Activity of IDP-023 Allogeneic g-NK Cells Without Antibody Targeting in First-in-Human Ph1/2 Study in Patients with Advanced Multiple Myeloma or Non-Hodgkin's Lymphoma

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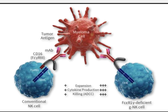
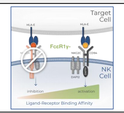
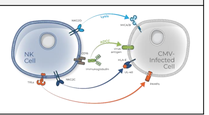
1) Background

Patients with relapsed or refractory (RR) multiple myeloma (MM) or Non-Hodgkin's lymphoma (NHL) have poor outcomes, with overall survival generally less than 12 months after best available therapies. More effective and tolerable treatments are needed.

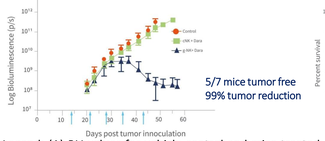
IDP-023 is an allogeneic natural killer cell product. By natural epigenetic reprogramming, g-NK cells are FcεR1g-negative and exhibit much higher antibody-dependent cytotoxicity (ADCC) following engagement of CD16 than conventional NK cells (cNK). In addition, g-NK cells are negative for the inhibitory checkpoint NKG2A and express high levels of the activating receptor NKG2C, making them uniquely suited to kill HLA-E-expressing target cells.

Superior ADCC for deep depletion of mAb targeted cells	Depletion of HLA-E expressing target cells	Elimination of virally infected cells
		

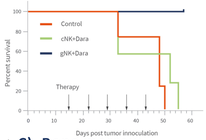
2) Immunotherapy using g-NK + Daratumumab (Dara) results in regression of established tumors where cNK + Dara show marginal effects.

Robust **pre-clinical activity** of g-NKs in combination with daratumumab has been demonstrated against MM cell lines, patient-derived primary tumor cells, and in an orthotopic xenograft myeloma model (MM.1S). IDP-023 efficacy was significantly better than expanded cNK cells [1].

A) Log-Scale Tumor Burden (BLI)



B) Survival



C) Bone marrow

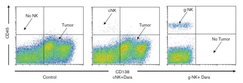
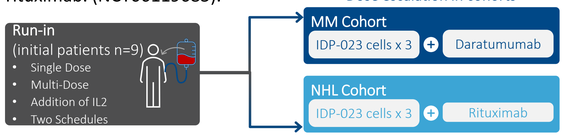


Figure Legend: (A) BLI values for vehicle control and mice treated with cNK plus Dara or g-NK plus Dara. (B) Effect of treatment with g-NK plus Dara on survival relative to treatment with cNK plus Dara or vehicle. (C) Representative flow cytometry dot plots depicting tumor burden (tumor) and persistence of NK cells in bone marrow. Values are mean ± SEM.

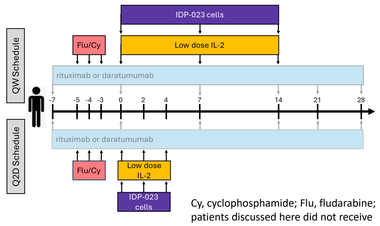
3) Trial Design

This is an open label, Phase 1/2, first-in-human, multiple ascending dose escalation, and dose-expansion study of IDP-023 administered as monotherapy +/- interleukin-2 (IL-2), and in combination with daratumumab or rituximab. (NCT06119685).



4) Treatment Schema

- The cohorts described here are the "run-in" cohorts only which received a matrix of two regimens:
  - Every week x3 (QWx3), or every other day x3 (Q2Dx3) with or withoutIL-2.
  - Patients received lymphodepleting chemotherapy (LD) followed by subcutaneous IL-2 and intravenous IDP-023.



Cy, cyclophosphamide; Flu, fludarabine; patients discussed here did not receive mAb

5) Eligibility

Multiple Myeloma:
- Adults with RR MM who have failed ≥ 3 prior lines of therapy.
- Exposure to ≥ 1 proteasome inhibitors, ≥ 1 immunomodulatory agents, and ≥ 1 anti-CD38 mAb.

