20P

IGN002* (antiCD20-IFNα2b) intravenously administered tumor targeted delivery of IFNα2b and its effects in Non-Hodgkin Lymphoma

SPECTRUM PHARMACEUTICALS
Redefining Cancer Care

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Abstract

Background: IFNα2b elicits potent anti-tumor antiproliferative and immunostimulatory activity; but with systemic toxicity. Delivering IFNα2b targeted to CD20+ lymphomas may lower systemic toxicity and increase therapeutic index. IGN002 is a novel recombinant protein comprised of anti-CD20 antibody (rituximab) fused to human IFNα2b by a peptide linker. Here, we report IGN002 stability in serum and tumor as well as efficacy in vivo in a B-cell Non-Hodgkin Lymphoma (NHL) xenograft model.

Methods: SCID mice bearing subcutaneous CD20+ tumors were administered i.v. rituximab at 10 mg/kg or IGN002 at 5, 10 or 15 mg/kg. Serum and tumors were collected at 1, 4, 24 or 48 hours (hrs) to assess IGN002 stability and tumor uptake using sandwich ELISA. In the same model, we examined tumor growth inhibition (TGI) and survival in mice treated with rituximab up to 5 mg/kg or IGN002 at doses up to 6 mg/kg.

Results: IGN002 increased in serum in a dose-related manner with the peak levels achieved at 1-4 hrs (5mg/kg: 33±3; 10mg/kg: 155±5; 15mg/kg: 177±11 µg/ml) and a half-life of 24 hrs. At 48 hrs, IGN002 was still detectable in the circulation (5mg/kg: 25±2; 10mg/kg: 44±6; 15mg/kg: 45±3 µg/ml). Increases in IGN002 were also observed in the tumor at similar levels to rituximab. In the tumor, as hypothesized, IFNα2b increased in as dose-related manner with Cmax levels at 4 hrs of 41±12, 57±14 and 92±22 ng/mg of tumor tissue at 5, 10 and 15 mg/kg dose groups, respectively. At 48 hrs, IFNα2b levels were still detected (range: 18-38 ng/mg of tumor tissue). IGN002 improved survival at all doses investigated and increased inhibition of tumor growth when compared to rituximab with no adverse clinical signs.

Conclusions: IGN002 demonstrated adequate stability in the tumor resulting in the reduction in tumor mass and increased survival when compared to rituximab. Thus, demonstrating that the targeted delivery of IFNα2b to CD20+ tumor warrants further investigation in NHL patients.

Introduction

IFNα2b (Type 1 interferon) exerts immunomodulatory effect resulting in increased tumor apoptosis. The clinical utility of IFNα2b is limited due to systemic dose-limiting toxicity

To overcome this limitation, we developed fusion proteins consisting of tumor-targeting monoclonal antibody and IFNα2b to preferentially deliver IFNα2b to the tumor resulting in increasing cytotoxic immune cell infiltrates into the tumor microenvironment thereby causing tumor kill

IGN002 is a novel recombinant protein comprised of anti-CD20 antibody (rituximab) fused to human IFNα2b by a peptide linker (Figure 1)

Xuan et al., and Trinh et al[1,2] demonstrated that CD20 antibody fusions with mouse IFNα and IFNß were safe and effective in syngeneic mouse B-cell lymphoma models expressing human CD20, with no signs of systemic toxicity

The present study was performed to assess the ability of IGN002 to maintain efficacy while improving the therapeutic index in a mouse model of low CD20 ($CD20^{lo}$)[3] expressing Diffuse Large B-Cell Lymphoma (DLBCL) in the presence of human PBMCs

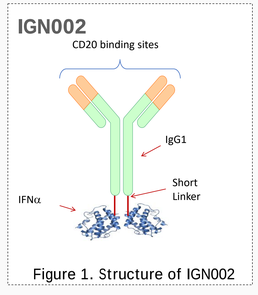
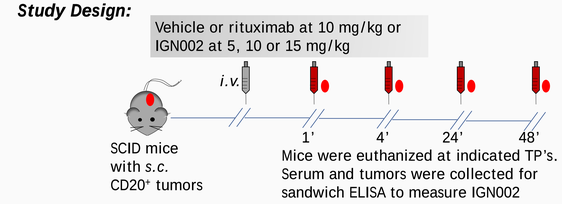


Figure 1. Structure of IGN002

Demonstration of IGN002 stability in serum and tumor in a $CD20^{lo}$ DLBCL xenograft model

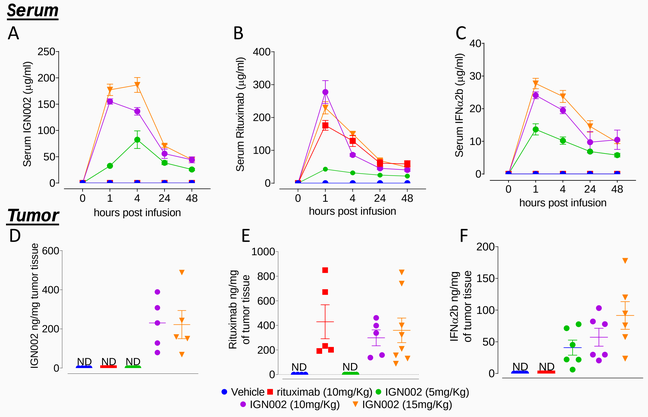
Study Design:



