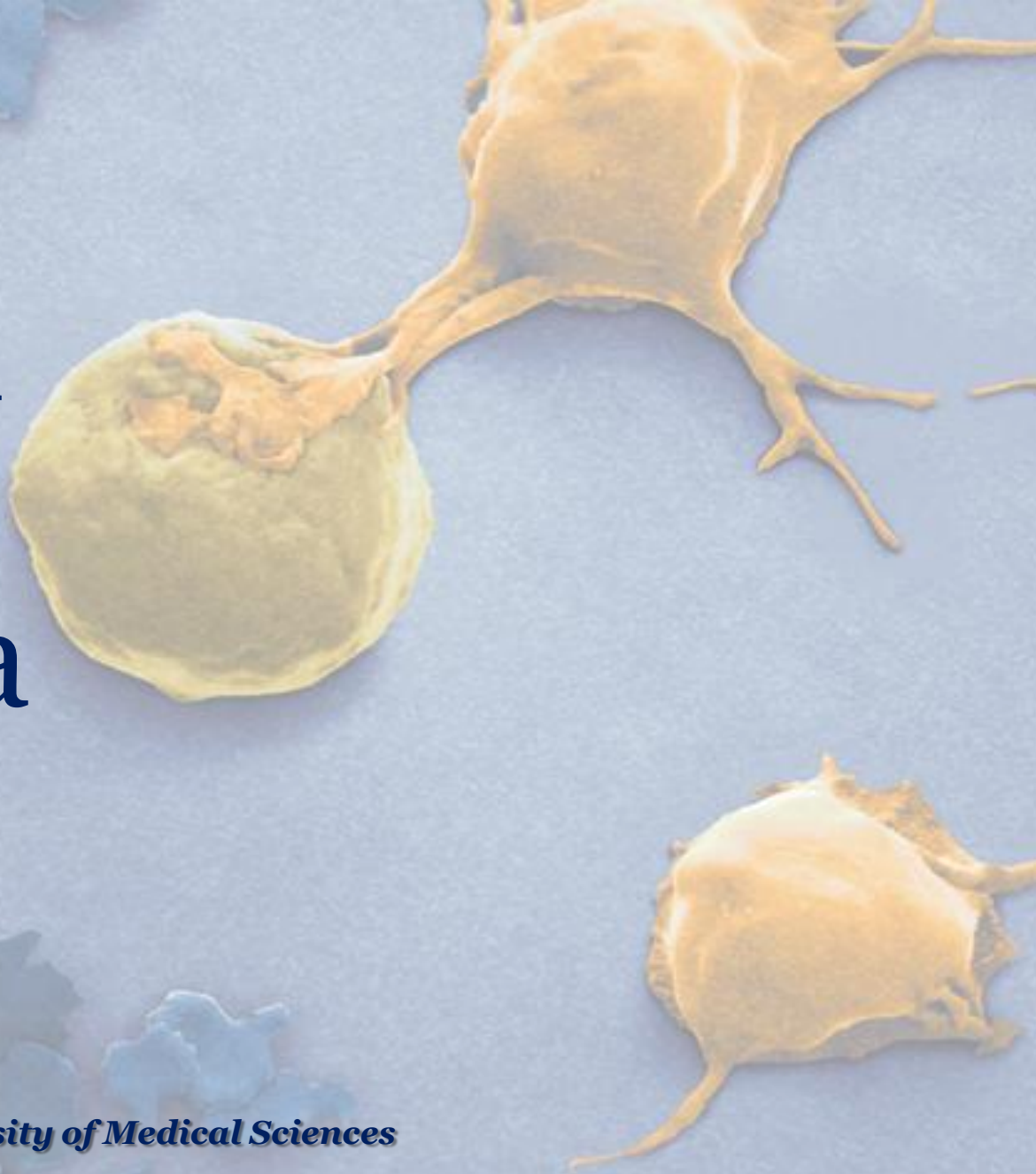
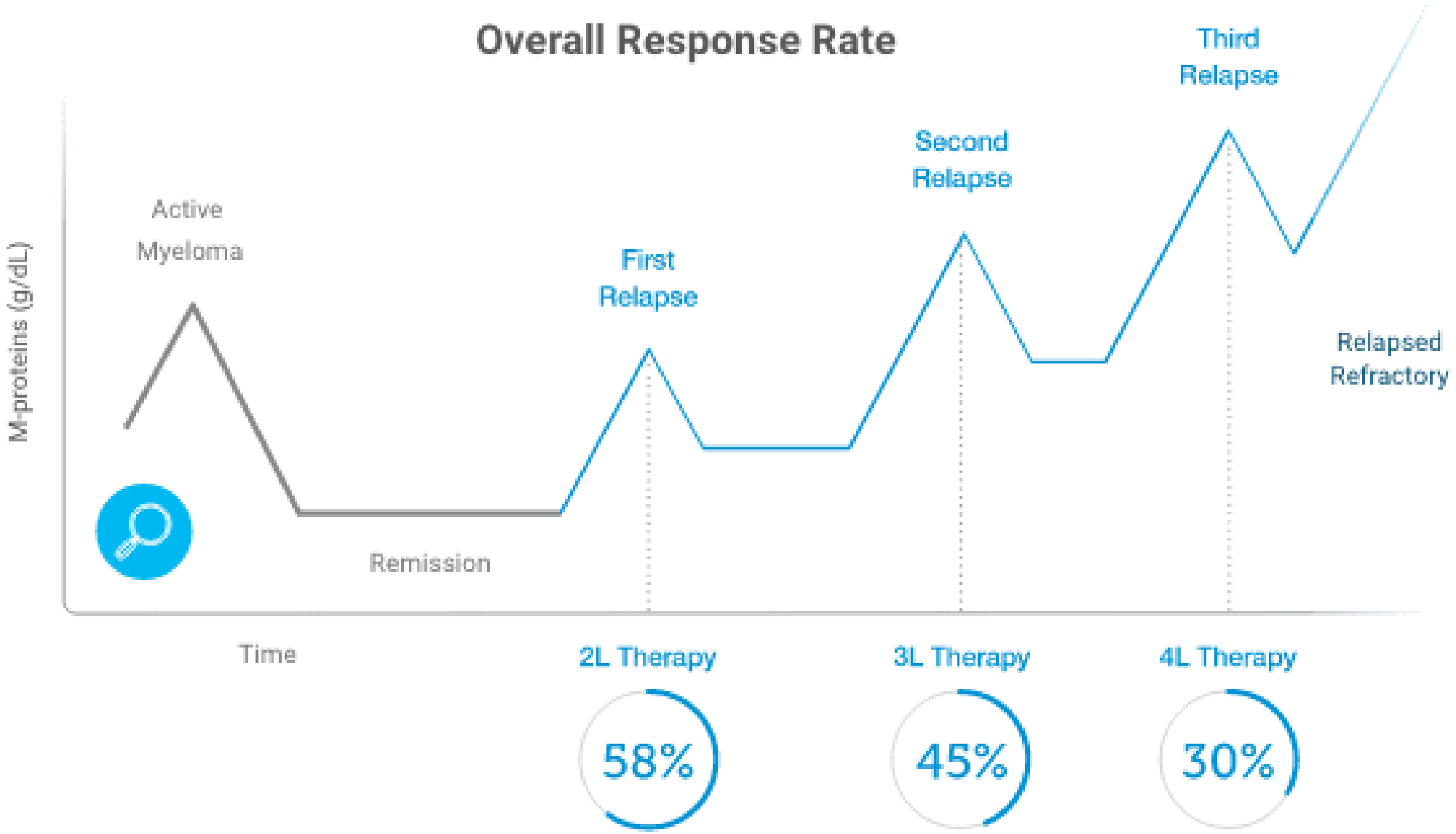
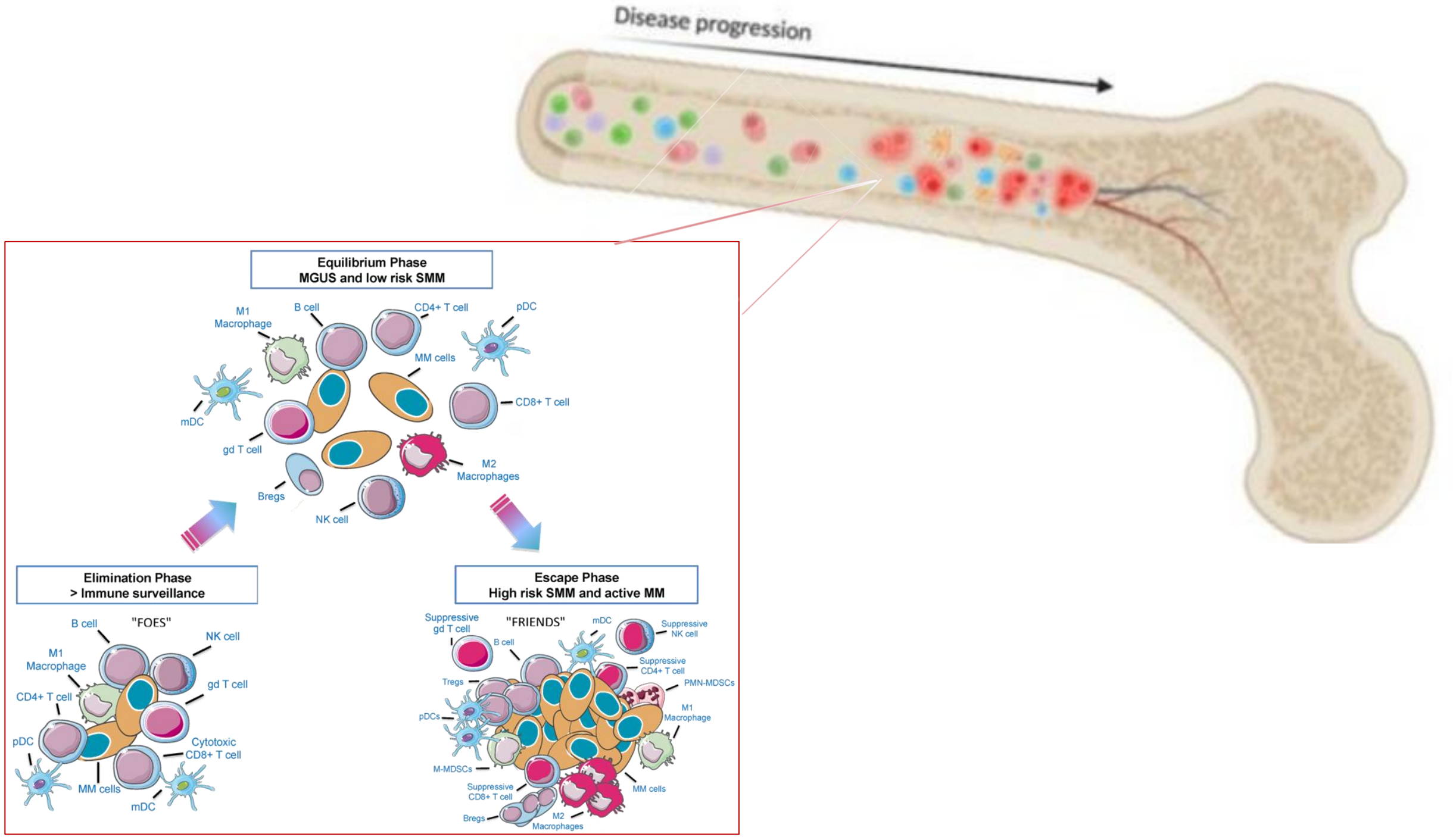
Natural killer cell therapy in multiple myeloma

