Abstract #1760

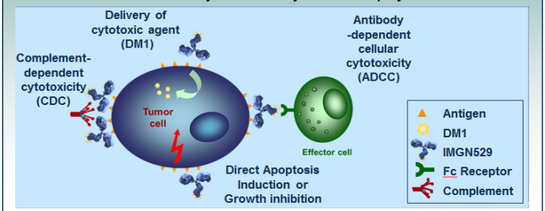
# A Phase I Study of IMGN529, an Antibody-Drug Conjugate (ADC) Targeting CD37, in Adult Patients with Relapsed or Refractory Non-Hodgkin Lymphoma (NHL)

**Stathis, A.[1], Freedman, A.[2], Flinn, I.[3], Maddocks, K.[4], Weitman, S.[5], Berdeja, J.[3], Mejia, A.[5], Zucca, E.[1], Green, R.[6], Romanelli, A.[7], Zildjian, S.[7], Ruiz-Soto, R.[7], Palomba, M.[6]**

Oncology Institute of Southern Switzerland, Bellinzona, Switzerland[1]; Dana Farber Cancer Institute, Boston, MA[2]; Sarah Cannon Research Institute, Nashville, TN[3]; Ohio State University, Columbus OH[4]; Institute for Drug Development, San Antonio, TX[5]; Memorial Sloan Kettering Cancer Center, New York, NY[6]; ImmunoGen, Inc., Waltham, MA[7]

## INTRODUCTION

- IMGN529 is a CD37-targeting ADC comprising a CD37-binding antibody conjugated to the maytansinoid anti-mitotic, DM1
- CD37 is present on the surface of normal and malignant B lymphocytes
- In preclinical studies, IMGN529 exhibits potent antitumor activity against NHL cells via direct inhibition, effector function and delivery of the maytansinoid payload




## Methods and Objectives

- **Primary Objective of the Phase 1 Clinical Study 301 (NCT01534715)**

  Determine MTD/recommended phase 2 dose of IMGN529 in adult patients with R/R NHL
- **Design**

  Standard 3+3 design during dose escalation
- **Treatment**

  IMGN529 administered intravenously (IV) once every 3 weeks

## Table 1: Patient Characteristics (N=33)

| | |
|---|---|
| Age, median (range), years | 63 (37–86) |
| Male, n (%) | 21 (63.6) |
| Disease stage at study entry, n (%) | 1 (3) missing |
| I | 3 (9.1) |
| II | 3 (9.1) |
| III | 8 (24.2) |
| IV | 18 (54.5) |
| Histology, n (%) | |
| Diffuse large B-cell lymphoma (DLBCL) | 15 (45.5) |
| Follicular lymphoma (FL) | 10 (30.3) |
| Mantle cell lymphoma (MCL) | 5 (15.2) |
| Marginal zone lymphoma (MZL) / MALT | 3 (9.1) |
| Number of prior regimens, n (%) | |
| 1 prior regimen | 3 (9.1) |
| 2 prior regimen | 11 (33.3) |
| ≥ 3 | 19 (57.6) |
| Min:Max | 1:8 |
| Median | 3.0 |
| Prior radiotherapy, n (%) | 10 (30.3) |
| Prior transplant, n (%) | 11 (33.3) |

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## Overview of Prophylaxis Administration

At low doses with no prophylaxis, neutropenia early after dosing was reported as was febrile neutropenia. As this transient neutropenia was thought to be related to cytokine release, at the 0.4 mg/kg dose peri-infusional steroids were added, and the early neutropenia subsided (as shown in figure 1). [*see IMGN529 pre-clinical abstract #3119 for more data regarding neutrophil depletion*].

