Response to g-NK is Associated with Higher CD8+ T Cells & Lower MDSC in Bone Marrow of Patients with Multiple Myeloma

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Background

Patients with relapsed or refractory (R/R) multiple myeloma (MM) have poor outcomes, with overall survival generally less than 12 months after best available therapies. More effective and tolerable treatments are urgently needed.

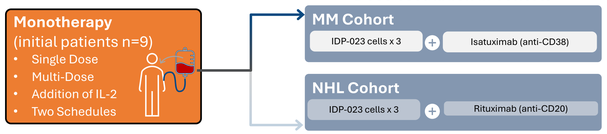
IDP-023 is an allogeneic natural killer (NK) cell product that comprises a subset of adaptive NK cells (named g-NK cells) that arise naturally in response to HCMV in some individuals. G-NK cells display a stable, unique phenotype through epigenetic reprogramming making them especially attractive for adoptive cell therapy:

- g-NK cells are FcεR1γ-negative and exhibit **superior antibody-dependent cytotoxicity (ADCC)** following engagement of CD16 compared to conventional NK cells (cNK)[1]
- g-NK cells are negative for the most dominant inhibitory checkpoint for NK cells: NKG2A and instead, express high levels of the activating receptor NKG2C, allowing them to **recognize and kill HLA-E-expressing target cells**

HLA-E, a non-classical HLA class I molecule, is significantly upregulated on myeloma cells, particularly in advanced stages and high-risk patients, contributing to immune escape[2]. High HLA-E expression is correlated with advanced disease stages, high-risk cytogenetic profiles, and potentially worse progression-free survival in newly diagnosed MM patients. Here we demonstrate impressive clinical activity in the monotherapy arm of our first-in human phase 1/2 clinical trial (NCT06119685).

Clinical Trial Design: NCT06119685

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), or in combination with isatuximab or rituximab for the treatment of patients with MM or NHL, respectively.



This poster focuses patients with MM treated in the monotherapy cohort of the study.

Eligibility Criteria for Clinical Trial Patients With MM

- 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.

References:

[1] Bigley AB, et al. *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

[2] Lagana A, et al. *Blood* (2018) 132 (Suppl_1) : 59. Increased HLA-E expression correlates with early relapse in multiple myeloma. http://doi.org/10.1182/blood-2018-99-116828

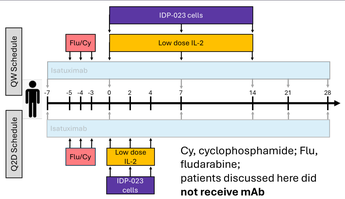
Poster Download

Clinical data cut 26Mar2025. Not all data have been source verified.

Treatment Schema

The results discussed here are from patients of the monotherapy cohorts, which received one of two treatment regimens:

- Every week x3 (QWx3), or every other day x3 (Q2Dx3) with or without subcutaneous IL-2.
- All patients received lympho-depleting chemotherapy (Flu/Cy) followed by intravenous IDP-023.



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

Patient Demographics and Clinical Summary of Patients with Multiple Myeloma Treated with IDP-023

Dose Cohort	Patient ID	Age	Sex	Cancer	# Prior Regimens	# of Prior Drug Classes[1]	Prior CAR-T/TCE	Prior BCMA	Prior anti-CD38	Prior Auto-SCT	Best Response
Single Dose	01	56	Male	MM	12	5 + anti-BCMA	BCMA-CAR BCMA TCE	X (x2)	Isa	X	SD
DL1 QW x 3	02	61	Male	MM	4	3			Dara	X	PR
DL1 QW x 3 +IL-2	04	59	Male	MM	7	5 + anti-BCMA	BCMA-CAR	X	Isa		VGPR
	06	68	Female	MM	3	3			Dara	X	PR
	09	71	Male	MM	6	5 + anti-BCMA	BCMA-CAR GPRC5D TCE	X	Dara Isa	X	SD
DL1 Q2D x 3	03	63	Male	MM	5	3			Dara		VGPR
DL1 Q2D x 3 +IL-2	07	74	Female	MM	5	3			Dara Isa		PR
	08	61	Male	MM	7	5 + anti-BCMA	BCMA TCE	X	Dara Isa		VGPR
DL2 QW x 3 + IL-2	13	68	Male	MM	3	3			Dara		SD

