Phase 1/2 Evaluation of Intratumoral INT230-6 for the Treatment of Solid Tumors

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Background

Intensity Therapeutics and the National Cancer Institute's Vaccine Branch have collaborated to examine the immunologic mechanism of action of INT230-6, which consists of cisplatin (CIS), vinblastine (VIN) and an amphiphilic cell penetration excipient small molecule (SHAO) that improves intracellular and tissue diffusion by passive diffusion.

A key component to initiating a tumor immune response is priming the immune system with a broad range of tumor antigens. Cisplatin, a component in INT230-6, has properties that can induce immunologic cell death locally in the tumor to recruit immune cells and stimulate a systemic immune response. Given the increased diffusion of the cytotoxic agents by the SHAO throughout the tumors and into cancer cells, data indicates INT230-6 increases the ability of cancer cells to present tumor antigens on the cell surface and for APCs to recognize these expressed antigens potentially much more effectively than local destructive modalities such as radiation.

The role of cytotoxic agents in augmenting the response of checkpoint inhibitors was established based on the Merck Keynote 189 trial in NSCLC[i]. It is our aim to reduce the side effects of systemic chemotherapy using INT230-6 to debulk injected lesions as well as to release greater quality and amounts of tumor specific antigens to prime the immune system. Preclinical studies indicate that local chemotherapy promotes an immune response to anti-PD1, while systemic chemotherapy abrogates the immune response that anti-PD1 creates. [ii]

INT230-6 is now in a Phase 1/2 clinical trial in the US and Canada. Here we report the most current safety and response data from 22 subjects having several different tumor types.

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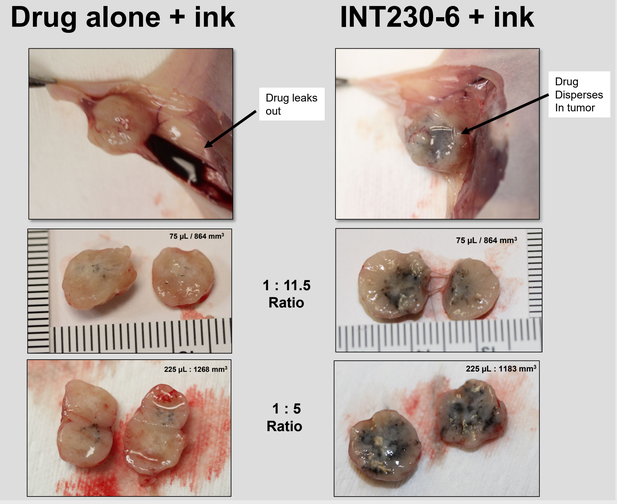
PRECLINICAL DATA

INT230-6 enhances diffusion into cancers cells while sparing normal cells. This study shows how placement of drug via a pump into the center of a dense murine pancreatic tumor (BxPc3) results in enhanced dispersion throughout the tumor without leakage only for INT230-6. Note black ink was added to INT230-6 and to the drug without Intensity's technology.



TREATMENT PLAN

Patients were dosed intratumorally initially once a month and then every 2 weeks. Procedure was repeated up to 5 times.

Dosing was performed by Oncologist or Interventional Radiologist under US or CT guidance using straight needles or multi pronged needles to help disperse INT230-6 throughout large tumors.

Initially subjects with superficial tumors for injection were enrolled. Once safety was reviewed by the Study Steering Committee (SSC), then subjects with deep tumors were enrolled.

Initial dosing was to achieve a target Drug Dose: Tumor Volume of 1mL : 4cc. Once safety was demonstrated, the target ratio increased to 1 : 2. Minimal leakage is noted from the tumors.

Dose escalation ranged from 0.3ml to 30ml with intra-patient dose escalation permitted (both the total and maximal dose may be increased on each subsequent cycle).

Current cohort allows in the 5th cycle up to 100mL of INT230-6 into any one tumor, 120mL total (still below the approved doses of cisplatin and vinblastine for intravenous use).

