Novel Drug, INT230-6 shows strong synergy with anti-PD-1 Antibodies and can induce high complete response rates with T-cell memory response in a colon cancer mouse model

Anja Bloom PhD[2], Lewis H. Bender[1], Masaki Terabe PhD[2], Jay A. Berzofsky MD, PhD[2,] Ian B. Walters MD*[1]

Summary

Intensity Therapeutics in collaboration with the National Cancer Institute is investigating new drug products consisting of potent anti-cancer agents formulated with compounds that improve intracellular and tissue diffusion. Intensity Therapeutics' drug INT230-6 shows strong tumor regression and long term immune-based protection in murine cancer models.

Experiments have shown that the new treatment approach is less toxic and more effective than conventional methods.

CONTACTS

* 1 Intensity Therapeutics, Inc.
Email: iwalters@intensitytherapeutics.com
Phone: 203 682-2434
8 Wright Street, Suite 107
Westport, CT 06880
Twitter @IntensityInc
Website: www.Intensitytherapeutics.com

2 Vaccine Branch, Center for Cancer Research NCI, Bethesda, Maryland;

INTRODUCTION

Intratumorally (IT) administered chemotherapy has mostly failed to provide greater efficacy than the same drugs delivered intravenously. The historical failure of local treatment is postulated to be due to weak transport into cells, poor dispersion throughout the tumor and the slow kinetics of the drug's coming out of the tumor and acting systemically.

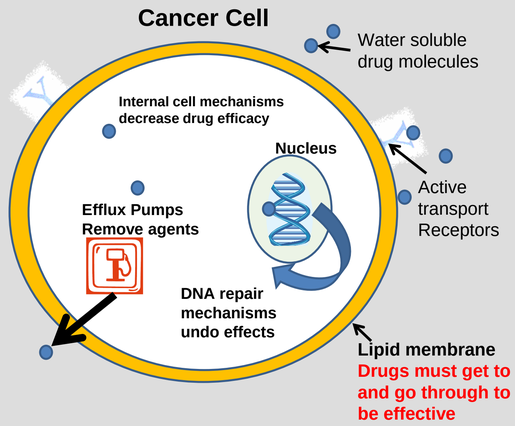
Intensity Therapeutics has developed a high throughput platform, DfuseRx^{sm}, to identify novel combinations of therapeutic agents and cell penetration enhancers. Formulations have shown strong potency in killing specific cancer types in vivo. These new drug products improve drug diffusion and passive uptake into the cancer cell of the therapeutic agent for enhanced tumor kill and greater antigen presentation.

The Company's lead compound INT230-6 is a fixed ratio (0.5 mg/mL of cisplatin, 0.1 mg/mL of vinblastine formulated with a cell-penetration excipient; IT-006 at 10 mg/mL) sterile liquid product for direct intratumoral injection. The compound has activity in multiple tumor types and ability to induce immunogenic cell death.

Here we describe the results using INT230-6 in immune competent mice with well-established large Colon26 tumors alone and in combination with checkpoint inhibitors anti-PD-1 and anti-CTLA4.

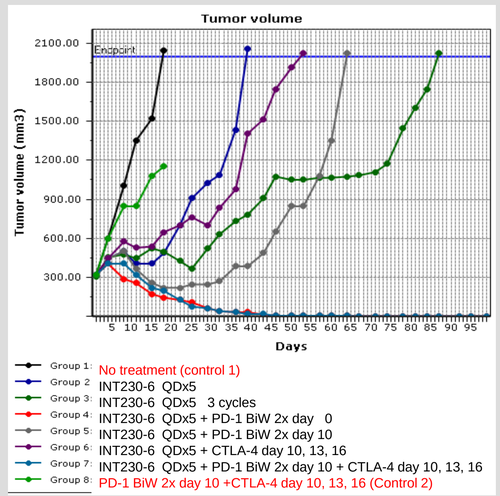
FUNDAMENTAL PROBLEMS OF CURRENT CHEMOTHERAPY EFFECTIVENESS

Cytotoxic drugs need to disperse throughout a tumor and enter the cells. Many standard agents enter cells via receptors. Cancer cells are highly resistant to drug diffusion. Often cell death requires high intracellular drug levels which are generally unattainable due to toxic effects on normal cells. Improving diffusion could bypass receptors, overcome efflux pumps and DNA repair mechanisms to improve efficacy.



