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

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Abstract **1548**

INTRODUCTION

- IMGN529 is a CD37-targeting ADC consisting of a CD37-binding antibody conjugated to the maytansinoid anti-mitotic, DM1.
- CD37 is highly expressed in many B-cell malignancies making it an ideal target for ADC-based therapy.
- IMGN529 has been shown to have potent, targeted, anti-tumor activity via antibody-mediated direct cell-killing, effector function, and the anti-mitotic activity of the DM1 payload (Beckwith *et* al. Leukemia (2014) 28:1501).
- IMGN529 has shown early signs of clinical activity at tolerable doses in an ongoing phase I trial in adult patients with relapsed/refractory NHL (R/R-NHL) (NCT01534715) (Deckert *et al.* Blood (2014) 124:1760).
- Rituximab, an anti-CD20 monoclonal antibody, is widely used for NHL therapy and remains a component of both front-line and late-line regimens.
- A strong synergy between IMGN529 and all anti-CD20 antibodies evaluated was identified using a high throughput combination screen (Horizon CombinatoRx). The notable activity of the IMGN529/rituximab combination was confirmed both *in vitro* and *in vivo* using cell line viability and xenograft models of DLBCL (both ABC and GCB subtypes). The molecular signaling responses to single agent and combinatorial treatment were investigated to elucidate the mechanism underlying the observed synergy.

METHODS

In Vitro

- Combination screen was performed by Horizon CombinatoRx and data analyzed using their proprietary software to identify synergistic interactions (represented by Synergy Scores) which significantly supersede self-cross additivity.
- Cell viability was assessed at 72 hours using ATP-Lite proliferation assay (PerkinElmer).
- Apoptosis was measured at 24 hours using Caspase3/7-Glo (Promega) and antibody array for cleaved PARP (CST#12856).

In Vivo

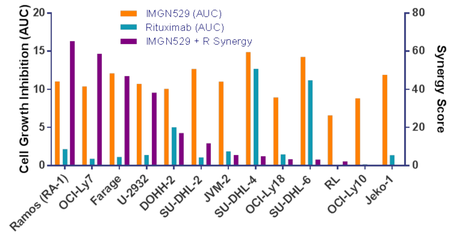
- U2932- Subcutaneous: 1x10^7 cells/mouse, IMGN529 single dose, rituximab 3x QW doses, R-CHOP (see figure).
- FARAGE- Disseminated: 1x10^7 cells/mouse IV, IMGN529 single dose, rituximab 3x QW doses.

IMGN529 + Rituximab Synergy

IMGN529 + anti-CD20 Synergy Scores

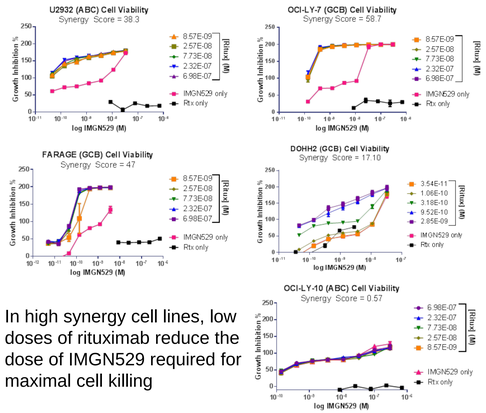
Synergy Scores in bold exceed self cross > 2xSD		DLBCL (ABC)			DLBCL (GCB)							MCL	CLL	BL
		OCI-Ly10	SU-DHL-2	U-2932	DOHH-2	Farage	OCI-Ly18	OCI-Ly7	RL	SU-DHL-4	SU-DHL-6	Jeko-1	JVM-2	Ramos (RA-1)
Type1	Rituximab	1.7	**6.6**	**24.1**	**10.7**	**37.6**	**3.4**	**26.7**	0.6	**5.0**	**4.1**	**6.1**	**8.4**	**18.9**
Type1	Ofatumumab	2.6	**10.0**	**44.3**	**16.9**	**51.0**	**5.0**	**59.5**	**2.5**	**1.8**	**6.7**	1.3	**7.3**	**76.1**
Type1	Obinutuzumab	0.6	**11.7**	**38.3**	**17.1**	**47.0**	**3.3**	**58.7**	**2.3**	**4.9**	**3.2**	0.2	**5.5**	**65.3**

