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

Abstract P-274

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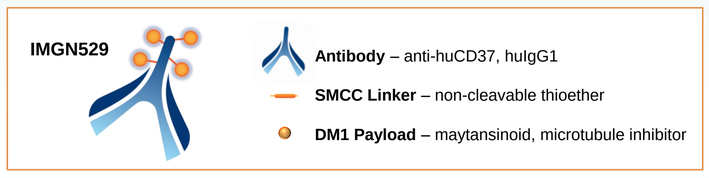
IMMUNOGEN

INTRODUCTION

IMGN529 is a CD37-targeting ADC consisting of a CD37-binding antibody, K7153A, conjugated to the maytansinoid anti-mitotic, DM1. In 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 payload[1,2].

IMGN529 has demonstrated preliminary single-agent clinical activity in an ongoing phase I study in adult patients with relapsed or refractory NHL (NCT01534715)[3]. Rituximab, a monoclonal antibody against CD20, is widely used for NHL therapy and in combination with cyclophosphamide /doxorubicin /vincristine /prednisone (R-CHOP) remains the standard frontline regimen for diffuse large B-cell lymphoma (DLBCL).

The combination potential of IMGN529 with rituximab and other CD20-targeting therapeutic antibodies was evaluated in clinically relevant pre-clinical models of NHL. The combination effects were ranked using synergy scores and further characterized for the mechanism underlying the synergy. The IMGN529/rituximab combination was also evaluated *in vivo* using human xenograft models of DLBCL.



Methods

In vitro combination screen

- 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 analyzed using their proprietary software. A statistical method was used to identify synergies significantly superseding baseline additivity values (determined using self-cross values).

Apoptosis assay

- Apoptosis was evaluated by caspase 3/7 activity using a caspase 3/7 Glo assay (Promega) after 20 hour incubation with 10 nM Abs and/or 1 nM IMGN529. 2 µM staurosporine was used as a positive control.

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

	Cell line	Synergy Score (Combination with IMGN529) Obinutuzumab	Ofatumumab	Rituximab
GCB DLBCL	DOHH-2	**14.5**	**25.1**	**14.4**
	OCI-Ly1	3.58	3.41	5.25
	OCI-Ly7	**20.4**	**62.9**	**50**
	RL	2.18	5.45	4.07
	SU-DHL-10	5.02	**9.91**	**18.2**
	SU-DHL-6	0.685	2.42	1.82
	WSU-NHL	1.64	**7.6**	**5.55**
	SU-DHL-4	**10.2**	**14.5**	**9.44**
ABC DLBCL	HBL-1	**8.88**	**23.3**	**19.8**
	OCI-Ly10	0.092	0.0278	0.112
	U-2932	25.1	48.9	41.6
	TMD8	1.03	1.56	6.07
MCL	GRANTA-519	**6.22**	**11.4**	**16.6**
	MAVER-1	**5.82**	**15.4**	**17.5**
	Jeko-1	2.46	6.2	4.66
CLL	JVM-13	**7.34**	**28.7**	**30.3**
	JVM-2	**4.94**	**7.5**	**8.24**
Burkitt	Ramos	8.6	44	33.1
	Namalwa	0.0837	1.2	2.49

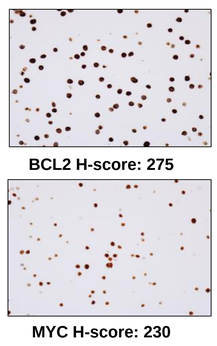
Values in bold represent synergy scores that exceed the self- cross X2 standard deviations

Increasing synergy

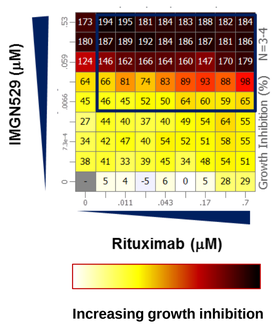
- Significant synergy was observed in a large number of cell lines, across all NHL subtypes.

IMGN529 + rituximab are synergistic in a model representing 'Double-Hit' lymphoma

The OCI-Ly18 GCB DLBCL cell line contains rearranged MYC and BCL2[4]. Protein overexpression is shown:

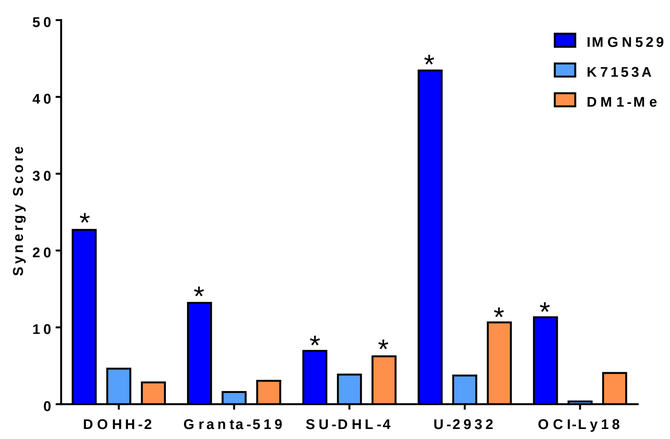


Immunohistochemical anaylsis of OCI-LY18 cells stained with either Leica's Anti-Bcl-2 (bcl-2/100/D5) Mouse mAb (top) or Ventana's Anti-c-MYC (Y69) Rabbit mAb (bottom)



- The OCI-Ly18 cell line is resistant to rituximab and moderately sensitive to IMGN529.
- Enhanced cell killing is seen with sub-optimal doses of IMGN529 in combination with rituximab.
- Synergy is significant (score=11.3)

Both IMGN529's CD37-targeting antibody and its DM1 are required for synergy with rituximab