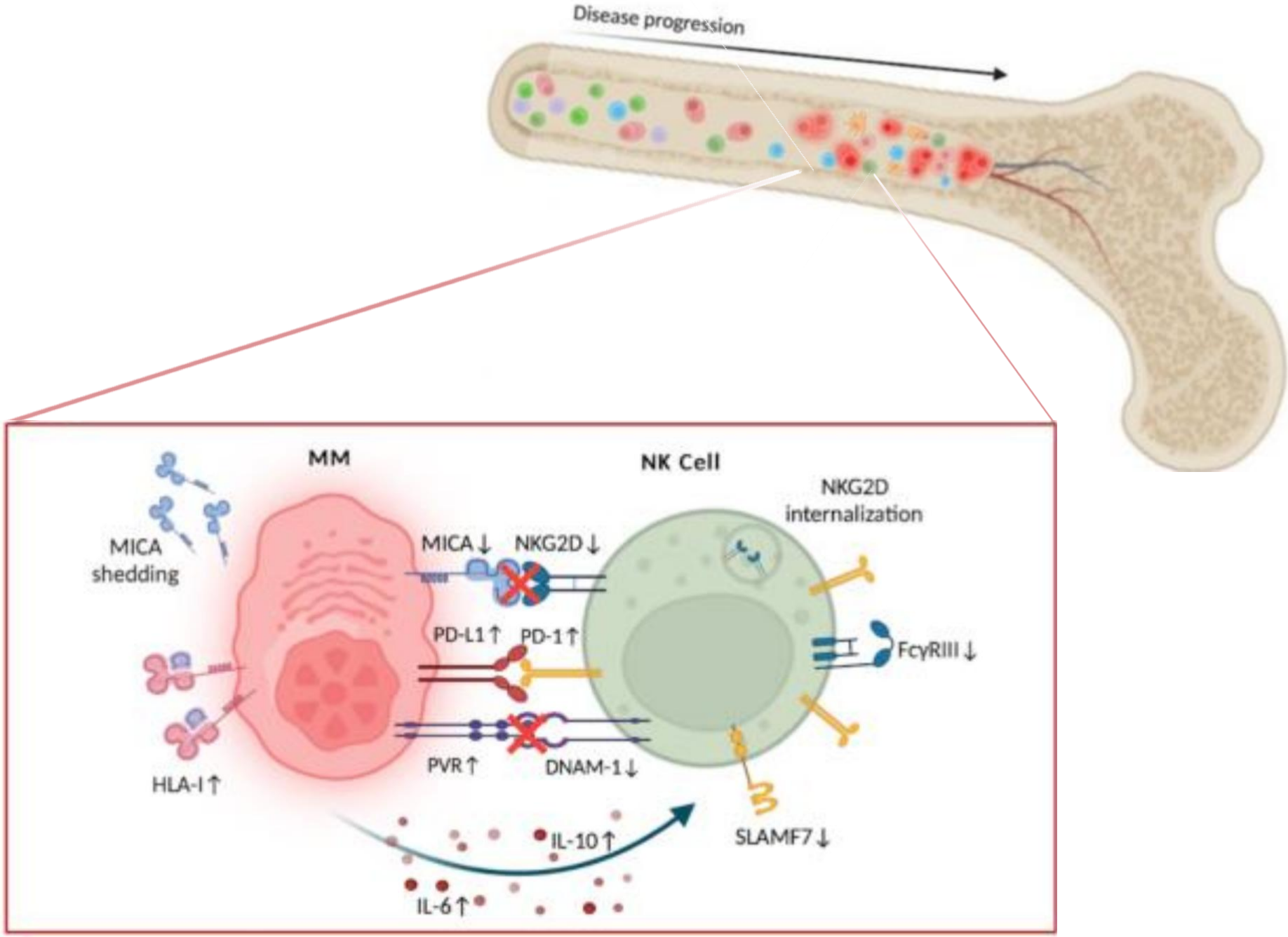


Dr. Abbas Hajifathali, MD.

