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

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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.

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 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 so 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. In animal models the combination of INT230-6 plus checkpoint inhibitors was better tolerated than the checkpoint inhibitors given alone. Both INT230-6 monotherapy and combination efficacy have been demonstrated in a variety of tumor models via a dual mechanism of cell death and immune activation.

INT230-6 is now in a Phase 1/2 clinical trial in the US and Canada. Here we report preliminary safety and response data from 18 subjects having several different tumor types.

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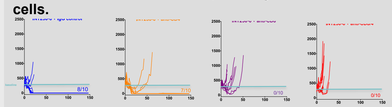
PRECLINICAL DATA

CD4 and CD8 T cells were depleted at the onset of INT230-6 treatment and confirmed with flow cytometry in a Colon 26 mouse model. INT230-6 treatment combined with an IgG control antibody (blue) induced CR's in 80% of mice. Interestingly, depletion of CD4 T cells did not significantly alter the effect (yellow). Depletion of CD8 T cells (purple) significantly shortened survival; even though transient regression from baseline was observed in the majority of animals, no complete response was obtained. This loss of immunity was further amplified by simultaneous depletion of both $CD8^+$ and $CD4^+$ T cells (red). This suggests the **initial reduction in tumor mass was due to the cytotoxic effect of the cytotoxic agents but complete response was dependent on recruitment of primarily effector CD8 T cells.**



$300mm^3$ tumors were injected on days 1-5 with INT230-6. 80% of animals achieved CR

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

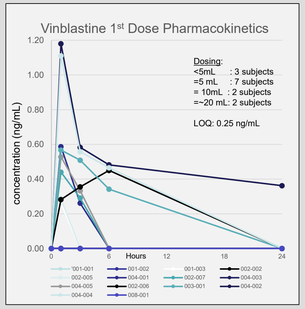
Additional Outcome Measures for Phase 1:

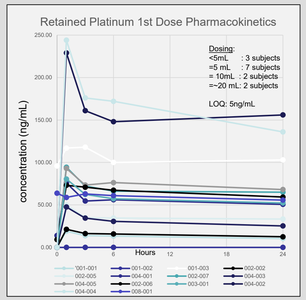
- Characterized the pharmacokinetic profile of multiple doses the three INT230-6 components (CIS, VBL, and SHAO) after single and then multiple IT tumor site injections.
- Assessed the preliminary efficacy of INT230-6 by measuring the injected tumor response using RECIST response thresholds
- Characterized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

DEMOGRAPHICS & EXPOSURE

20 subjects treated as of October 1, 18 of which have on study data in the database, pharmacokinetic data available on the first 14 subjects

Age	Median 60 (46-72)
Gender	5 male, 13 female
Race	83% Caucasian
	6% African American
	11% Asian
ECOG	22% ECOG 0
	72% ECOG 1
	6 % ECOG 2
Tumor types	5 Squamous cell carcinoma
	3 Ovarian
	2 Head & Neck
	2 CRC
	Sarcoma
	Cholangiocarcinoma
	Thyroid
	Chordoma
	Breast
	Melanoma
# with prior Platinum	9/18
# with prior PD1	9/18





- Dose escalation ranged from 0.3ml to 30ml with repeated intratumoral injection and multiple tumors injected
- Target drug to tumor ratio of 1:4 or 1:2 achieved 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
- Peak concentrations of vinblastine and reduced platinum are ~10% of predicted based on historical IV kinetics indicating drug remains in the tumor

SAFETY

To date, 20 subjects have been treated. There were no DLT's or drug related SAEs (15 SAE's in 8 subjects all related to underlying disease). 18 subjects were evaluable for safety.