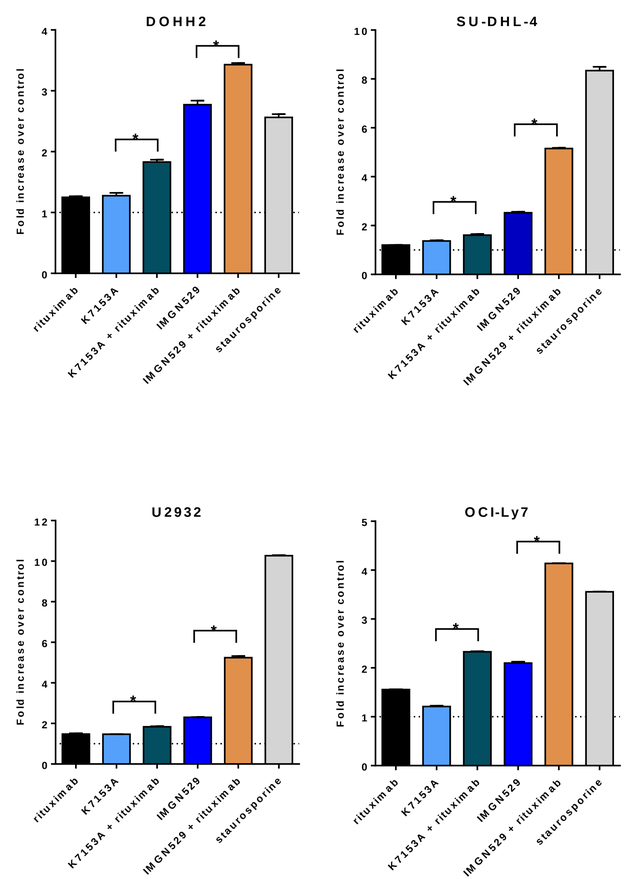


- With the exception of the SUDHL-4 cell line, only IMGN529 shows significant synergy with rituximab

*= significant synergy

IMGN529 + rituximab: enhanced apoptosis

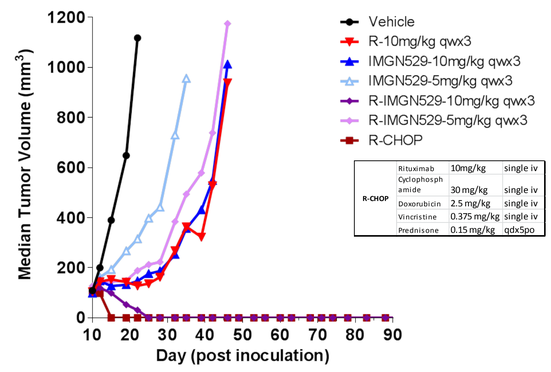
- Apoptosis shown as fold increase in caspase-3/7 activity



Pairwise comparison were performed using Exact Wilcoxon Test Statistics.
Note: * significant at α=0.05

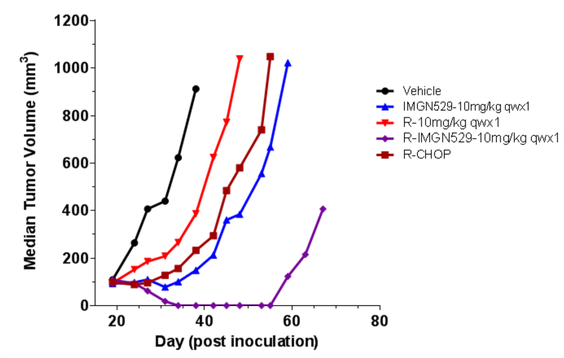
The IMGN529 and rituximab combination is highly active in *in vivo* models of DLBCL

DOHH2 - GCB DLBCL



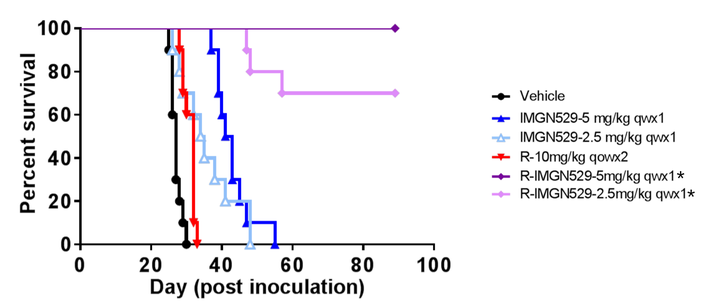
	T/C	PR	CR	TFS	Comment
PBS	-	0/8	0/8	0/8	
Rituximab 10mg/kg (R)	13%	3/8	3/8	2/8	Active
IMGN529 10mg/kg	14%	1/8	1/8	1/8	Active
IMGN529 5 mg/kg	30%	0/8	0/8	0/8	Active
IMGN529 10 mg/kg + R	4%	7/8	7/8	7/8	Highly active
IMGN529 5 mg/kg +R	18%	1/8	1/8	0/8	Active
R-CHOP	0%	8/8	8/8	5/8	Highly active

SUDHL-4 - GCB DLBCL



	T/C	CR	TFS	Comment
PBS	-	0/8	0/8	-
Rituximab 10 mg/kg (R)	42%	2/8	2/8	Active
IMGN529 10 mg/kg	16%	1/8	0/8	Active
IMGN529 10 mg/kg + R	0%	5/8	4/8	Highly active
R-CHOP	25%	2/8	1/8	Active

FARAGE – GCB DLBCL



* R was dosed qwx3 in the R-IMGN529 combination arms

CONCLUSIONS

- IMGN529 shows significant synergy with CD20-targeting antibodies in *in vitro* 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:

1. Deckert et al. Blood. 2013 Nov 14;122(20):3500-10
2. Beckwith et al. Leukemia. 2014 Jul;28(7):1501-10
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