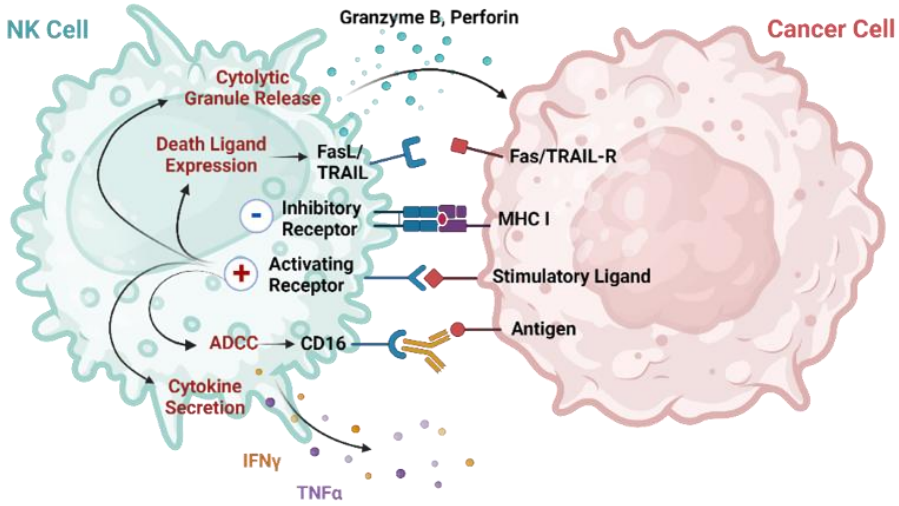
Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences


Overall Response Rate
M-proteins (g/dL)
Active
Myeloma
Remission
First
Relapse
Second
Relapse
Third
Relapse
Relapsed
Refractory
Time
2L Therapy
58%
3L Therapy
45%
4L Therapy
30%


Disease progression
Equilibrium Phase
MGUS and low risk SMM
M1 Macrophage
B cell
CD4+ T cell
pDC
MM cells
CD8+ T cell
mDC
gd T cell
M2 Macrophages
Bregs
NK cell
Elimination Phase
> Immune surveillance
B cell
"FOES"
NK cell
M1 Macrophage
gd T cell
CD4+ T cell
pDC
Cytotoxic CD8+ T cell
MM cells
mDC
Escape Phase
High risk SMM and active MM
Suppressive gd T cell
"FRIENDS"
mDC
Suppressive NK cell
B cell
Suppressive CD4+ T cell
Tregs
PMN-MDSCs
pDCs
M1 Macrophage
M-MDSCs
MM cells
Suppressive CD8+ T cell
Bregs
M2 Macrophages

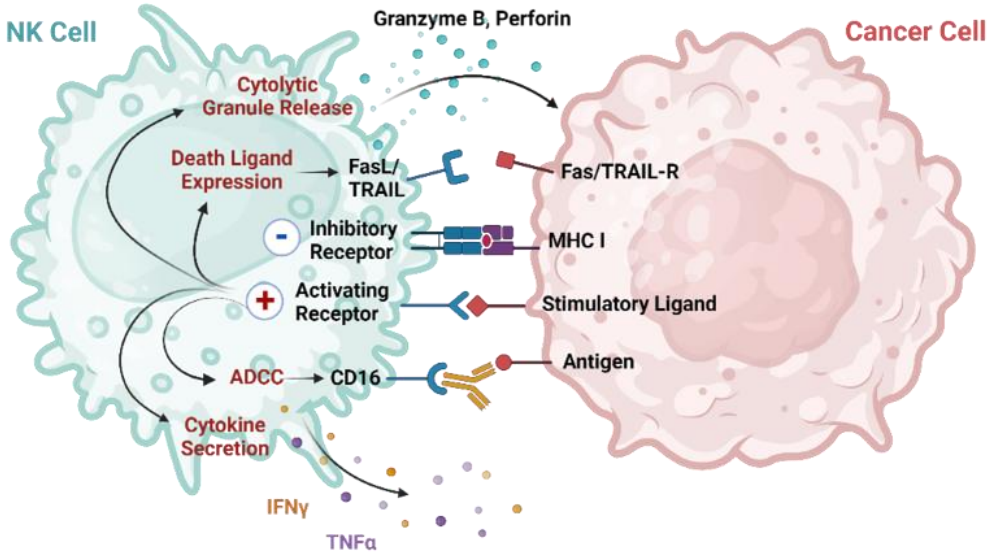

Disease progression
MM
NK Cell
MICA shedding
MICA ↓
NKG2D ↓
NKG2D internalization
PD-L1 ↑
PD-1 ↑
FcγRIII ↓
HLA-I ↑
PVR ↑
DNAM-1 ↓
IL-10 ↑
SLAMF7 ↓
IL-6 ↑

- capable of rapidly killing malignant cells, including MM, without prior sensitization and gene rearrangement to acquire antigen-specific receptors.



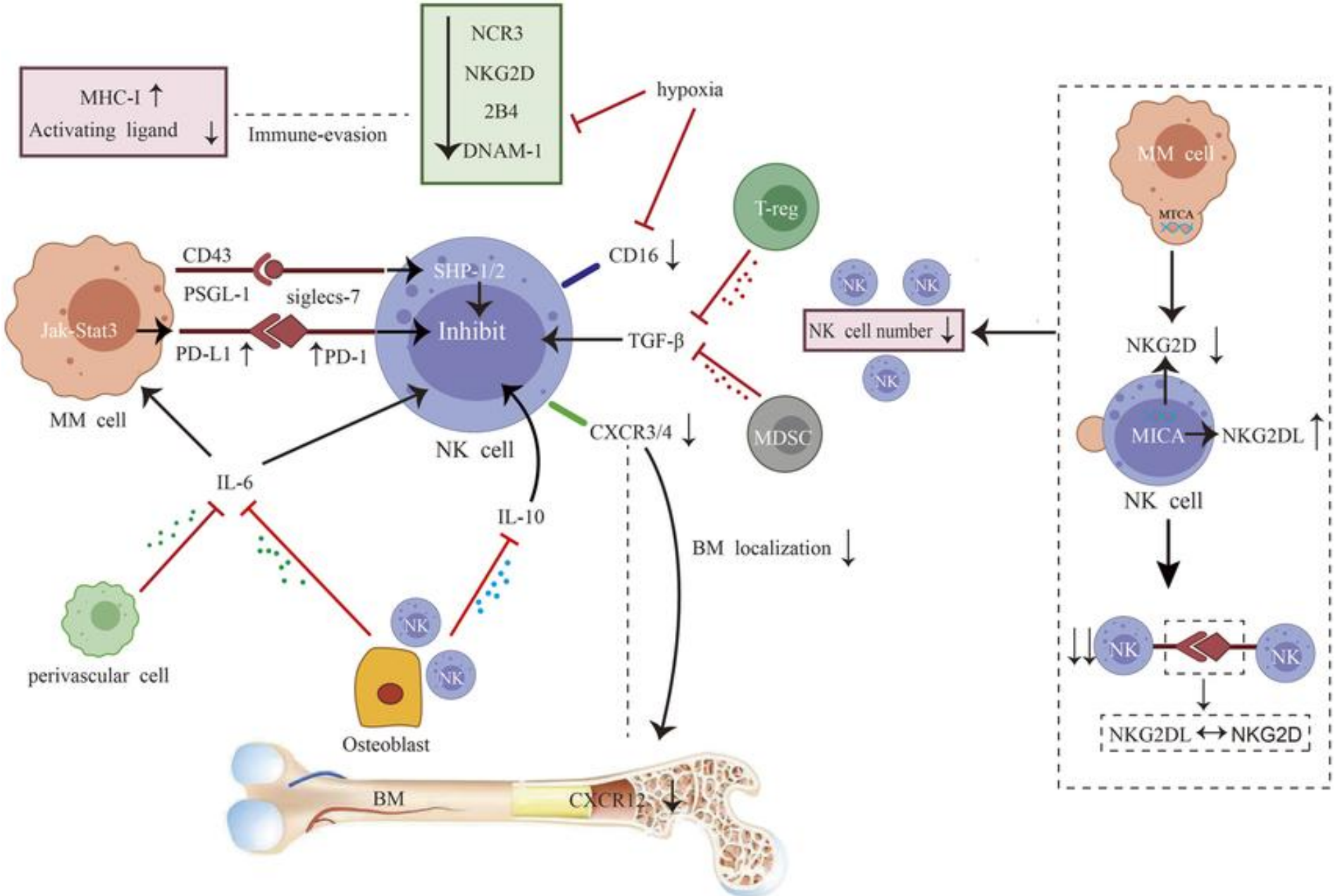
- NK cells employ death ligands and degranulation to eliminate target cells

