Phase 1/2 trial evaluating intratumoral administration of INT230-6 alone and in combination with an anti-PD1 antibody for advanced malignancies

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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.

A key component to initiating a tumor immune response is priming the immune system with a broad range of tumor antigens. INT230-6 induces immunologic cell death locally in the tumor which recruits inflammatory cells and stimulates a potent systemic immune response. This can occur without disrupting the 3D cell structure, or impact on normal cells.

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 and release personalized tumor 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.

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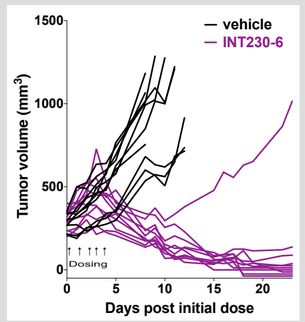
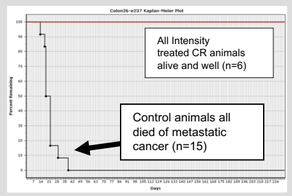
PRECLINICAL DATA

INT230-6 has shown high rates of complete regression in drug-injected and bystander large colon26 (C26) mouse tumors[ii]. Responses and immunologic memory are dependent on recruitment and activation of dendritic cells (DC's) and CD4 and CD8 T-cells

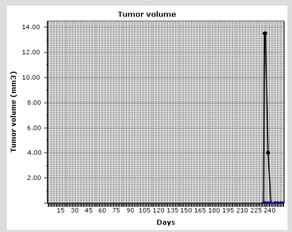


300mm^3 tumors were injected on days 1-5 with INT230-6. 80% of animals achieved CR

IV re-inoculation



SC Rechallenge at end of life



Small growth spontaneously clears

ENDPOINTS

Primary Outcome Measures:

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

Secondary Outcome Measures:

- Assess the preliminary efficacy of INT230-6 by measuring the injected tumor response
- Characterize the pharmacokinetic profile of multiple doses the three INT230-6 components (CIS, VBL, and SHAO) after single and then multiple IT tumor site injections.

Exploratory Outcome Measures:

- Characterize tumor response in non-injected sites
- Evaluate various tumor and circulating immune response biomarkers that may correlate with tumor response
- Evaluate overall response by RECIST 1.1
- Characterized the pharmacodynamics (PD) profile of the INT230-6 formulation in subject blood and treated and untreated tumors
- To assess the progression free and overall survival in subjects receiving INT230-6.

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;

COHORTS

Planned cohorts to include increased dose frequency, increased loading of drug into tumor and higher starting dose, higher total dose and escalating the number of tumors injected per patient. Intra-patient dose escalation is allowed, which can be achieved by increased dose or by injecting more tumors. A sentinel patient was included for superficial cohort (A1) and then for the deep tumor cohort (B1). The Study Steering Committee(SSC) reviews the ongoing safety and conduct of the study to help enable decision making on which cohorts to open and the proper patient population and dose for new cohorts

Cohort	frequency	drug dose to tumor volume	starting dose	peak dose	NOTES
A1	Q month	1ml to 4cc	5ml	15ml	superficial tumors only
B1	Q month	1ml to 4cc	5 ml	30ml	
B2	Q month	1ml to 4cc	30ml	120ml	
B3	Q month	1ml to 4cc	TBD	TBD	
C1	Q month	1ml to 2cc	5ml	15ml	
C2	Q month	1ml to 2cc	30ml	120ml	
C3	Q month	1ml to 2cc	TBD	TBD	
D	TBD	TBD	TBD	TBD	combination with PD1
E	Q 2week	TBD	TBD	TBD	

* Dose that approximately the approved IV dose of Cisplatin

The following cohort was opened following SSC discussion of the safety and Pk results:

Cohort	frequency	drug dose to tumor volume	starting dose	peak dose	NOTES
EA	Q 2week	1ml to 4cc	up to 20	60	superficial tumors only

STATUS

To date, 13 patients have been accrued. The SSC reviewed safety in cohorts A (superficial tumors once monthly), and opened B1(deep tumors) and EA(superficial tumors twice monthly). As of June 1st, 2018 no DLT's have been recorded.

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