INT230-6, a novel intratumoral (IT) formulation demonstrated a favorable safety profile during injections into a variety of refractory deep and superficial tumors with evidence of tumor regression and immune activation

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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.

INT230-6 has demonstrated the ability to induce an adaptive immune response in animal models. A key component to initiating an anti-tumor immune response is priming the immune system with a broad range of 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 into cancer cells of the cytotoxic agents using SHAO, nonclinical data indicates INT230-6 increases antigen presentation, increases influx of antigen presenting cells (APCs) to the tumor microenvironment and improves APCs ability to recognize expressed antigens - potentially 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 improve cancer treatment, reduce the side effects associated with systemic therapies and improve patient outcomes using intratumorally dosed INT230-6. In addition, our direct intratumoral injection approach has 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]

INT230-6 is now in a Phase 1/2 clinical trial in the US and Canada at 5 major academic centers. Here we report preliminary safety and response data from 34 subjects having several different tumor types.

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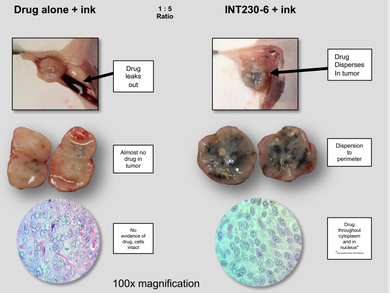
NONCLINICAL DATA

INT230-6 or control (aqueous cisplatin solution) with 150 µL of India ink was injected via a pump into the center of a dense large murine pancreatic tumor (BxPc3 ~1.2 cm^3). The tumors were immediately imaged and excised for sectioning. The results indicated enhanced dispersion throughout the tumor and entry into the nucleus dosing INT230-6. While the control formulation mostly leaked out of the tumor, did not disperse or enter the cancer cells.



CLINICAL STUDY PATIENT POPULATION

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:

1. WBC ≥ 2000/µL (≥ 2 x 10^9/L)
2. Neutrophils ≥ 1000/µL (≥ 1 x 10^9/L)
3. Platelets ≥ 70x10^3/µL (≥ 70 x 10^9/L) (superficial tumor dosing only)
4. Hemoglobin ≥ 8 g/dL (≥80 g/L) (superficial tumor dosing only)
5. Creatinine within the institution's laboratory upper limit of normal or calculated creatinine clearance >50 ml/min
6. ALT/AST ≤ 2.5 x ULN without, and ≤ 5 x ULN with hepatic metastases
7. Bilirubin ≤ 2 x ULN (except subjects with Gilbert's syndrome, who must have total bilirubin < 3.0 mg/dL (< 52 µmol/L))
8. 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.

ENDPOINTS

Primary Outcome Measures for Phase 1:

- The primary objective was to assess the safety and tolerability of multiple intratumoral doses of INT230-6 in subjects with advanced or recurrent malignancies. This was assessed by the rate of ≥ grade 3 adverse events attributed to INT230-6 and not the underlying disease

Additional Outcome Measures for Phase 1:

- Characterized the pharmacokinetic profile of multiple doses of the three INT230-6 components (CIS, VBL, and SHAO) after single and then multiple IT tumor site injections.
- Assessed the preliminary efficacy of INT230-6 by measuring the injected tumor response using RECIST 1.1 response thresholds
- Characterized tumor response in non-injected sites
- Evaluated various tumor and anti-tumor immune response biomarkers that may correlate with tumor response.