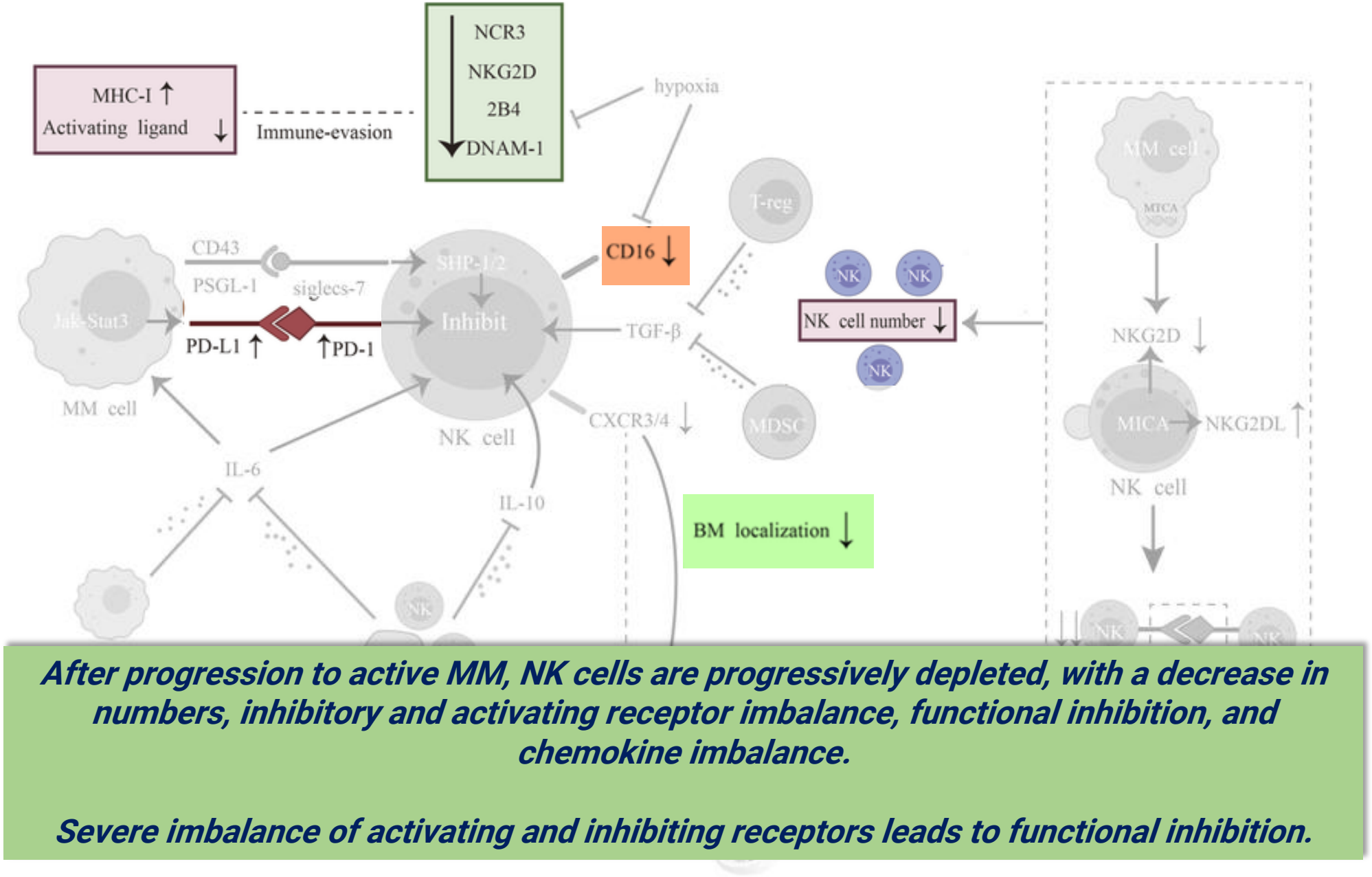
- The fine-tuned balance between a complex array of inhibitory and activating receptors regulates their cytotoxic responses.



In MM, NK cell functionality and immunity are negatively regulated by myeloma cells and their immunosuppressive microenvironmental factors.

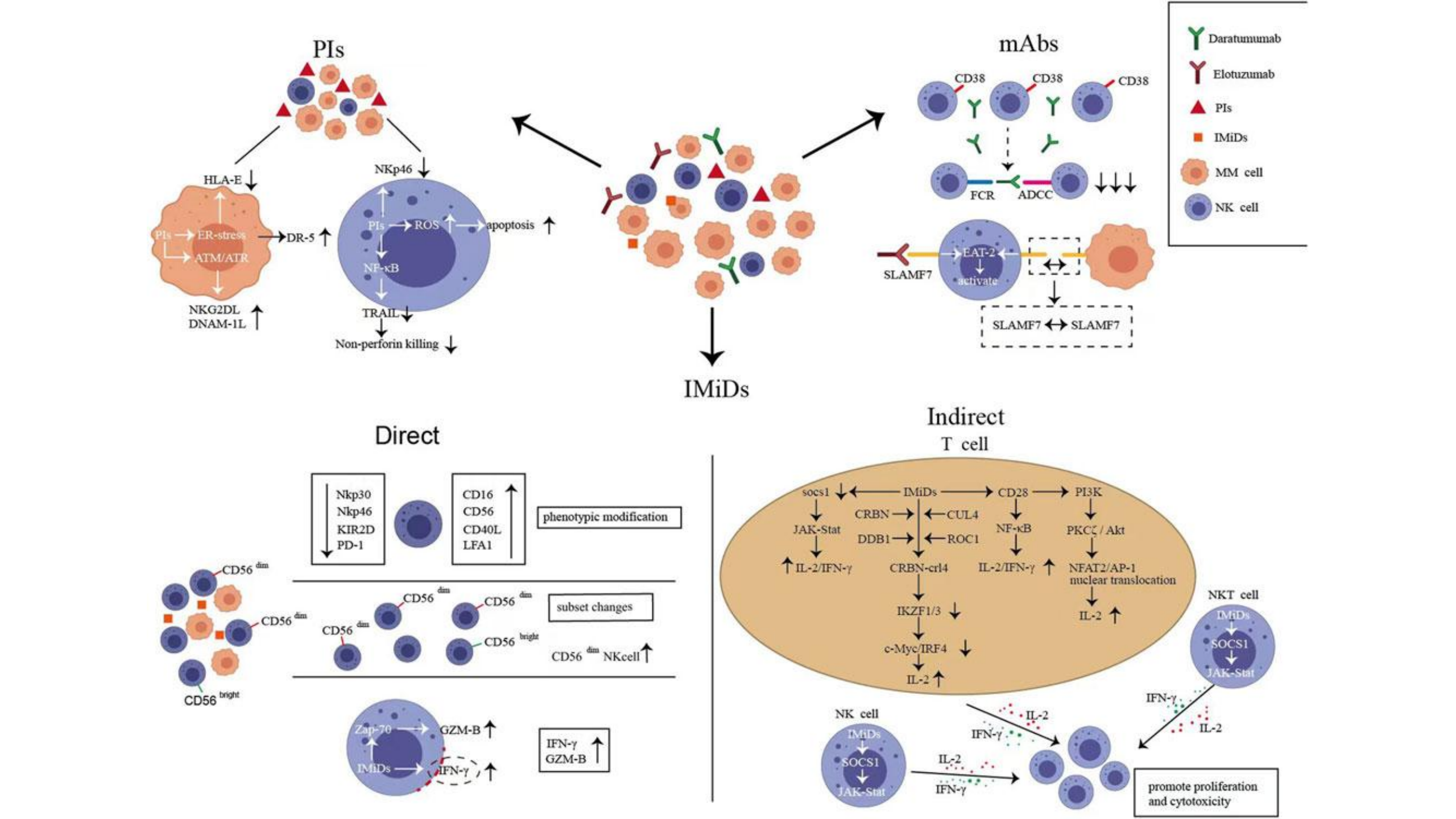
The ***diminished activity*** and ***the reduced number of NK cells*** isolated from advanced-stage MM are associated with adverse prognostic factors