- IMGN529 shows significant and broad synergy with both type-I and type-II anti-CD20 therapeutics across a diverse panel of NHL cell lines



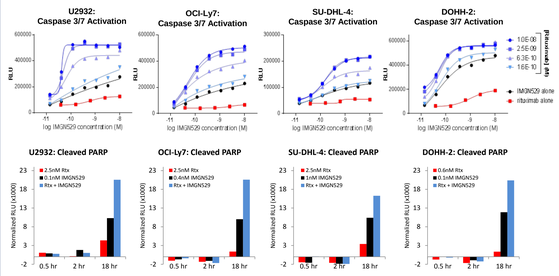
- Synergy is not correlated with the single agent activity of either agent, suggesting a synthetic-lethal type interaction

Low Doses of Rituximab Increase IMGN529 Potency



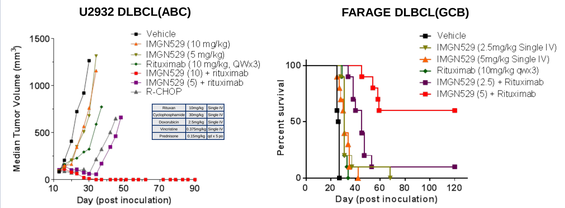
- In high synergy cell lines, low doses of rituximab reduce the dose of IMGN529 required for maximal cell killing

IMGN529 + Rituximab Leads to Synergistic Induction of Apoptosis



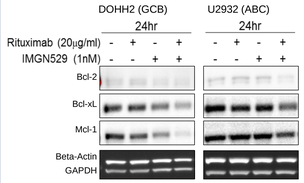
- Treatment with IMGN529 plus rituximab results in dramatic caspase3/7 activation leading to cell death

The Combination of IMGN529 + Rituximab is Highly Efficacious in *In Vivo* Models of NHL



- Combination IMGN529 + rituximab treatment results in superior efficacy compared to monotherapy in both ABC and GCB subtypes of DLBCL

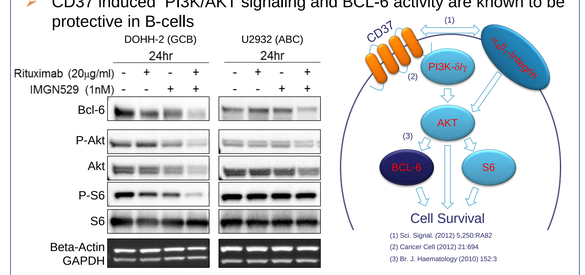
IMGN529 + Rituximab Down Regulates BCL-2 Family Proteins



- Combined treatment with rituximab and IMGN529 leads to down regulation of multiple BCL-2 family members

IMGN529 + Rituximab Reduces PI3K/AKT Axis Signaling in GCB cells

- CD37 induced PI3K/AKT signaling and BCL-6 activity are known to be protective in B-cells



- Combination treatment down regulates PI3K/AKT signaling in DOHH2(GCB) to a greater extent than U2932(ABC)
- The pro-survival transcriptional repressor BCL-6 is also down regulated by combination treatment

CONCLUSIONS

- IMGN529 shows broad synergistic activity with type-I and type-II anti-CD20 targeting antibodies in *in vitro* and *in vivo* models of NHL. Notably, activity is observed in both ABC and GCB DLBCL subtypes.
- The combination of IMGN529 and rituximab, but not the single agents, down regulates BCL-2 family members, potentially leading to enhanced apoptosis.
- These data support the clinical assessment of IMGN529 in combination with rituximab in NHL. A clinical study is planned:

<u>A Phase 2 Study to Evaluate the Efficacy and Tolerability of IMGN529 in Combination with Rituximab in Patients with Relapsed and/or Refractory DLBCL and Other Forms of Non-Hodgkin's Lymphoma</u>

Safety Run In

15 patients
R/R DLBCL & FL

IMGN529
+
Rituximab

Phase 2

30 patients
R/R DLBCL

30 patients
R/R other NHL
(FL, MCL, MZL/MALT)

<u>1° Objectives</u>
- Efficacy and tolerability of IMGN529 in combination with rituximab

<u>2° Objectives</u>
- PK
- PFS, OS, ORR, DoR.

<u>Exploratory Objectives</u>
- Correlate target expression, relevant Mutations, and COO with clinical benefit