Non-Hodgkin's Lymphoma:
- Any of the following types: diffuse large B-cell (DLBCL), high grade B-cell lymphoma (HGBL), transformed follicular lymphoma (tFL), primary mediastinal large B-cell lymphoma (PMBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), or mantle cell lymphoma (MCL).
- Progressive disease or best response to most recent chemotherapy containing regimen was stable disease ≤ 12 months.
- Must have failed at least 2 lines of systemic chemotherapy and have additional criteria depending on type.

6) Patient Demographics and Clinical Summary

Dose Cohort	Patient ID	Age	Sex	Cancer	# Prior Regimens	Any Aes >= grade 3 and SAEs	Best Response
Single Dose	01	56	Male	MM	12 (Incl. Auto SCT, Isa, BCMA TCE, BCMA CAR-T)	Anemia, Hypophosphatemia, Plt decreased, Neut decreased	PD
DL1 QW x 3	02	61	Male	MM	4 (Incl. Auto SCT, Dara)	Lymph decreased, WBC decreased	PR
DL1 QW x 3 +IL-2	04	59	Male	MM	7 (Incl. Isa, BCMA CAR-T)	Neut decreased, Plt decreased, WBC decreased, Anemia	VGPR
	06	68	Female	MM	3 (Incl. Auto SCT, Dara)	Lymph decreased, Neut decreased, WBC decreased	MR
	09	71	Male	MM	6 (Incl. Auto SCT, Dara, BCMA CAR-T, GPRC5D TCE)	Lymph decreased, WBC decreased	SD
DL1 Q2D x 3	03	63	Male	MM	5 (Incl. Dara)	Insomnia, Lymph decreased, Nausea, Neut decreased, WBC decreased	SD
DL1 Q2D x 3 +IL-2	05	77	Male	NHL (DLBCL)	3 (Incl. Ritux, CD19 CAR-T)	Anaemia, Lymph decreased, Neut decreased, Muscular weakness, Plt decreased, Urine output decreased, WBC decreased	SD
	07	74	Female	MM	5 (Incl. Radiotx, Dara, Isa)	Anaemia, Febrile neutropenia, Hypertension, Lymph decreased, Neut decreased, Plt decreased, WBC decreased	PR
	08	61	Male	MM	7 (Incl. Dara, Isa, BCMA TCE)	Anemia, Febrile Neutropenia, Neut decreased, Plt decreased, WBC decreased	PR

Auto SCT, autologous stem cell transplant; BCMA, B cell maturation antigen; CAR, chimeric antigen receptors; Dara, daratumumab; DL1, Dose level 1; Isa, isatuximab; Lymph, Lymphocyte count; Neut, Neutrophil count; PR, partial response; PD, progressive disease; Ritux, rituximab; TCE, T-cell engager; VGPR, very good partial response; WBC, White blood cell count

7) Dosing Cohorts

Cohort	IL-2 (with each infusion)	Dose regimen (all DL1)	# patients	Disease
1	no	Single dose	1	MM
2	no	Q2D x3	1	MM
3	no	QW x3	1	MM
4	6 M IU s.c.	Q2D x3	3	MM/NHL
5	6 M IU s.c.	QW x3	3	MM

M= Million; IU = international units; DL1 = dose level 1; s.c. = subcutaneously

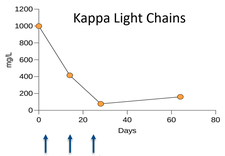
Objectives: The primary objective of the cohorts without antibody was to define safety & tolerability.

8) Clinical Activity (FDG PET)

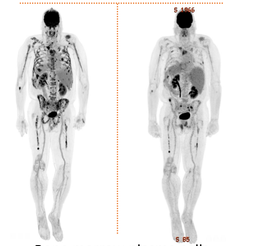
Patient #4: 59 yo male

Relapsed/refractory MM

- 7 prior lines of therapy including: autologous stem cell transplant, BCMA CAR-T (Abecma)



Pre-Treatment **Post-Treatment (D28)**



Bone marrow plasma cells:
11% → 1%

Patient #5: 77 yo male

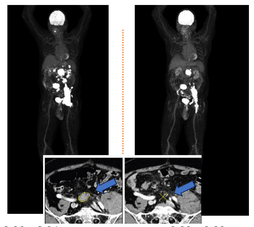
Relapsed/refractory DLBCL

- 3 prior lines of therapy: ADC (Polivy) with R-CHP, ADC (Polivy) with rituximab, CD19 CAR-T (Breyanzi)

Radiologist Impression: "Partial treatment response evidence in decreased size in mesenteric nodal masses and masse predominantly along left pelvic musculature. Abdominal mass abut/encase bowel segments with no evidence of bowel obstruction. Decreased retroperitoneal lymphadenopathy."