Treatment related AE	NCI-CTCAE Toxicity Grade n (%)				
PT	**1**	**2**	**3**	**4/5**	**Total**
Pain	1 (5.6%)	2 (11.1%)	0	0	3 (16.7%)
Fatigue	0	2 (11.1%)	0	0	2 (11.1%)
Injection site pain	1 (5.6%)	1 (5.6%)	0	0	2 (11.1%)
Musculoskeletal pain	2 (11.1%)	0	0	0	2 (11.1%)
Chills	1 (5.6%)	0	0	0	1 (5.6%)
Injection site erythema	1 (5.6%)	0	0	0	1 (5.6%)
Malaise	0	1 (5.6%)	0	0	1 (5.6%)
Mucosal inflammation	1 (5.6%)	0	0	0	1 (5.6%)
Oedema	0	1 (5.6%)	0	0	1 (5.6%)
Dry mouth	1 (5.6%)	0	0	0	1 (5.6%)
Nausea	1 (5.6%)	0	0	0	1 (5.6%)
Swollen tongue	0	1 (5.6%)	0	0	1 (5.6%)
Blister	1 (5.6%)	0	0	0	1 (5.6%)
Rash erythematous	1 (5.6%)	0	0	0	1 (5.6%)
Urticaria	1 (5.6%)	0	0	0	1 (5.6%)
Dizziness	1 (5.6%)	0	0	0	1 (5.6%)
Headache	0	1 (5.6%)	0	0	1 (5.6%)
Wound infection	0	1 (5.6%)	0	0	1 (5.6%)
Blood creatinine increased	1 (5.6%)	0	0	0	1 (5.6%)
Decreased appetite	0	1 (5.6%)	0	0	1 (5.6%)
Tumour pain	0	0	1 (5.6%)	0	1 (5.6%)

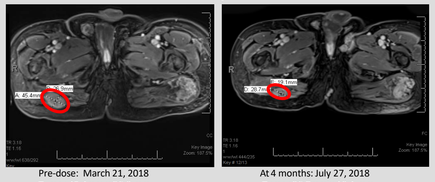
Pt Treated Population = All subjects who receive at least 1 dose or any partial dose of INT230-6.
Note: The highest known severity within each SOC and PT will be assigned to the event.
MedDRA = Medical Dictionary for Regulatory Activities. PT=Preferred Term. Version 18.0 or higher of MedDRA was used to code AE.
NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

Most adverse events were low grade and transient. This is consistent with local tissue expansion from fluid injections

ILLUSTRATIVE CASE

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.

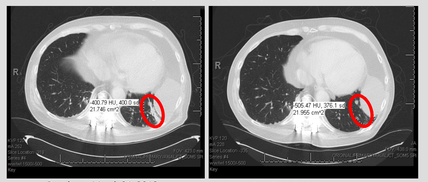
Gluteal mass: Injected tumor PR



Pre-dose: March 21, 2018
Tumor 45.4mm x 26.9 mm

At 4 months: July 27, 2018
Tumor 26.7mm x 19.1 mm

Lung lesion: Abscopal response

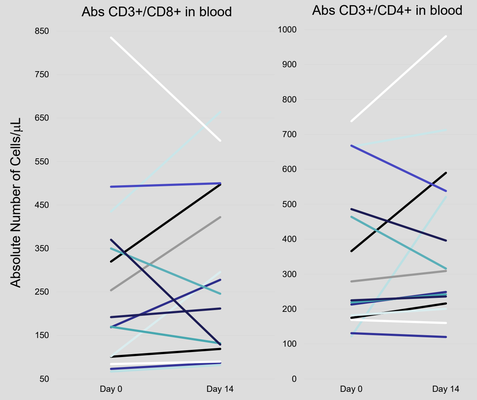


Pre-dose: March 21, 2018

At 4 months July 27, 2018

BLOOD BIOMARKERS

Blood samples at 2 weeks show increases in CD8+ and CD4+ T-cells compared to baseline in some subjects (n=15).



RESULTS AND CONCLUSIONS

- INT230-6 was well tolerated at doses up to 30ml in multiple 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
- Injected tumors exhibited initial tumor size increase (potentially due to tissue expansion by IT injection and/or immune cell infiltration)
- Injected tumors demonstrated visible necrosis, decreased contrast uptake size reduction. Some patients have reported decreases in cancer related symptoms.
- Increases in circulating CD8 and CD4 T-cells and evidence of abscopal responses in non-injected tumors support preclinical findings of immune cell engagement following 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-PD1. On study tumor biopsy has been initiated to evaluate on study tumor biopsies. Tumor specific phase 2 expansion cohorts will be determined by the study steering committee.

i. Ghandi et al NEJM 4/2018 ii. Bloom et al, manuscript submitted