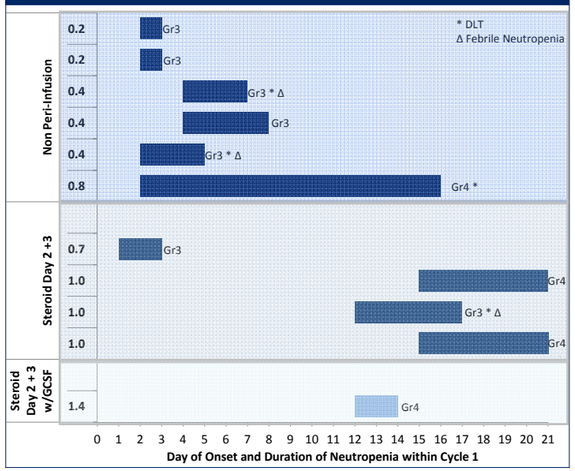
At the dose of 1.0 mg/kg with peri-infusional prophylaxis, the first pt had G3 febrile neutropenia at day 12 and the subsequent 2 patients had G4 neutropenia at day 15. G-CSF support was subsequently added, and no other incidences of febrile neutropenia have been reported in additional patients.

The use of G-CSF and corticosteroids has allowed further dose escalation which resulted in patients staying on treatment longer and achieving clinical benefit.

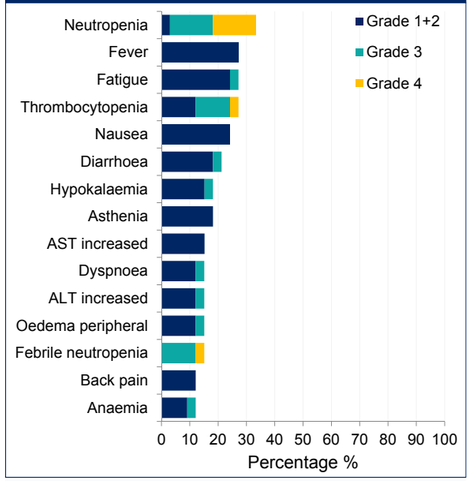
## Table 2: Dose Limiting Toxicities

| IMGN529 (mg/kg) | N pts treated/ N pts with DLT | Nature of DLT |
|---|---|---|
| 0.1, 0.2, 0.4 | 3/0, 9/0, 3/0 | |
| 0.8 | 2/2 | Gr4 neutropenia lasting more than 7 days, Gr2 peripheral neuropathy |
| 0.4 | 2/2 | Gr3 Febrile neutropenia (for 2 pts) |
| 0.4, 0.7 + day 2&3 steroids | 3/0, 3/0 | |
| 1.0 + day 2&3 steroids | 6/1 | Gr3 Febrile Neutropenia |
| 1.4 + steroids and G-CSF | 4/1 | Gr4 Thrombocytopenia |

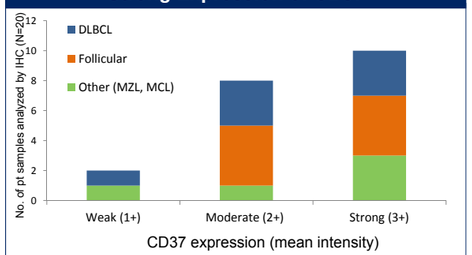
## Figure 1: Corticosteroids on Day 2 and 3 After Administration of IMGN529 Decreases the Incidence of Grade 3,4 Neutropenia Seen Early After Dosing




## Figure 2: Adverse Events Greater than 10% in All Patients



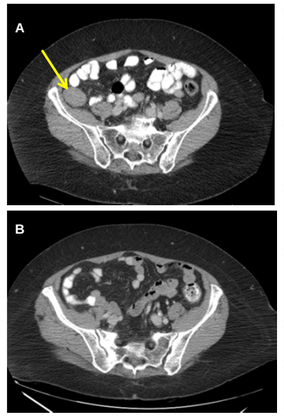

## Figure 3: Study Patients Show Moderate to Strong Expression of CD37




These results confirm previous published reports of homogenous and relatively strong expression of CD37 across NHL subtypes (Xu et al. #2513, Proceedings: AACR 103rd Annual Meeting 2012-- Mar 31-Apr 4, 2012; Chicago, IL)