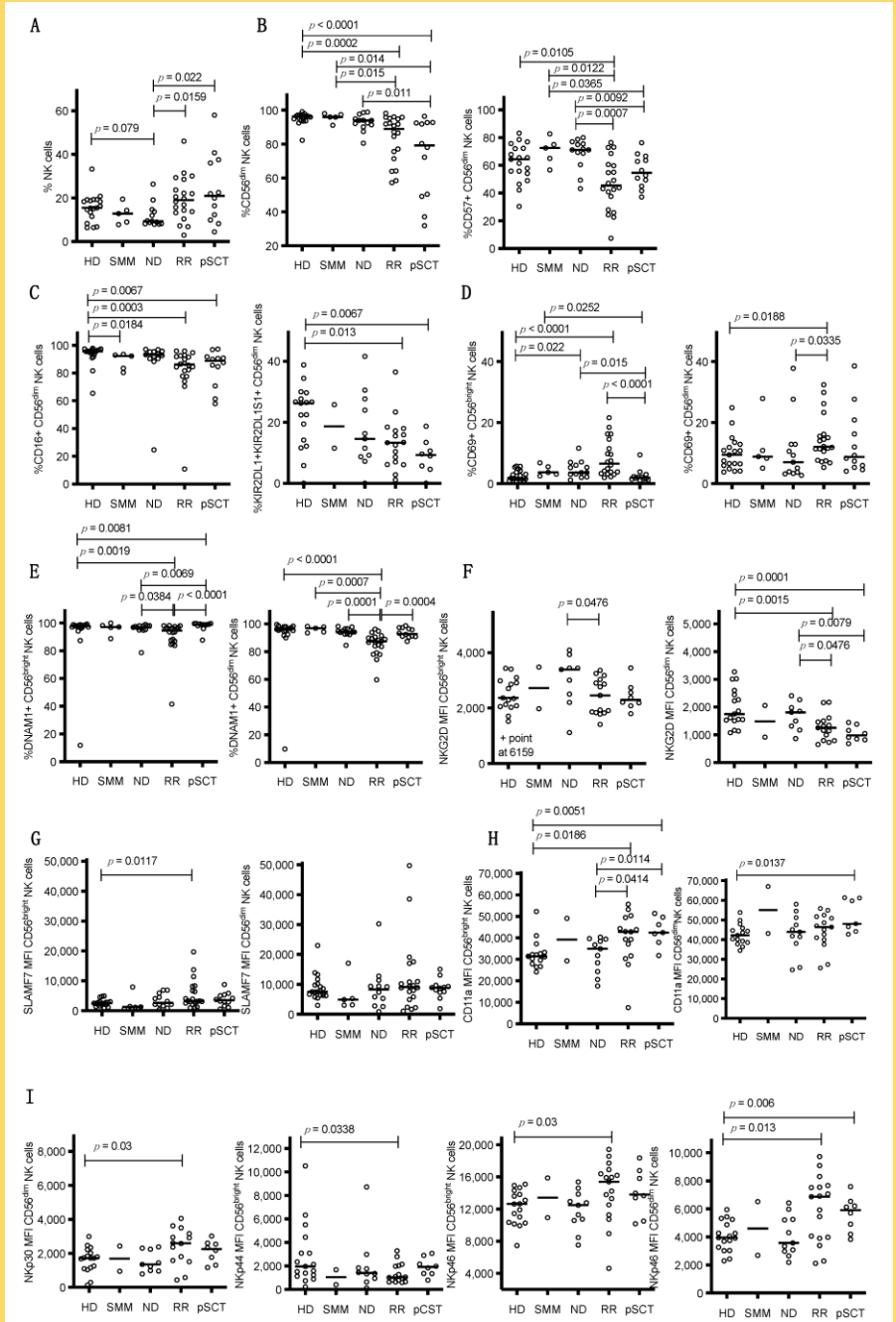

MHC-I ↑
Activating ligand ↓
Immune-evasion
NCR3
NKG2D
2B4
DNAM-1
hypoxia
T-reg
CD16 ↓
CD43
PSGL-1
siglecs-7
SHP-1/2
Jak-Stat3
PD-L1 ↑
↑PD-1
Inhibit
TGF-β
MM cell
NK cell
CXCR3/4 ↓
MDSC
NK cell number ↓
IL-6
IL-10
BM localization ↓
perivascular cell
Osteoblast
BM
CXCR12 ↓
MM cell
MICA
NKG2D ↓
MICA
NKG2DL ↑
NK cell
NKG2DL ↔ NKG2D



After progression to active MM, NK cells are progressively depleted, with a decrease in numbers, inhibitory and activating receptor imbalance, functional inhibition, and chemokine imbalance.

Severe imbalance of activating and inhibiting receptors leads to functional inhibition.


PIs
HLA-E
PIs
ER-stress
ATM/ATR
DR-5
NKG2DL
DNAM-1L
NKp46
PIs
ROS
apoptosis
NF-κB
TRAIL
Non-perforin killing
IMiDs
mAbs
CD38
CD38
CD38
FCR
ADCC
SLAMF7
EAT-2
activate
SLAMF7
SLAMF7
SLAMF7
Daratumumab
Elotuzumab
PIs
IMiDs
MM cell
NK cell
Direct
Nkp30
Nkp46
KIR2D
PD-1
CD16
CD56
CD40L
LFA1
phenotypic modification
CD56 dim
CD56 dim
CD56 bright
CD56 dim
CD56 dim
CD56 dim
CD56 bright
subset changes
CD56 dim NKcell
Zap-70
GZM-B
IMiDs
IFN-γ
IFN-γ
GZM-B
Indirect
T cell
socs1
IMiDs
CD28
PI3K
JAK-Stat
CRBN
CUL4
DDB1
ROC1
NF-κB
PKCζ / Akt
IL-2/IFN-γ
CRBN-crl4
IL-2/IFN-γ
NFAT2/AP-1
nuclear translocation
IKZF1/3
IL-2
c-Myc/IRF4
IL-2
NKT cell
IMiDs
SOCS1
JAK-Stat
IFN-γ
IL-2
NK cell
IMiDs
SOCS1
JAK-Stat
IL-2
IFN-γ
IL-2
IFN-γ
promote proliferation
and cytotoxicity

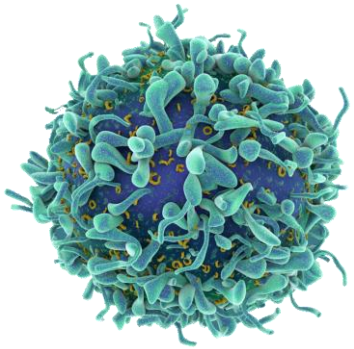


- The quantitative profile (number and fitness) of NK cells in MM is different from that under normal homeostatic conditions.
- High activity and increased number of NK cells correlate with lower tumor burden.
- A higher number of and more active NK cells exist in PB during early-stage MM (MGUS) than during later stages as disease progresses

