INT230-6, a Novel Intratumoral Anticancer Agent, is able to Eradicate Large Established Tumors and Stimulate Potent Antitumor Immunity

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

Summary

Intensity Therapeutics in collaboration with the National Cancer Institute are collaborating to investigate 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 against murine cancers.

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 kinetics of the drug coming out of the tumor and acting systemically.

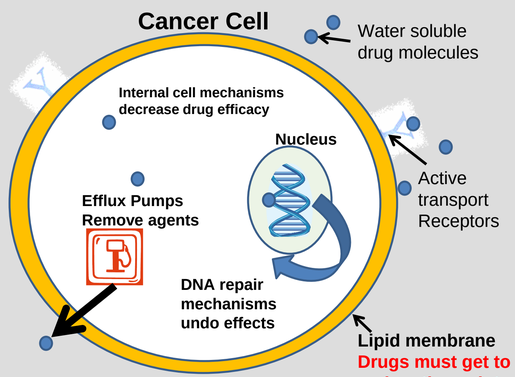
Intensity has developed the DfuseRx^{sm} platform which can rapidly identify potent combinations of anticancer agents and specific cell penetration enhancers against specific cancer types. The new drug products improve drug diffusion and passive uptake into the cancer cell for improved tumor kill to allow for 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. Cisplatin was chosen as a drug component based on its efficacy in the screening platform, its activity in multiple tumor types and ability to induce immunologic cell death.

Here we describe the results using INT230-6 in immune competent mice with well-established large Colon26 tumors.

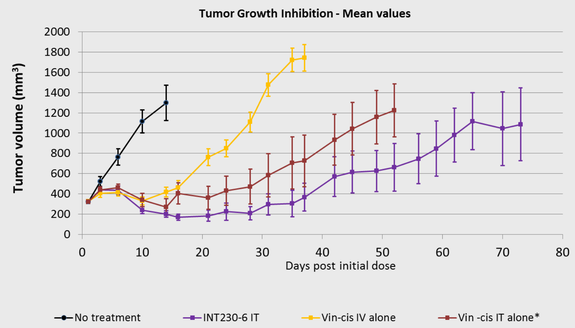
FUNDAMENTAL PROBLEMS OF CURRENT CHEMOTHERAPY EFFECTIVENESS

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.



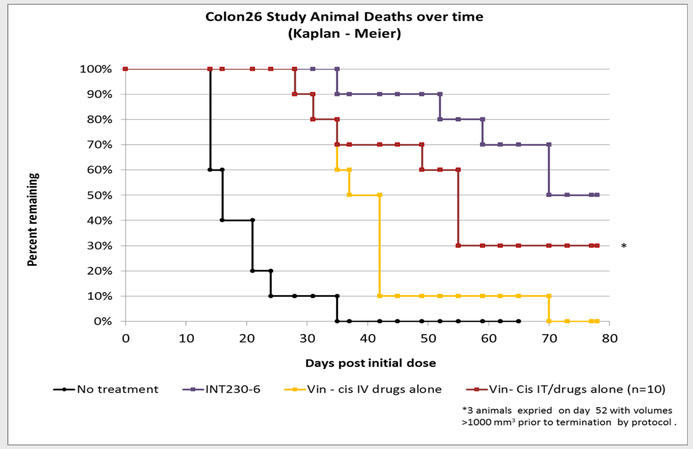
IN VIVO DATA & RESULTS

We conducted a study in syngeneic female BALB/c mice inoculated subcutaneously (SC) with 1x10^6 Colon26 syngeneic colon carcinoma cells. Tumors grew to mean volumes of 325mm^3 pre-dose. The study comprised four groups of 10 animals: 1) no treatment, 2) INT230-6 given IT, 3) the drugs given intravenously (IV) alone and 4) the drugs given IT without the excipient. Animals in the IT treatment groups received 0.1 mL per 400mm^3 of tumor volume for 5 days. IT & IV doses were comparable. There was no adjustment for body weight. Tumor growth inhibition was best observed in the group given INT230-6.



Median overall survival (MOS) for no treatment was 16 days versus 77 days for INT230-6, ratio of 0.2078 with 95% CI of 0.074 to 0.637 with a hazard ratio using Mantel-Haenszel of 0.03501 (95% CI 0.00862 to 0.1422).

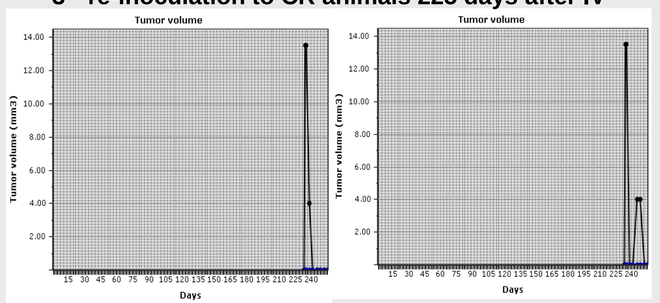
20% of animals had a complete response (CR) using INT230-6



LONG TERM TUMOR IMMUNITY

CR animals along with naïve controls were re-inoculated SC with 1x10^6 CT26 cells, all survived. A second re-inoculation was done IV all survived. All of the INT230-6 CR animals were fully protected against both SC and IV re-inoculation. Near the usual end of the female BALB/c mouse normal life at 440 days, half of the CR animals were re-inoculated for a 3rd time SC with and spontaneously cleared the tumors.

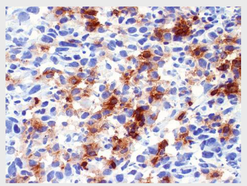
3rd re-inoculation to CR animals 225 days after IV



RECRUITMENT OF TUMOR INFILTRATING LEUKOCYTES

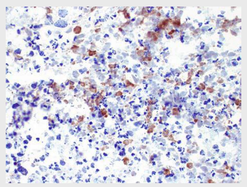
Separate studies to look at the mechanism of action of this approach revealed a high proportion of tumor cell death (potentially from apoptosis) following 3 days of INT230-6 treatment. There also was an increase in the infiltration of CD4 lymphocyte and dendritic cells observed10 days after the first dose of INT230-6.

Anti-CD4



40X

Anti-CD11c



DISCUSSION & CONCLUSIONS

These results suggest that intratumoral administration of INT230-6 may offer the dynamics of rapid and profound tumor cell death for the production of endogenous antigen presentation leading to the recruitment of TILs and the enablement of an adaptive immune response to develop personalized antitumor immunity.