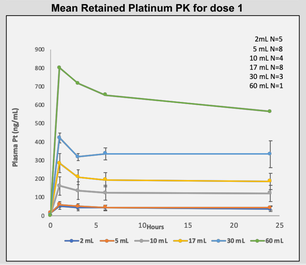
DEMOGRAPHICS & EXPOSURE

DEMOGRAPHICS	
Age	Median 59 (42-76)
Gender	14 male, 20 female
Race	82% Caucasian
	6% African American
	12% Asian
ECOG	35% ECOG 0
	56% ECOG 1
	9 % ECOG 2
Tumor types	5 cut Squamous cell carcinoma
	3 Ovarian
	4 Head & Neck 3 CRC 3 Sarcoma
	2 Cholangiocarcinoma
	Anal
	Urothelial
	Adrenal corticoid
	Pancreatic
	Lung
	Thyroid
	3 Chordoma
	3 Breast
	3 Melanoma
Median number of prior therapies (range)	3 (0,9)
# with prior Platinum	44%
# with prior PD1	47%

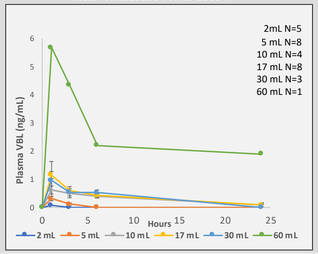
34 subjects have been treated as of data cut off date, May 3, 2019. Pharmacokinetic data reflects analysis as of January 31, 2019 (N=29 subjects)

- Dose escalation ranged from 0.3ml to 120ml (INT230-6 was dosed by tumor volume) with repeated intratumoral injection and multiple tumors injected (equates to 0.15mg-60mg dose of CIS, and 0.03mg to 12mg dose of VIN)
- 117 deep tumor injections given (including liver, lung, lymph nodes) with minimal leakage
- Dose response proportionality observed in PK profile
- 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 in most patients
- Peak concentrations of vinblastine and reduced platinum are ~10% of predicted based on historical IV kinetics, indicating drug remains in the tumor

Mean Retained Platinum PK for dose 1



Mean Vinblastine PK for dose 1



SAFETY

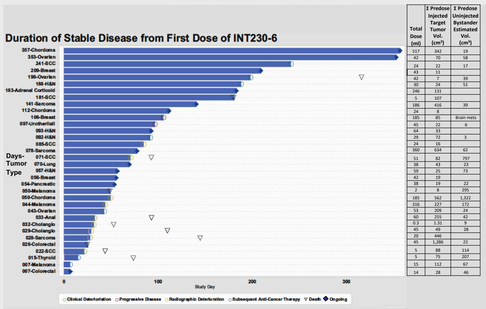
There were no DLT's and one drug related SAE (grade 3 abdominal pain); 20 unrelated SAE's were reported in 10 subjects, all related to underlying disease.

Related AE's by max severity in more than 1 patient

Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4 or 5	Total
Any	8 (23.5%)	15 (44.1%)	3 (8.8%)	0	26 (76.4%)
Localized pain at injection site	8 (23.5%)	6 (17.6%)	1 (2.9%)	0	15 (44.1%)
Fatigue	4 (11.8%)	6 (17.6%)	1 (2.9%)	0	12 (35.3%)
Nausea	8 (23.5%)	2 (5.9%)	0	0	10 (29.4%)
Vomiting	8 (23.5%)	2 (5.9%)	0	0	10 (29.4%)
Decreased appetite	2 (5.9%)	5 (14.7%)	0	0	7 (20.6%)
Abdominal pain	1 (2.9%)	1 (2.9%)	1 (2.9%)	0	3 (8.8%)
Dry mouth	2 (5.9%)	1 (2.9%)	0	0	3 (8.8%)
Back pain	2 (5.9%)	1 (2.9%)	0	0	3 (8.8%)
Dizziness	3 (8.8%)	0	0	0	3 (8.8%)
Anaemia	1 (2.9%)	2 (5.9%)	0	0	3 (8.8%)
Chills	2 (5.9%)	0	0	0	2 (5.9%)
Injection site erythema	2 (5.9%)	0	0	0	2 (5.9%)
Groin pain	1 (2.9%)	1 (2.9%)	0	0	2 (5.9%)
Rash maculo-papular	2 (5.9%)	0	0	0	2 (5.9%)
Urticaria	1 (2.9%)	1 (2.9%)	0	0	2 (5.9%)
Dysgeusia	1 (2.9%)	1 (2.9%)	0	0	2 (5.9%)
Headache	1 (2.9%)	1 (2.9%)	0	0	2 (5.9%)
Blood creatinine increased	1 (2.9%)	1 (2.9%)	0	0	2 (5.9%)