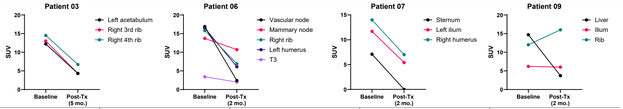
Auto SCT, autologous stem cell transplant; BCMA, B cell maturation antigen; CAR, chimeric antigen receptors; Dara, daratumumab; DL1, Dose level 1; Isa, isatuximab; Lymph, Lymphocyte count; Neut, Neutrophil count; PR, partial response; PD, progressive disease; Ritux, rituximab; TCE, T-cell engager; VGPR,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

Best Response by current IMWG criteria.

1 - Drug classes include IMiD, PI, anti-CD38

- Therapy was well-tolerated; no dose limiting toxicities. Most common adverse events were cytopenias due to conditioning therapy

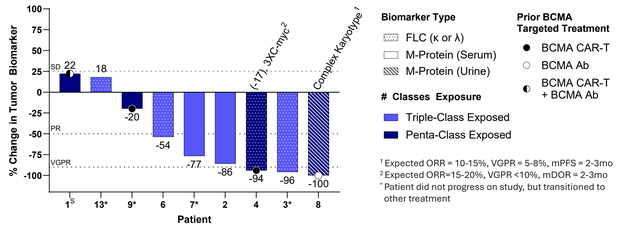
Reduction in PET SUVs of Patients with MM Following IDP-023



Patient (IMWG Response)	03 (SD)	06 (MR)	07 (PR)	09 (SD)
Avg. % SUV Change from Baseline (% range)	-62% (-54 to -67)	-54% (-22 to -86)	-67.9% (-50 to -100)	-14.9% (33 to -75)

Figure 1. Change in PET SUV from baseline to post-treatment in four patients treated with IDP-023. Matched lesion PET SUV results at baseline and post-treatment. The mean change in SUV was determined by averaging the change in SUV of each evaluable lesion. The range of percent change in SUV from baseline is shown in parentheses. All post-treatment PET results were 2 months from baseline, except Pt 03 which was 5 months. MR, minimal response; PR, Partial response; SD, stable disease; SUV, standardized uptake units

IDP-023 Produces Deep Responses in Heavily Pretreated Highly Refractory MM



[1] Expected ORR = 10-15%, VGPR = 5-8%, mPFS = 2-3mo
[2] Expected ORR=15-20%, VGPR <10%, mDOR = 2-3mo
* Patient did not progress on study, but transitioned to other treatment

Figure 2: % Maximum Change in Tumor Serum Biomarker. The maximum change in serum tumor biomarker from baseline was determined based on either M-protein (serum and urine) or free-light chains (FLC) when M-protein was undetectable or unavailable. Prior therapies are indicated as shown in the legend to the right, including number of prior drug classes and if prior BCMA-targeting therapy (and modality) had been received. Abbreviations: Ab, antibodies; mDOR, median duration of response; mPFS, median progression-free survival; ORR, overall response rate; PR, partial response; VGPR, very good partial response

- Deep responses achieved, even post-BCMA therapy
- Responses observed across all lines of therapy
- Disease control rate = 100%
- ORR = 67% (6/9), VGPR = 33% (3/9)

Increased T Cell Infiltration & TME Remodeling Following Treatment with IDP-023

Case Study: Patient (03) With Very Good Partial Response by IMWG Shows Impressive Reduction of Tumor By PET Scan with TME Remodeling

- 63 yo male diagnosed with R/R MM
- Treated with LD chemo + IDP-023 (Q2Dx3) *NO* IL2
- Pre-treatment BM blasts 20-25% monotypic plasma cells and were 'Rare' ~4 months after IDP-023 (0.02% by flow).
- Marked reduction/elimination of lesions on PET at 4 months after IDP-023
- Normalization of sFLC ratio at 2- and 4-months post IDP-023
- Patient was progression free for 5 months (IMWG=VGPR) and then had CR on BCMA CAR-T (received July 2024) and has remained in CR*.