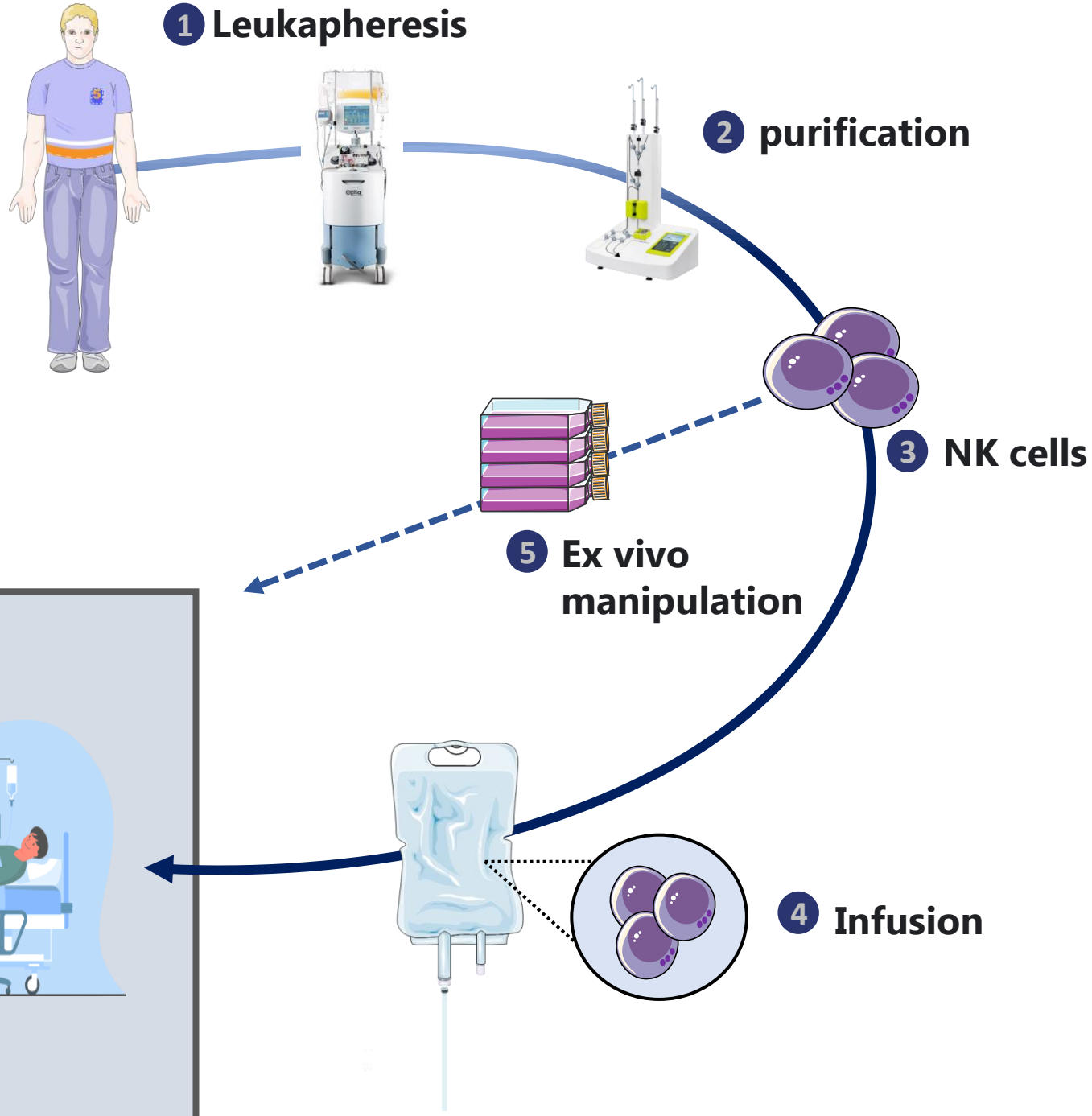
Safety and efficacy of haplo-identical mismatched NK cells for high-risk multiple myeloma patients in the setting of autologous stem cell transplantation

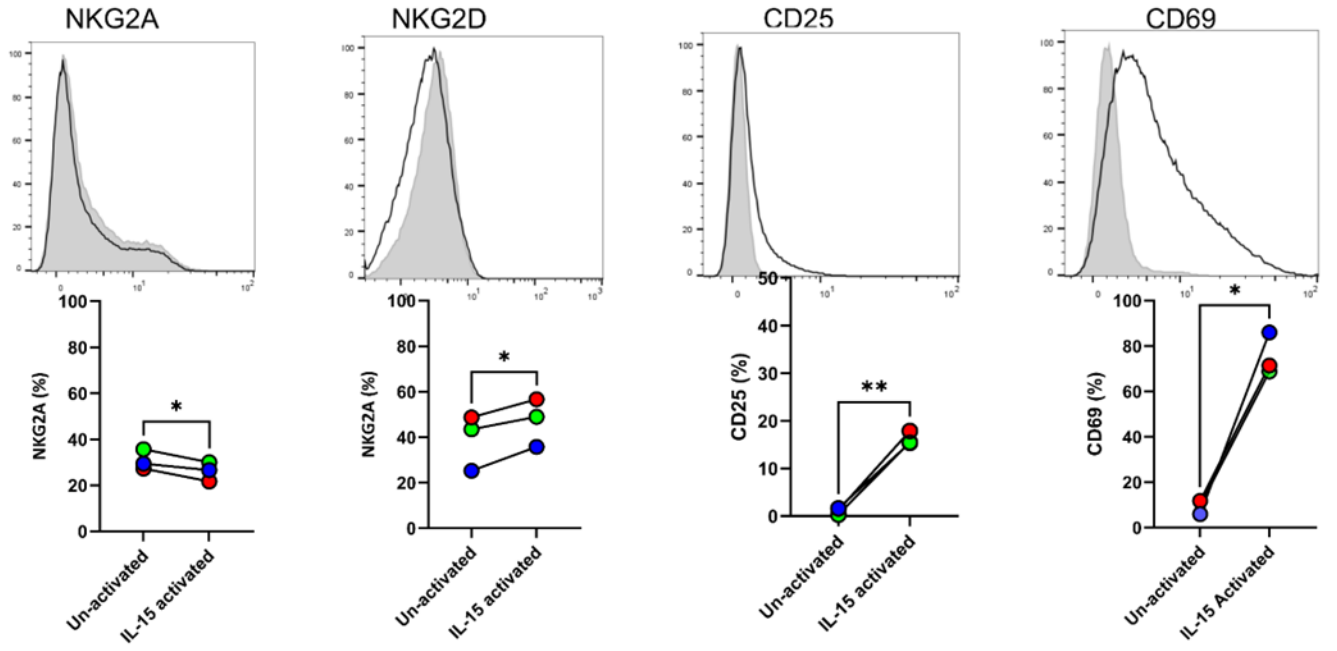
Safety and efficiency of allogenic natural killer cell therapy in relapsed/refractory multiple myeloma and high-risk multiple myeloma patients

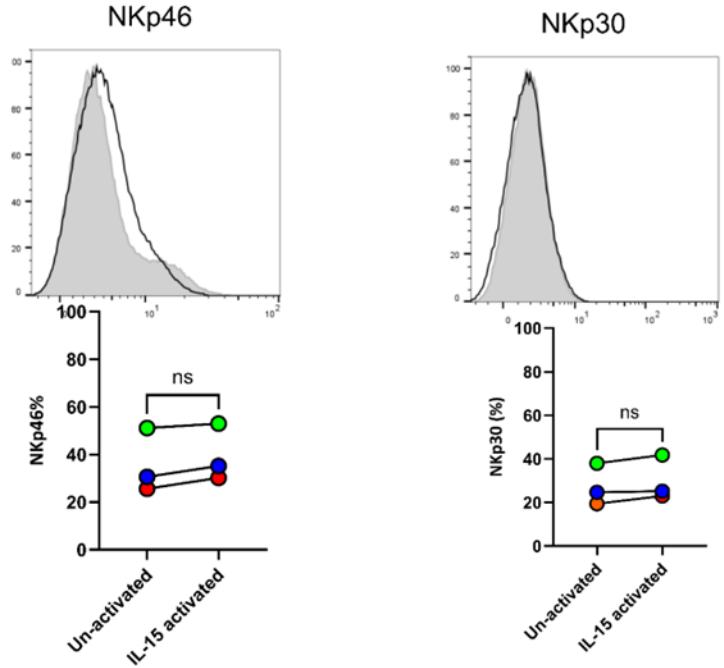
Efficacy of allogeneic natural killer cell therapy in combination with medicinal treatment relapsed/refractory multiple myeloma and high-risk multiple myeloma patients



Overview of What We Did...







