Pharmacodynamic, safety and efficacy results of a phase 1/2 trial of intratumoral INT230-6 alone (IT-01) or in combination with Pembrolizumab (PEM) (Keynote A10) in patients with advanced solid tumors

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BACKGROUND

INT230-6 consists of cisplatin (CIS), vinblastine (VIN) and an amphiphilic cell penetration excipient small molecule (SHAO) that improves intracellular transport and tissue dispersion by passive diffusion.

In non-clinical studies, INT230-6 has demonstrated the ability to differentially be absorbed by cancer cells and cause cell death, followed by systemic immune activation. INT230-6 monotherapy has achieved proof of concept in humans with 95% of the drugs active ingredients remaining in the tumor, with a good safety profile even in patients who received substantially more agents than typically administered IV. Patients had evidence of tumor cell destruction, with systemic immune activation and local infiltration with CD4 and CD8 T-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 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 chemotherapy potentiates activity.[ii] Previously published data show that INT230-6 with a PD1 antibody has synergistic activity in mouse models.

Here we report preliminary safety and response data from 52 subjects with different solid tumors who received monotherapy and 7 subjects in the pembrolizumab combination arm.

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

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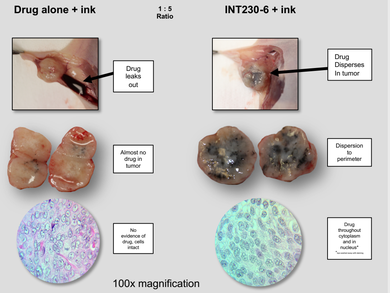
NONCLINICAL DATA

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 human pancreatic tumor (BxPc3 ~1.2 cm^3) in a SCID mouse. The tumors were immediately imaged and excised for sectioning. The results indicated enhanced dispersion throughout the tumor and entry into the nucleus with INT230-6. However, the control formulation mostly leaked out of the tumor and did not disperse or enter the cancer cells.



CLINICAL STUDY PATIENT POPULATION

Key pembrolizumab combination Inclusion Criteria:

1.≥ 18 years of age with ECOG performance status ≤ 1;

2. Phase 1: Dosing in superficially palpable tumors in subjects with histologically or cytologically confirmed advanced or metastatic disease

3. Phase 2: Subjects with histologically or cytologically confirmed advanced or metastatic Pancreatic, Cholangiocarcinoma, non-MSI-H and/or MMR proficient colorectal cancer, and Squamous Cell Carcinoma tumors;

4. Subjects must have measurable disease by RECIST 1.1 criteria including at least one target tumor for injection;

5. Two to four week washout from prior therapies depending on agent;

6. Typical hematologic and chemistry parameters for a phase 1 trial

Key Exclusion Criteria:

1. History of severe hypersensitivity reactions to cisplatin or vinblastine or other products of the same class;
2. Has received prior PD1 therapy (Note for the SCC subjects may have received one prior therapy course with one of these agents)
3. Has received prior therapy with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher irAE
4. 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;
5. 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 of combination cohort is to assess safety and tolerability of INT230-6 with pembrolizumab

Additional Outcome Measures for Phase 1:

- To characterize the overall safety of INT230-6 combined with pembrolizumab by the rate of grade 3 or higher adverse events attributed to the combination and not the underlying disease
- Assess the injected tumor response
- Characterize 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.

DEMOGRAPHICS & EXPOSURE

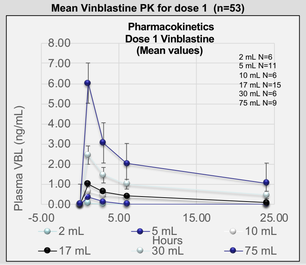
DEMOGRAPHICS	
Age	Median 61 (42-85)
Gender	30 male, 29 female
Race	82% Caucasian
	6% African American
	12% Asian
ECOG	27% ECOG 0
	64% ECOG 1
	9% ECOG 2
Median number of prior therapies (range)	3 (0,10)
# with prior Platinum	42%
# with prior PD1	44%

Tumor types	# of subjects
Sarcoma	9
Breast	7
SCC	6
Melanoma	5
Chordoma	5
CRC	5
Ovarian	4
H&N	4
Pancreatic	3
Cholangiocarcinoma	2
RCC	2
Other	7

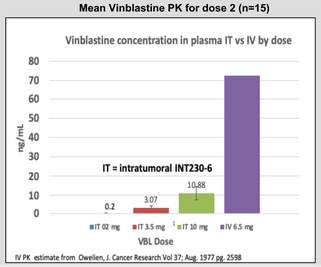
59 subjects (52 mono, 7 combo with PD1) have been treated as of data cut off date, April 17th, 2020. Pharmacokinetic data reflects analysis as of January 31, 2020

- Doses from 0.3 ml up to-160 ml of INT230-6 (80 mg CIS and 16mg of VIN) were injected (INT230-6 was dosed by tumor volume) with repeated intratumoral injection and multiple tumors injected
- **>206 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 concentrations of vinblastine are ~5% of predicted based on historical IV kinetics, indicating drug remains in the tumor.
  - Some subjects received 3X the typical IV dose of vinblastine

Mean Vinblastine PK for dose 1 (n=53)



Mean Vinblastine PK for dose 2 (n=15)



IV PK estimate from Owellen, J. Cancer Research Vol 37; Aug. 1977 pg. 2598

SAFETY

Monotherapy Related AE's by max severity in more than 2 patients(n=52)

