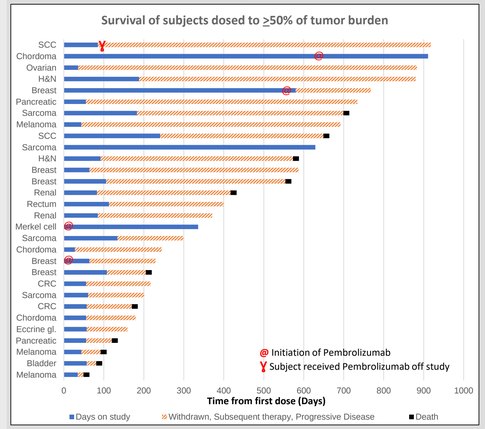
Mono: 2 related SAEs (localized tumor-related pain, and abdominal pain).
Pembrolizumab Combination: No related SAEs.

PRELIMINARY EFFICACY

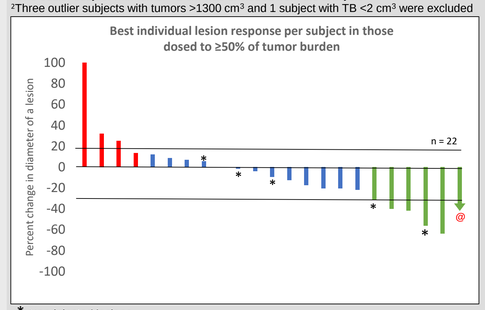
Subjects were grouped with INT230-6 dosed to ≥ 50% total tumor burden vs. < 50% total tumor burden for analysis.

- Groups were reasonably balanced with respect to age, gender, ethnicity, tumor types and mean baseline tumor burden (243 cc vs. 270 cc (p =0.7045)).

Subjects dosed to ≥50%:	Subjects dosed to <50%:
• 19 of 30 subjects alive (11 deaths)	• 7 of 26 subjects alive (19 deaths)
• Tumor burden: mean (243 cm^3) & median (109 cm^3)[1]	• Tumor burden: mean (270 cm^3) & median (179 cm^3)[2]

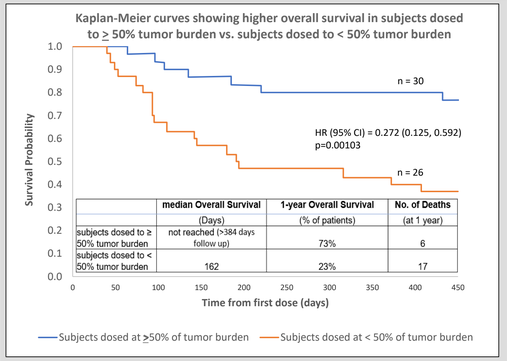


[1]One outlier subject with tumor <2 cm was excluded from the analysis
[2]Three outlier subjects with tumors >1300 cm^3 and 1 subject with TB <2 cm^3 were excluded



* Non-injected lesions
@ PD-1 Combo, >30% reduction by visual inspection in telehealth visit

PRELIMINARY EFFICACY continued



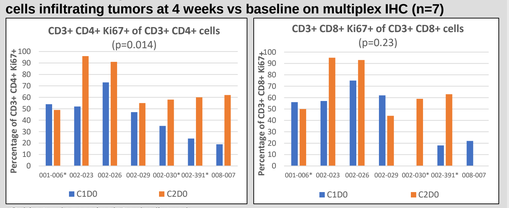
	median Overall Survival (Days)	1-year Overall Survival (% of patients)	No. of Deaths (at 1 year)
subjects dosed to ≥ 50% tumor burden	not reached (>384 days follow up)	73%	6
subjects dosed to < 50% tumor burden	162	23%	17

- CT scans with IV contrast demonstrated necrosis in injected tumors.
- Abscopal effects seen in non-injected lung, liver and lymph node lesions in 9 monotherapy subjects.

BIOMARKERS

Previously presented biopsy data showed substantial reduction of viable tumor cells after 2 doses, and an influx of CD4 and CD8 T cells.

Paired tumor samples show Ki67 increases in CD3+ CD4+ and CD3+ CD8+ T cells infiltrating tumors at 4 weeks vs baseline on multiplex IHC (n=7)



*Subjects who received Pembrolizumab

Immune cells were negative for FoxP3, suggesting increased active anti tumor immunity after treatment.

RESULTS AND CONCLUSIONS

- INT230-6 is well tolerated as monotherapy or in combination with pembrolizumab.
- PK data indicate that ~95% of INT230-6 active agents are retained in the tumor.
- Increases in activated CD4/CD8 T-cell in the tumors.
- INT230-6 demonstrates direct tumor killing (necrosis on CT and biopsy), and abscopal effects.
- Injection of ≥ 50% of visible tumor burden (recommended treatment strategy) leads to overall clinical benefit (PR + SD) in multiple tumor types.
- Overall survival is significantly higher in subjects dosed to ≥ 50% tumor burden vs. < 50% tumor burden.

i. Ghandi et al NEJM 4/2018 ii. Mathios et al Sci Transl Med 12/2016 iii. Bender et al Int J Mol Sci 6/2020 iv. historical pK data from IV administration: Owelien, J Cancer Res 8/1977