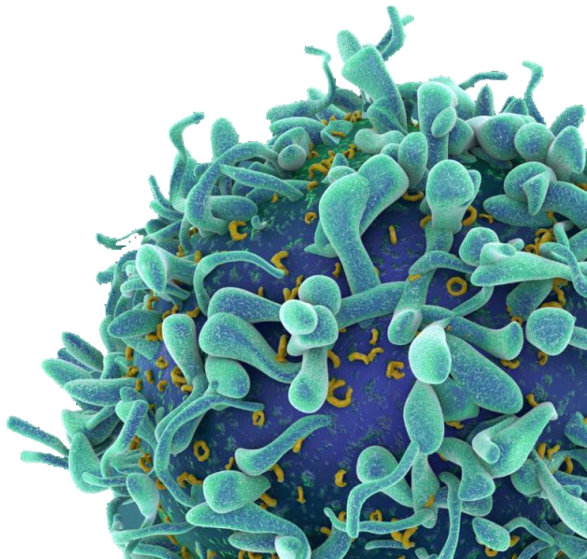
Un-activated

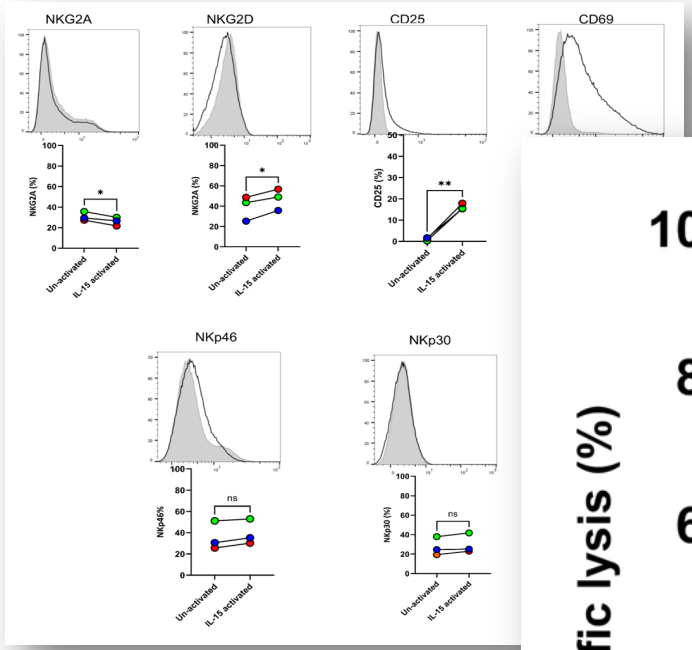
IL-15-activated

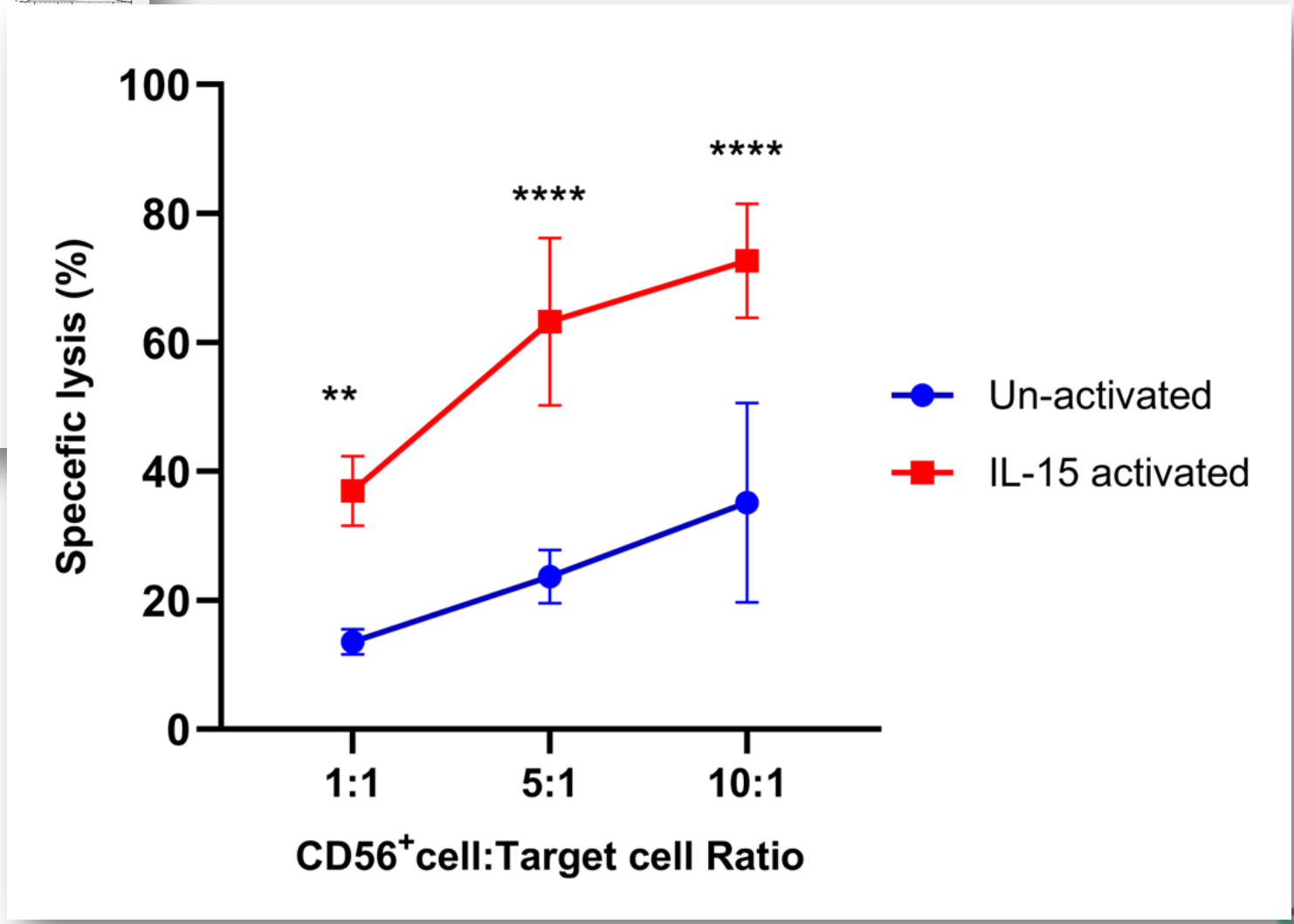
Donor 1

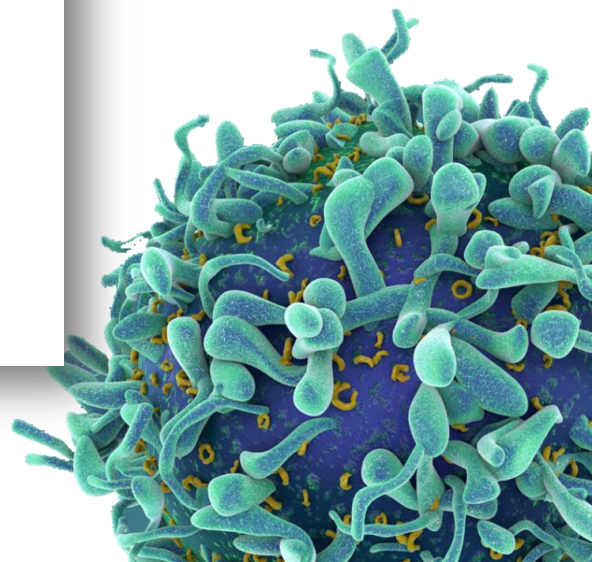
Donor 2

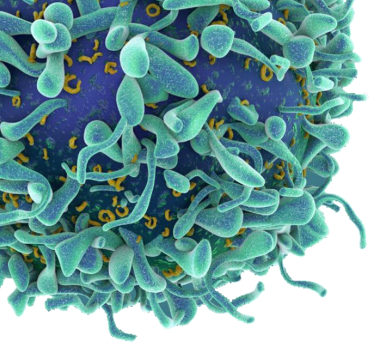
Donor 3




NKG2A
NKG2D
CD25
CD69
NKG2A (%)
NKG2A (%)
CD25 (%)
*
*
**
Un-activated
IL-15 activated
NKp46
NKp30
Nkp46%
Nkp30 [%]
ns
ns


