**Novel CD37-Targeting Antibody-Drug Conjugate (ADC), IMGN529, Has Synergistic Activity in Combination with Rituximab in Non-Hodgkin Lymphoma (NHL) Models**

**Abstract**

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**INTRODUCTION**

IMGN529 is a CD37-targeting ADC consisting of a CD37-binding antibody, K7153A, conjugated to the maytansinoid anti-mitotic, DM1. Preclinical studies. IMGN529 exhibits targeted, potent activity against NHL cells via antibody-mediated direct cell-killing and effector function, and via tubulin disruption from the DM1 activity against NHL cells via antibody-mediated direct cell-killing. Antibody, K7153A, conjugated to the maytansinoid anti-mitotic, IMGN529 has demonstrated preliminary single-agent clinical activity in an ongoing phase I study in adult patients with relapsed or refractory NHL (NCT01534715). Rituximab, a monoclonal antibody against CD20, is widely used for NHL therapy and in combination with cyclophosphamide/doxorubicin/vinristine/doxorubicin/melphalan (R-CHOP) remains the standard frontline regimen for NHL.

**Methods**

- **in vitro** screen combination
  - IMGN529 was evaluated in combination with CD20-targeting antibodies across a panel of twenty NHL cell lines, including DLBCL (GCB and ABC sub-type), Mantle Cell Lymphoma (MCL), Chronic Lymphocytic Leukemia (CLL) and Burkitt Lymphoma. Cell viability was assessed using an anti-proliferation assay (ATP-lite) after a 72 hr incubation and reported as GI (Growth Inhibition). The combination screen was performed by Horizon CombinatoRx and data were reported as GI (Growth Inhibition).
  - A statistical method was used to identify synergies significantly superseding baseline activity values (determined using self-cross values). Synergy is significant (score=11.3)
  - Data was analyzed using their proprietary software. A statistical method was used as a positive control.
  - The OCI-Ly18 GCB DLBCL cell line contains a high level of CD20 and MYC. The strong combination effect was demonstrated in 3 models (data not shown) and more active than either monotherapy.

- **in vivo efficacy studies**
  - In vivo proof-of-concept (POC) for the combination effect was demonstrated in xenograft or disseminated models established from DOHH2 or SU-DHL-4 cells implanted subcutaneously or Farage cells inoculated intravenously, respectively, into SCID mice.

- IMGN529 shows strong synergy with CD20-targeting antibodies
  - IMGN529 + rituximab is synergistic in a model representing ‘Double-Hit’ lymphoma
  - Both IMGN529’s CD37-targeting antibody and its DM1 are required for synergy with rituximab
  - With the exception of the SU-DHL-4 cell line, only IMGN529 shows significant synergy with rituximab
  - *significant synergy

**CONCLUSIONS**

- IMGN529 shows significant synergy with CD20-targeting antibodies in vivo models of diverse NHL subtypes, with contribution from both components of the ADC.
  - Of note, synergy with rituximab was observed in a ‘double-hit’ DLBCL model, suggesting that IMGN529 + rituximab may be active in refractory disease settings.
  - In vivo POC of the combination was established. The combination of IMGN529 and rituximab was well tolerated (data not shown) and more active than either monotherapy. The strong combination effect was demonstrated in 3 models of GCB DLBCL resulting in numerous complete responses. Enhanced cell killing by the combination is a result of increased induction in apoptosis as evidenced by an increase in Cleaved-Caspase-3 activity.
  - Additional in vivo models and the potential mechanisms underlying the synergy are currently being investigated.
  - These results support clinical assessment of IMGN529 used in combination with rituximab in NHL.

**References**

3. Stathis et al. ASH 2014 Abstract 1760
6. IMGN529 shows strong synergy with CD20-targeting antibodies in vivo models of diverse NHL subtypes, with contribution from both components of the ADC.
7. Of note, synergy with rituximab was observed in a ‘double-hit’ DLBCL model, suggesting that IMGN529 + rituximab may be active in refractory disease settings.
8. In vivo POC of the combination was established. The combination of IMGN529 and rituximab was well tolerated (data not shown) and more active than either monotherapy.
9. The strong combination effect was demonstrated in 3 models of GCB DLBCL resulting in numerous complete responses.
10. Enhanced cell killing by the combination is a result of increased induction in apoptosis as evidenced by an increase in Cleaved-Caspase-3 activity.
11. Additional in vivo models and the potential mechanisms underlying the synergy are currently being investigated.
12. These results support clinical assessment of IMGN529 used in combination with rituximab in NHL.