- Most adverse events were low grade and transient.
- Systemic side effects do not appear dose related or to worsen with repeat dosing

PRELIMINARY EFFICACY

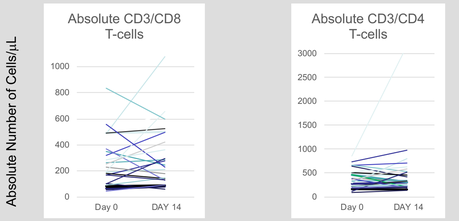


Total Dose (mL)	‡ Predose Injected Target Tumor Vol. (cm³)	‡ Predose Uninjected Bystander Estimated Vol. (cm³)
517	342	19
42	30	58
16	22	17
42	11	7
42	7	39
30	24	51
246	131	
5	107	
186	416	39
28	8	
185	85	Brain mets
45	22	6
64	33	
25	72	3
24	59	
90	634	62
51	82	797
30	47	23
45	25	73
45	19	
36	18	22
3	8	255
185	562	1,102
316	227	172
53	209	24
60	255	42
8.5	1.15	9
45	49	28
30	446	
45	1,396	22
5	88	114
5	75	207
15	112	87
14	28	46

- Early cohort patients had large tumor burden and received low doses
- In latest cohort EC (1:2 ratio every 2 weeks) equates to 200% more volume added to the tumor by the time of the 2 month scan
- As indicated in the preclinical and biopsy data, the drug enters the cells and the nucleus, as well as immune cells enter the tumor
- Many tumors are larger than baseline at the 2 month scan, and then regress from baseline on 4 month scan. Several subjects withdrew from the study due to enlarging lesions and tumor related symptoms, which may have been pseudo-progression.
- Not all non injected lesions were tracked in the CRF
- 8 patients showed some size reduction of one or more non injected lesions in LN, liver, lung, perineum, and retroperitoneal areas

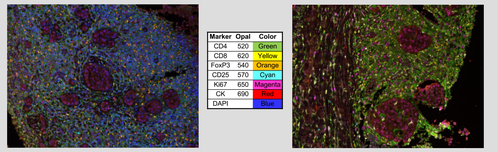
BIOMARKERS

Blood samples at 2 weeks show increases in CD8+ and CD4+ T-cells compared to baseline (n=25 evaluable).



10/25 with >30%increases

7/25 with >30% increases



Marker	Opal	Color
CD4	520	Green
CD8	620	Yellow
FoxP3	540	Orange
CD25	570	Cyan
Ki67	650	Magenta
CK	690	Red
DAPI		Blue

Example of a breast cancer subject with a pre- and one month post first dose biopsy. There was a 75% reduction in Ki 67+ cells (magenta) and 73% reduction in FoxP3 (orange) with increases in CD4 and CD8 T-cells (using whole section image analysis)

RESULTS AND CONCLUSIONS

- INT230-6 was well tolerated at doses up to 120 mL in multiple deep and superficial tumor injections
  - Some patients received IT twice the approved IV dose for VIN without substantial cytotoxic side effects
  - PK suggests that the majority of the drug remains in the tumor (based on AUC comparison to historical IV data)
- The study drug and dosing procedure were well tolerated
- Multiple different types of injected tumors demonstrated visible necrosis, decreased contrast uptake and size reduction. Some patients reported decreases in cancer related symptoms.
- Eight patients had a decrease in size of un-injected lesions
- Increases in tumor and circulating CD8 and CD4 T-cells and abscopal responses in non-injected tumors support preclinical findings of immune cell engagement following INT230-6 treatment

Enrollment of various tumor types is ongoing to better characterize the safety and efficacy at higher doses. Future cohorts to include INT230-6 plus anti-PD-1 and anti-CTLA-4 drugs. Present specific phase 2 expansion cohorts will be determined by the study steering committee.

i. Ghandi et al NEJM 4/2018 ii. Mathios et al Sci Transl Med 12/2016

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