Tx = treatment with IDP-023, Teff = terminal effector memory + effector memory, MDSC myeloid-derived suppressor cells, PMN polymorphonuclear, TME Tumor microenvironment.
* as of last follow up Mar2025 per communication with investigator

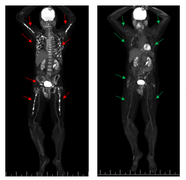


Figure 3: FDG-PET images at baseline (left) and four months after treatment (right). Red arrows indicate FDG-avid lesions at baseline and Green arrows indicate improvement in those regions after treatment with IDP-023.

Bone marrow Cytof shows remodeling of TME with a massive influx of T cells & elimination of PMN-MDSCs

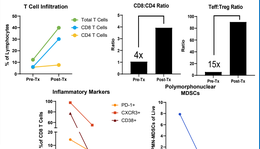
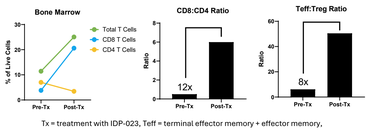


Figure 4: 37-marker Cytof of bone marrow cells at baseline (pre-tx) and one month after initiation of IDP-023 treatment (post-tx). Analysis of T cells showed increase CD8 infiltration with a decrease in inflammatory markers and elimination of PMN-MDSCs.

Case Study: Patient (13) r/r MM Patient IDP-023 Induces T cell Infiltration with TME Remodeling

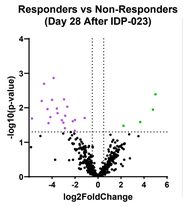
- 68 yo male diagnosed with R/R MM
- Treated with LD chemo + IDP-023 (DL2, Q2Dx3) + IL-2
- Baseline PET imaging was negative for FDG-avid lesions.
- Patient was progression free for 3 months post-IDP-023 (IMWG = SD, no progression on study and remained progression free at time of last follow up at 6 months).
- Patient went on to receive anti-CD38 after 2 months and subsequently went onto triple therapy (revlimid + dexamethasone) and remains in CR as of April 2025.



Tx = treatment with IDP-023, Teff = terminal effector memory + effector memory,

Figure 5: 37-marker Cytof of bone marrow cells at baseline (pre-tx) and one month after initiation of IDP-023 treatment (post-tx). Analysis of T cells showed increase in bone marrow T cell infiltration specifically within the CD8 T cell subset. The post-treatment ratios of CD8:CD4 and Teff:Treg ratio

Significant Down-Regulation of Tumor & Neutrophil Associated Genes in Responding Patients Post-Treatment



Downregulated (in responders)	Upregulated (in responders)
CD28	EGF
CLEC1L1	ITGB3
DEPTOR	NID2
DUSP2	PF4
DUSP5	
FCGR2B	
FCRL2	
GPR160	
HLA-DOB	
ITGA6	
LY9	
MAGEA1	
MAGEA12	
MAGEC2	
PDK1	
PTCD2	
SLAMF7	
SMAD5	
TNFRSF17 (BCMA)	
TNFSF8 (CD30 Ligand)	
WNT10A	

Functional Associations:

- T cell co-stimulation/ inhibition (*CD28, SLAMF7, TNFRSF17*)
- Antigen presentation (*HLA-DOB, CLECL1*)
- DNA damage response and repair (*SMAD5, DUSP5*)
- Metabolic signaling (*DEPTOR, PDK1*)

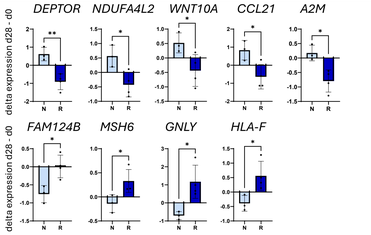
▷ **Reduced Tumor Burden**: Down-regulation of these tumor-associated genes aligns with effective immunotherapy, likely reflecting a reduction in tumor cells and/or modulation of the tumor microenvironment.