Term	G1	G2	G3	Total*
Localized pain	16 (29.6)	9 (16.7)	2 (3.7)	27 (50.0)
Fatigue	6 (11.1)	12 (22.2)	1 (1.9)	19 (35.2)
Nausea	14 (25.9)	4 (7.4)	0	18 (33.3)
Vomiting	11 (20.4)	2 (3.7)	0	13 (24.1)
Decr. appetite	4 (7.4)	8 (14.8)	0	12 (22.2)
Anaemia	1 (1.9)	5 (9.3)	3 (5.6)	9 (16.7)
Abdominal pain	1 (1.9)	1 (1.9)	2 (3.7)	4 (7.4)
Back pain	3 (5.6)	1 (1.9)	0	4 (7.4)
Chills	4 (7.4)	0	0	4 (7.4)
Dizziness	4 (7.4)	0	0	4 (7.4)
Myalgia	3 (5.6)	1 (1.9)	0	4 (7.4)
Incr. creatinine	3 (5.6)	0	0	3 (5.6)
Dry mouth	2 (3.7)	1 (1.9)	0	3 (5.6)
Dysgeusia	2 (3.7)	1 (1.9)	0	3 (5.6)
Groin pain	2 (3.7)	1 (1.9)	0	3 (5.6)

* note, 2 subjects were retreated and denominator was 54

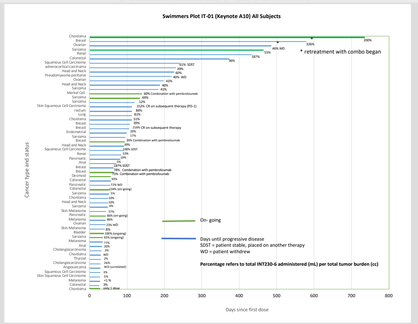
- Most adverse events were low grade and transient
- No grade 4 or higher events
- There were 2 drug related SAE's (pain)
- No events that limited dosing

INT230-6 + Pembrolizumab Related AE's by max severity (n=7)

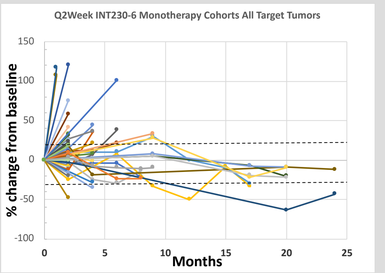
Term	G1	G2	G3	Total
Localized pain	2 (28.6)	3 (42.9)	0	5 (71.4)
Vomiting	2 (28.6)	0	1 (14.3)	3 (42.9)
Axillary pain	1 (14.3)	0	0	1 (14.3)
Decr. appetite	0	1 (14.3)	0	1 (14.3)
Dehydration	0	0	1 (14.3)	1 (14.3)
Dizziness	0	1 (14.3)	0	1 (14.3)
Headache	0	1 (14.3)	0	1 (14.3)
Injection site bruising	1 (14.3)	0	0	1 (14.3)
Muscular weakness	1 (14.3)	0	0	1 (14.3)
Nausea	1 (14.3)	0	0	1 (14.3)
Neck pain	0	1 (14.3)	0	1 (14.3)
Pruritus	1 (14.3)	0	0	1 (14.3)

- Similar safety profile as monotherapy
- No treatment related SAE's
- No DLTs

PRELIMINARY EFFICACY



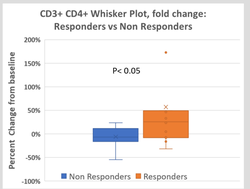
- 13 highly refractory patients have had disease stabilization for more than 6 months.
- INT230-6 is dosed per volume tumor. Tumor burden varied from 2-11,000cm^3. Analysis of dose response relationship is ongoing. A minimum threshold of dose per volume needed to saturate tumors in preclinical models appears to be relevant in humans
- Many subjects' tumors increase over baseline, then regress on subsequent scans (potential pseudo progression)
- 10 patients showed some size reduction of one or more non injected lesions in LN, liver, lung, perineum, and retroperitoneal areas **(abscopal effects to visceral lesions)**

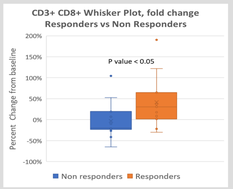


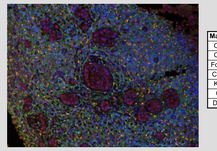
- Some Pseudo-progression
- long term stabilization after treatment

BIOMARKERS

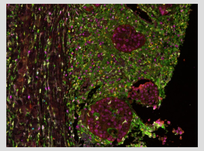
Blood samples at 2 weeks show increases in CD8+ and CD4+ in responding patients (n=25 evaluable, 11 responders with disease stabilization).







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 after INT230-6 monotherapy. 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, 7 pairs available for assessment)

RESULTS AND CONCLUSIONS

The novel INT230-6 formulation enables cytotoxic drugs to disperse and stay within the tumor, which results in:

- Injections completed without complications or drug leakage leading to favorable safety profile as monotherapy and in combination with pembrolizumab
- Direct tumor killing (necrosis on CT and biopsy) with recruitment of immune cells and abscopal responses
- Prolonged disease control off active treatment

Trial continues to recruit in the pembrolizumab combination and monotherapy arms, additional ipilimumab combo to open soon