## Evidence of Efficacy

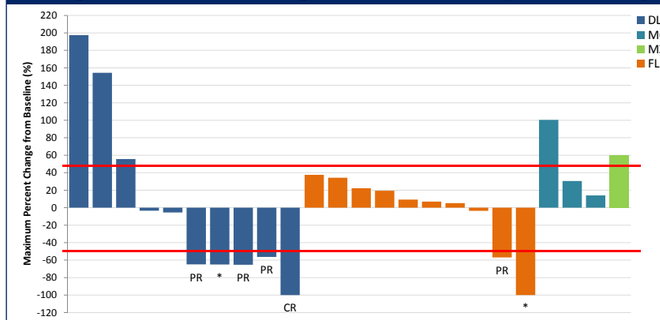
* 67 year old DLBCL pt who achieved a CR on study. Showing scans at baseline (A) and C3D15 (B)




| Type of Patient | Prior therapies with best response |
|---|---|
| 69 old male with G3 transformed FL | R-CHOP: CR; R-DHAP with vinorelbine, Zevalin: CR followed by ASCT; R-bendamustine: CR IMGN529 (0.2mg/kg): PR |
| 54 old male with GCB DLBCL | R-CHOP: PR; R-DHAP: PR; Fostamatinib: PD IMGN529 (0.4mg/kg): PR |
| 77 old female with GCB DLBCL | R-CHOP: CR; R-Bendamustine: PD; R-GEMOX: PD IMGN529 (0.4mg/kg): PR |
| 57 old male with unspecified DLBCL | R-CHOP: CR; R-ICE: PD; DEAP: CR followed by ASCT IMGN529 (1.0mg/kg): PR |
| *67 old female with non-GCB DLBCL | R-CHOP: CR; R-ICE: PR followed by ASCT IMGN529 (1.0mg/kg): CR (*see figure at left*) |

In addition to these responses, other evidence of efficacy include 1 pt with TLS, and a reduction in lymphocyte count seen early after dosing (D2) in the majority of pts that is suggestive of a CD37-mediated reduction in lymphocytes, consistent with the mechanism of action of a CD37-targeted therapy *(data not shown)*

## Figure 4: Maximum Change in SPD at Best Response on Study




*Two patients had a reduction/disappearance of target lesions, but developed a new lesion

## CONCLUSIONS

IMGN529, a CD37-targeting ADC, demonstrates clinical activity in patients with NHL and has the potential to be a novel therapeutic for B-cell lymphoproliferative malignancies.

IMGN529 shows encouraging anti-tumor activity especially amongst the 10 evaluable Relapsed/Refractory Diffuse Large B-Cell Lymphoma patients treated. Of 4 DLBCL pts that achieved a response, 1 was a CR and 3 PRs. In addition, one Grade 3 FL pt achieved a PR.

Transient grade 3-4 neutropenia occurring soon after dosing was reported in 6 of 19 patients (32%) receiving doses at or below 0.8 mg/kg, potentially attributed to cytokine release. Peri-infusional steroid administration was added to the study protocol, and the incidence and severity of this neutropenia was significantly reduced. Overall the incidence of neutropenia and/or febrile neutropenia has declined since adding corticosteroids and G-CSF *(currently G4 neutropenia lasting 2 days was reported in 1 of 5 pts with available data (20%), see Figure 1)*.

IMGN529 exhibits a manageable toxicity profile with the most common grade 3-4 AEs being hematologic in nature, as is not unexpected for heavily pre-treated NHL patients.

The exposures of IMGN529 increased with an increase in dose in a greater than dose-proportional manner indicating that the PK of IMGN529 is non-linear. The mean apparent elimination half-life of IMGN529 in the 1.4 mg/kg dose group was approximately 47.2 hours (*data not shown*).

Patient enrollment continues and dose escalation is ongoing.

***The authors would like to especially thank the patients who have consented to be included in this study, as well as their families.***
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***Conflict of interest disclosure: A. Romanelli, S. Zildjian, and R. Ruiz-Soto. are Employees of ImmunoGen, Inc.***