Total reduction in tumor burden 23.6%.

Small insert shows central pericolic Lymph Node that completely regressed



3.06 x 2.04 cm
6.24 cm²
N/A

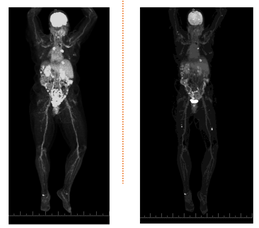
0.00 x 0.00 cm
0.00 cm²
-100%

Patient #6: 68 yo female

Relapsed/refractory MM

- 5 prior lines of therapy: RVD, Cytoxan followed by ASCT, daratumumab + dexamethasone, Kyprolis

Radiologist Impression: "There is evidence of treatment response with interval decrease in uptake within multiple myelomatous lesions involving hypermetabolic mediastinal lymph nodes and multiple osseous lesion in axial and appendicular skeleton as detailed above."

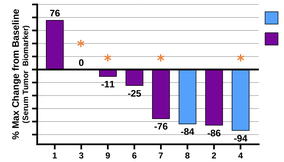


9) Initial Activity

Cohort	IL-2	# of doses	# patients	Disease	ORR MM (IMWG*, 2016) NHL (Lugano, 2014)	Summary Response Assessment
1	no	1	1	MM	0/1	1 PD
2+3	no	3	2	MM	1/2	1 PR, 1 SD
4+5	6 M IU	3	5	MM	4/5	1 VGPR, 2 PR, 1 MR, 1 SD
	6 M IU	3	1	NHL	0/1	SD, 23.6% reduction

Response determined by: MM (IMWG, 2016), *MM response assessment by PI using modified IMWG criteria without 24h urine collection, NHL (Lugano, 2014); VGPR =very good partial response; PR=Partial response; MR= minor response

Maximum Change in Serum Tumor Biomarker



Free light chain (FLC) values were used where M-protein not evaluable.

- Pts were on study for 1-3 months
- 4 pts (*) went on to subsequent therapy prior to disease progression including CAR T or T cell engager therapy. Therefore, durability could not be formally addressed.
- Mean Maximum Change in Serum Tumor Biomarker in responding pts was -73%

10) Summary & Conclusions

Summary:
- As of 10/15/24, nine patients were treated with IDP-023 without antibody.
- Eight patients received multiple doses of cells at the lowest dose and 6 also received IL-2.
- No DLTs were noted. Patients experienced cytopenias consistent with the LD. Two patients experienced serious AEs (febrile neutropenia) that were deemed unrelated to IDP-023.
- Of the patients who received IDP-023 + IL2, objective antitumor activity was seen in 4 of 5 MM patients who were heavily pretreated (3-7 prior lines of therapy, including 1 patient with prior CAR-T) and one patient with NHL who received prior CAR-T.

Conclusions:
- IDP-023 was well tolerated in both, every week x3 and every other day x3 regimens.
- Unexpected, encouraging initial activity was observed with IDP-023 + IL-2 in advanced MM and NHL, even in the absence of combination with ADCC mediating monoclonal antibodies.
- In preclinical models, combinations of IDP-023 plus anti-CD38 mAb resulted in durable regression of established tumors with demonstrated activity in the bone marrow.
- The cohorts of IDP-023 + IL2 + monoclonal antibodies will be very informative; enrollment is ongoing

References:

[1] Austin B. Bigley, Shanae Spade, Nadia H. Agha, Sujit Biswas, Suni Tang, Muhammad H. Malik, Lu Dai, Shalaleh Masoumi, Bonell Patiño-Escobar, Martina Hale, Guy DiPierro, Ronald Martell, Byron Hann, Nina Shah, Arun P. Wiita, Xinli Liu. *Blood Adv* (2021) 5 (15): 3021–3031. FcεRIγ-negative NK cells persist in vivo and enhance efficacy of therapeutic monoclonal antibodies in multiple myeloma. https://doi.org/10.1182/bloodadvances.2020002440

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