SAFETY

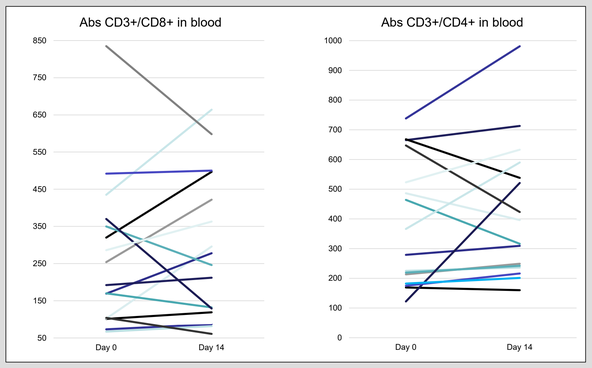
Data available on 22 patients, INT230-6 was well tolerated, no drug related SAE's, no DLT's, only one transient grade 3 pain reported in a patient who received an injection into the base of the tongue.

Adverse Event Related to Drug or Procedure	Grade 1	Grade 2	Grade 3	Grade 4	Total
Localized tumor-related pain	5 (22.7)	4 (18.2)	1 (4.5)	0	10 (45.5)
Nausea	1 (4.5)	1 (4.5)	0	0	2 (9.1)
Decreased appetite	0	2 (9.1)	0	0	2 (9.1)
Fatigue	0	2 (9.1)	0	0	2 (9.1)
Chills	1 (4.5)	0	0	0	1 (4.5)
Injection site erythema	1 (4.5)	0	0	0	1 (4.5)
Injection site haemorrhage	1 (4.5)	0	0	0	1 (4.5)
Malaise	0	1 (4.5)	0	0	1 (4.5)
Mucosal inflammation	1 (4.5)	0	0	0	1 (4.5)
Oedema	0	1 (4.5)	0	0	1 (4.5)
Pyrexia	1 (4.5)	0	0	0	1 (4.5)
Swelling	0	1 (4.5)	0	0	1 (4.5)
Abdominal pain	0	1 (4.5)	0	0	1 (4.5)
Dry mouth	1 (4.5)	0	0	0	1 (4.5)
Swollen tongue	0	1 (4.5)	0	0	1 (4.5)
Vomiting	0	1 (4.5)	0	0	1 (4.5)
Blister	1 (4.5)	0	0	0	1 (4.5)
Erythema	1 (4.5)	0	0	0	1 (4.5)
Rash erythematous	1 (4.5)	0	0	0	1 (4.5)
Urticaria	1 (4.5)	0	0	0	1 (4.5)
Dizziness	1 (4.5)	0	0	0	1 (4.5)
Headache	0	1 (4.5)	0	0	1 (4.5)
Wound infection	0	1 (4.5)	0	0	1 (4.5)
Blood creatinine increased	1 (4.5)	0	0	0	1 (4.5)

Each subject is counted per SOC for the worst severity of the event. Note all local pain conditions were grouped under new term"localized tumor-related pain"

BIOMARKERS

Blood samples at 2 weeks show >30% increases in CD8+ (n=6) and CD4+ T-cells (n=3) compared to baseline in (n=17).



INCLUSION CRITERIA

Key Inclusion Criteria:

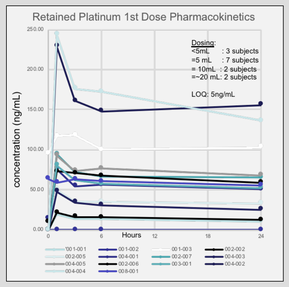
1. ≥ 18 years of age with ECOG performance status ≤ 2;
2. Subjects with advanced or metastatic solid tumors that have disease progression after treatment with approved, available therapies for the cancer type or for whom available therapies have limited benefit and the subject refuses the available therapy. Includes subjects with locoregional disease that have relapsed/recurred within 6 months of chemo-radiation; or who have no standard of care or beneficial options;
3. Subjects must have measurable disease by RECIST 1.1 criteria including one target tumor for injection;
4. Four week washout from prior therapies;
5. Screening laboratory values must meet the following criteria:
   - WBC ≥ 2000/µL (≥ 2 x 10^9/L)
   - Neutrophils ≥ 1000/µL (≥ 1 x 10^9/L)
   - Platelets ≥ 70x10^3/µL (≥ 70 x 10^9/L) (superficial tumor dosing only)
   - Hemoglobin ≥ 8 g/dL (≥80 g/L) (superficial tumor dosing only)
   - Creatinine within the institution's laboratory upper limit of normal or calculated creatinine clearance >50 ml/min
   - ALT/AST ≤ 2.5 x ULN without, and ≤ 5 x ULN with hepatic metastases
   - Bilirubin ≤ 2 x ULN (except subjects with Gilbert's syndrome, who must have total bilirubin < 3.0 mg/dL (< 52 µmol/L))
   - For patients with planned deep tumor injections: PT, aPPT, and INR within normal limits; Platelet count ≥ 100,000/µL; hemoglobin ≥ 9 g/dL.