CB.17 SCID mice were implanted with SU-DHI-4 cells ($1x10^7$ cells/mouse) and Matrigel (50% Matrigel/50% Media in 0.1ml). Approximately 4 weeks later, when the tumors reached ~150 mm^3 rituximab at 10 mg/kg or IGN002 at 5, 10 or 15 mg/kg was administered i.v. to 6 animals per timepoint (TP). At 1, 4, 24, and 48 hours post drug administration, animals were euthanized, serum and tumor IGN002 levels were determined via ELISA

Serum and tumor concentrations of IGN002 in DLBCL xenograft model

Serum

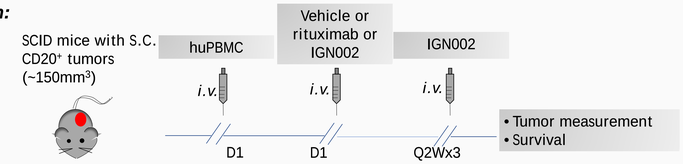


- IGN002 reached peak levels in serum between 1-4 hours (A, B) and a half-life of 24-hours. Serum IFNα2b increased in a dose-related manner with C_{max} levels at 1 hours (C).
- In the tumors, IGN002 (D) 10 and15 mg/Kg and rituximab (E) were detected at similar levels
- In tumors, IGN002 elicited dose-related increases in IFNα2b (F), C_{max} levels at 4 hours

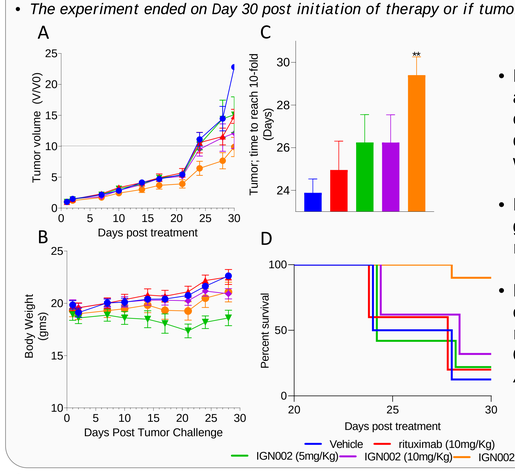
A-F, All values expressed as Mean ± SEM; N=6 per TP; ND: Not Detected

IGN002 improves survival and reduces tumor growth in $CD20^{lo}$ expressing SU-DHL-4 (DLBCL) xenograft model supplemented with human PBMCs

Study Design:



- *5-6 weeks old female CB.17 SCID mice (n=8 for control fusion protein and n=10 for all other groups) were implanted with $CD20^{lo}$ expressing SU-DHL-4 cells ($1x10^7$ cells/mouse in 50% matrigel) S.C. on day 0. When tumors reached ~150mm^3, animals were randomly assigned to one of the four treatment groups. Vehicle, rituximab: 10mg/Kg i.v. single dose or IGN002: 5mg/Kg; 10mg/Kg; 15mg/Kg i.v. Q2W for 3 weeks*
- *Change in tumor volume was assessed 2 times per week using the following formula ($L* W^2$)/2*
- *The experiment ended on Day 30 post initiation of therapy or if tumor size >2000 mm^3 or animals became moribund*



- In SU-DHL-4 DLBCL tumors, IGN002 administration attenuates tumor growth compared to rituximab (A; the dotted line denotes 10-fold increase in tumor volume) with no change in body weight (B)
- IGN002 15mg/Kg significantly reduced tumor growth rate when compared to vehicle and rituximab(C; p≤ 0.05; Dunnett's test)
- IGN002 (15mg/Kg) significantly improved overall survival when compared to vehicle and rituximab treated groups (D, Kaplan Meier Curve)

All values are the Mean ± SEM. N≥8

Summary

- IGN002 increased in serum in a dose-related manner with the peak levels achieved at 1-4 hours; the elimination half-life was 24 hours
- Increases in IGN002 were observed in the tumor similar to rituximab
- In the tumor, IFNα2b increased in a dose-related manner with C_{max} at 4 hours. At 48 hours, IFNα2b levels were still detectable
- A dose-related reduction in tumor growth rate and increased survival when compared to rituximab in the $CD20^{lo}$ expressing SU-DHL-4 DLBCL xenograft model supplemented with human PBMCs

Conclusions

These results with IGN002 demonstrate that targeting IFNα2b in $CD20^{lo}$ DLBCL xenograft mouse model resulted in greater anti-tumor activity and improved overall survival compared to rituximab alone. Thus, demonstrating that the targeted delivery of IFNα2b to CD20 expressing tumors warrant further investigation in NHL patients. A study is ongoing to confirm these findings in patients (trial # NCT02519270)

***IGN002 is an investigational agent not approved for marketing.**

RD-IGN-0002

Spectrum's Development Pipeline:
https://www.sppirx.com/300-spectrum-products-portfolio.html

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3) Kim SJ et al., Int. J. Mol. Sci. 2020, 21(12), 4377