▷ **Immune Clearance**: Many of these genes are involved in immune evasion (e.g., MAGE family, Wnt signaling). Down-regulation suggests immunotherapy has successfully reactivated immune responses to target tumor cells.

▷ **Microenvironment Reprogramming**: Genes like *CLECL1*, *WNT10A*, and *ITGA6* point to changes in the TME, reducing its support for tumor growth and survival.

Figure 6: Volcano plot showing differential gene expression (normalized counts obtained by Nanostring analysis) in bone marrow of non-responding and responding patients at day 28. Response is defined at ≥MR by IMWG in this analysis.

Differentially Regulated Genes at Baseline vs Post-Treatment in Responders and Non-Responders



Gene name	pathway	Regulation, P value
A2M	complement /coagulation	↓, * 0.0142
DEPTOR	signaling	↓, ** 0.0047
FCGR2B	Fc-GammaR, Fc epsilon RI pathway / disease	↓, ns 0.0571
NDUFA4L2	antiproliferative, metabolic pathways	↓, * 0.0243
WNT10A	WNT/β-catenin signaling pathway	↓, * 0.0481
CCL21	chemotaxis	↓, * 0.0274
AKT1	survival, growth pathway	↑, ns 0.0565
AXIN1	WNT/β-catenin signaling pathway	↑, ns 0.0561
FAM124B	negative regulator of Wnt pathway	↑, * 0.0170
MSH6	DNA repair	↑, * 0.0369
ROCK1	growth pathway	↑, ns 0.0528
GNLY	immunity	↑, * 0.0199
HLA-F	immunity	↑, * 0.0331
KIR2DL3	immunity	↑, ns 0.0571
TNFSF12	MIF, TNFR1 signaling, immunity	↑, ns 0.0568

Table: List of genes that are regulated (or show a trend) between baseline and day 28 in N and R.

Figure 7: Difference in gene expression in Bone Marrow samples (normalized counts obtained by Nanostring analysis) between baseline and day 28 is shown for Non-Responder (N) and Responder (R), respectively. Response is defined at ≥MR by IMWG criteria in this analysis.

Responders differentially:

▷ **Downregulate disease-associated genes**, e.g. *DEPTOR, WNT10A*

▷ **Upregulate cytotoxic immune-associated genes**, e.g. *granulysin, HLA-F*

DEPTOR, DEP domain-containing mTOR-interacting protein; ***WNT10A***, Wnt Family Member 10A; ***CCL21***, Chemokine (C-C motif) ligand 21; ***A2M***, Alpha-2-macroglobulin; ***FAM124B***, family with sequence similarity 124 member B; ***MSH6***, mutS homolog 6; ***GNLY***, granulysin; ***HLA-F***, Human leukocyte antigen F

Summary & Conclusions

- The allogeneic g-NK cell product IDP-023 induces favorable responses in highly pretreated patients with r/r MM including 33% rate of VGPR:
  - VGPR (-100% urine M protein) achieved in penta-refractory post-BCMA pt with *complex karyotype*; pt alive ~11mo after IDP-023
  - VGPR (-94% FLC) achieved in penta-refractory pt with p53-deleted/3Xmyc MM
  - Results in these two patients exceed expected outcomes, where the probability of VGPR+ was <10%, PFS<3 mo, and OS ~ 3-5 mo.
- Correlative Cytof studies suggest anti-tumor mechanisms in addition to direct NK cell activity may be important. Individual case studies show remodeling of the TME (BM) including influx of non-exhausted CD8 T cells with resulting improved Teff to Treg ratios.
- We observed distinct regulation in genes associated with immune responses, pro-tumorigenic signaling and reprogramming of the microenvironment in the bone marrow of responding individuals.

Further development of IDP-023 for the treatment of patients with r/r MM either alone or in combination with targeting therapeutic Ab is warranted.