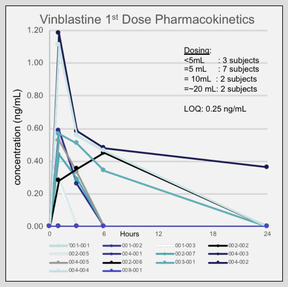
Key Exclusion Criteria:

1. History of severe hypersensitivity reactions to cisplatin or vinblastine or other products of the same class;
2. Underlying medical condition that, in the Principal Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events;
3. For deep tumor cohorts, patients who require uninterrupted anticoagulants of any type, on daily aspirin therapy, or NSAIDs;

PATIENT POPULATION

Age		Median 60 (46-73)
Gender		6 male, 16 female
Race		77% Caucasian
		9% African American
		14% Asian
ECOG		23% ECOG 0
		73% ECOG 1
		5 % ECOG 2
Tumor types	3	Skin
	3	Ovarian
	3	Head & Neck
	3	CRC + anal
	2	Sarcoma
	2	Cholangiocarcinoma
	1	Pancreas
	1	Thyroid
	1	Adrenalcorticoid
	1	Chordoma
	1	Breast
	1	Melanoma
Median number of prior treatments		3 (0,9)
# with prior Platinum		13/22
# with prior PD1		10/22





- Preliminary PK profile suggests dose proportionality in first 14 patients
- Baseline level of platinum measured in patients with prior platinum exposure
- Drug levels drop to baseline or lower limit of detection in first 6-12 hours
- Peak concentrations of vinblastine and reduced platinum are ~10% of predicted based on historical IV kinetics indicating lack of significant systemic exposure

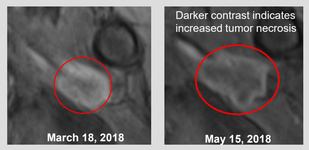
PRELIMINARY EFFICACY

Many subjects in early cohorts did not receive optimal dose/tumor volume ratio

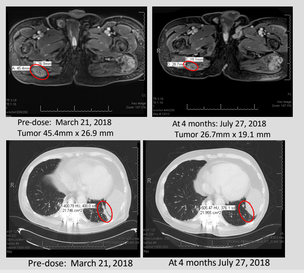
- Superficial tumors showed visible necrosis, cysts, and caliper measured regression
- Several subjects experienced symptomatic improvement
- Many tumors increased in size, then regressed from baseline
- Better outcomes were noted if > 40% of total tumor burden was treated

CASE EXAMPLES:

1. 68 year old patient with locally recurrent cutaneous squamous cell carcinoma of left arm status post multiple resections, radiotherapy and chemotherapy. Patient presented with 2 lesions of upper arm and received INT230-6 into both lesions once a month for 4 cycles at a 1:4 ratio. Patient tolerated the procedures well with no reported related AE's. On the first MRI, the tumors appeared larger, but the contrast uptake was diminished. CD8+ and CD4+ T cells increased at day 14.



2. 60 year old subject with metastatic Chordoma, Status post surgery, radiation, 5 prior regimens (chemotherapy, immunotherapy and targeted agents). Tumors showed interval growth on each subsequent scan. Subject received 5 doses of INT230-6 into 3 sacral lesions with grade 1 pain reported as only AE. As seen here, subject experienced >30% reduction in the injected gluteal mass lesion and reduction in the untreated lung metastasis



SUMMARY

- INT230-6 was well tolerated at doses up to 30ml in multiple image guided deep and superficial tumor injections
- No recorded systemic AEs that would be associated with either of the two cytotoxic agents
- >90% of the IT injected drugs appears to remain in the tumor (based on the systemic PK levels)
- Increases in circulating CD8 and CD4 T-cells and evidence of abscopal responses in some patient's non-injected tumors support preclinical findings of immune cell engagement following treatment
- Initial tumor size increase was observed in some patients (potentially due to tissue expansion by IT injection and/or immune cell infiltration), currently dosing injects up to an additional 200% of the tumor volume in the first 2 months

i. Ghandi et al NEJM 4/2018 ii. Mathios et al Sci Transl Med. 2016 December 21