IN VIVO DATA & RESULTS

Previously we reported results using INT230-6 alone in immune competent animals to treat large Colon26 tumors. In this study syngeneic female BALB/c mice were inoculated subcutaneously (SC) with 1x10^6 Colon26 colon carcinoma cells. Tumors grew to mean volumes of 313mm^3 pre-dose. The study comprised eight groups each with 10 animals. INT230-6 was dosed IT at 0.1 ml per 400 mm^3 of tumor volume and the checkpoint inhibitors were administered Intravenously (IV). Median tumor volumes over time are shown in the figure below.



Treatment of INT230-6 alone, in multiple cycles and in combination with anti-PD-1 or CTLA4 resulted in animals with complete response (CR).

Number of CRs by group

Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8
0	1	3	5	3	2	5	0

Repeated injections of INT230-6 resulted in improved CR rates and prolonged survival

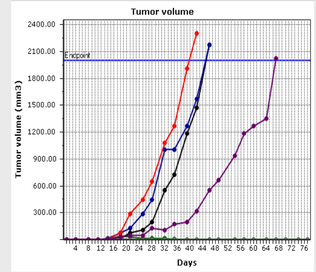
CTLA4 combinations did not appear to add much benefit

Sequenced INT230-6 followed by anti-PD1 was inferior to concomitant anti-PD1

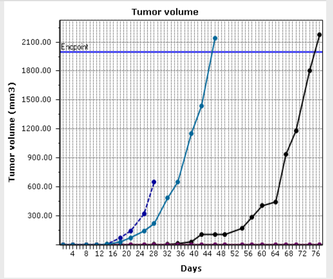
5 out of 9 (55%) of animals had a CR using INT230-6 + concomitant anti PD-1

CD4 or CD8 depletion

CR animals were re-randomized into 3 groups, either no depletion (IgG antibody), CD8 depletion or CD4 depletion. Once depleted, animals were re-inoculated SC with 1x10^6 Colon26 cells. All control animals survived with no tumor growth. Either CD8 or CD4 T-cell depletion partially abrogated the immunity and following re-challenge tumors now grew in some animals. The surviving animals and controls were then randomized again and both CD8 and CD4 T-cells were depleted simultaneously. The animals were again re-challenged 1x10^6 Colon26 cells SC. All but one dual depleted animal developed lethal tumors.

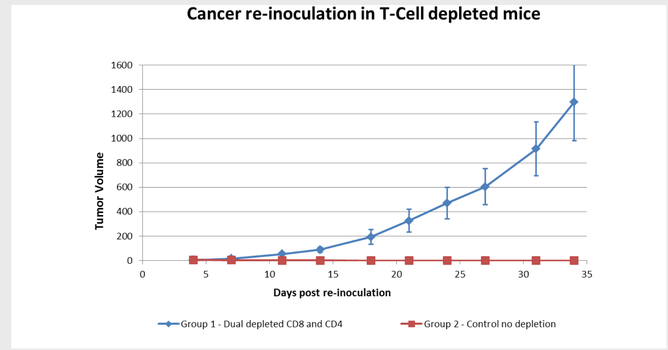


4 of 6 CD8 T-cell depleted animals develop tumors*



3 of 7 CD4 T-cell depleted animals developed tumors

CD4/CD8 Dual Depletion



DISCUSSION & CONCLUSIONS

Together, these results suggest that INT230-6 dosed with anti-PD-1 drugs concurrently shows significant anti-tumor synergy. CR animals have a durable response in these established colorectal tumor models (data previously reported). The data further support the hypothesis that the mechanism of action of INT230-6 therapy and the long term immunization observed (previously reported) includes induction of tumor specific memory via CD8$^+$ and CD4$^+$ T-cells. These data also indicate that CD8$^+$ T-cells may play a greater role in protection. Given regression of primary tumors as well as those of distal metastases (data not shown) with the immune activation, INT230-6 with and without anti-PD-1 may be an effective treatment for patients with metastatic disease.