Specefic lysis (%)
100
80
60
40
20
0
**
****
****
1:1
5:1
10:1
CD56+cell:Target cell Ratio
Un-activated
IL-15 activated

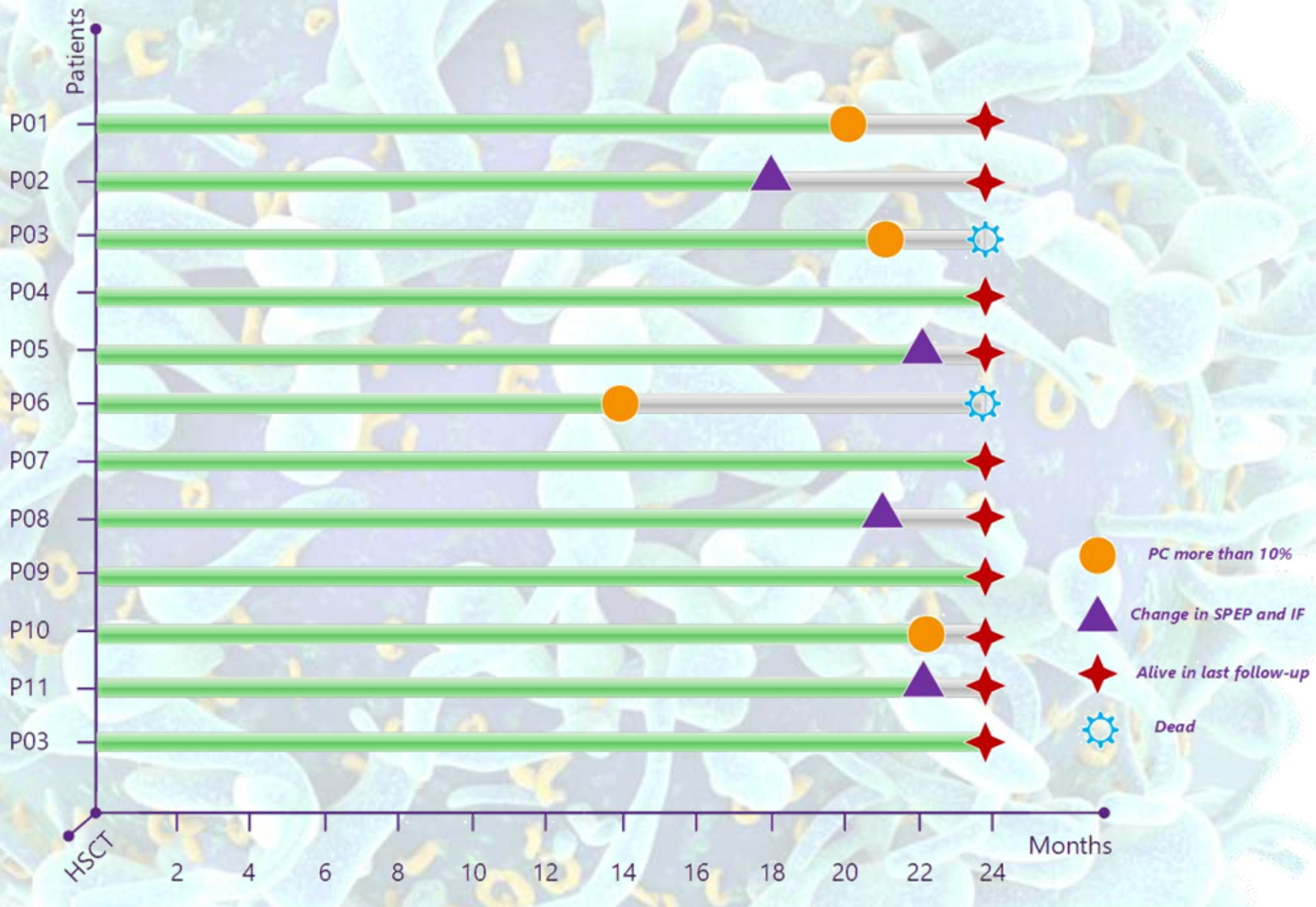


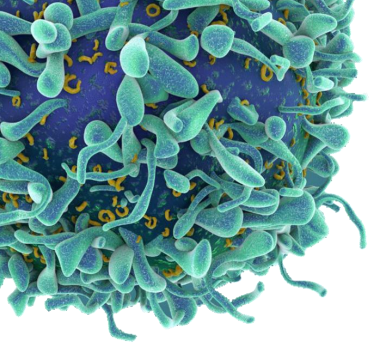


Safety and efficacy of haplo-identical mismatched NK cells for high-risk multiple myeloma patients in the setting of autologous stem cell transplantation

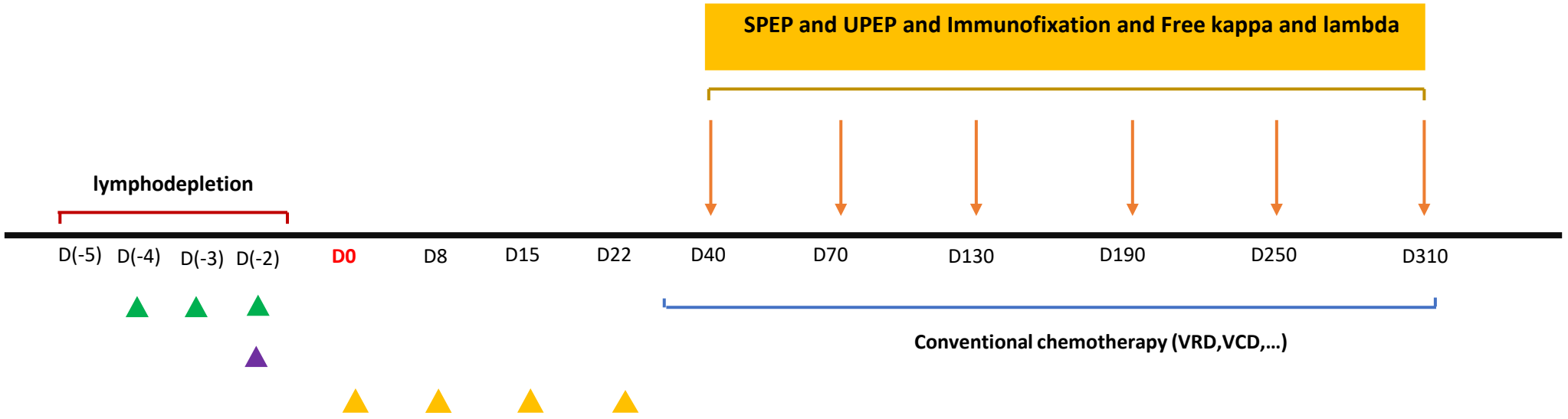
▲ NK cell infusion (escalating dose)

▲ Melphalan (200 mg/m2)


Patients
P01
P02
P03
P04
P05
P06
P07
P08
P09
P10
P11
P03
HSCT
2
4
6
8
10
12
14
16
18
20
22
24
Months
PC more than 10%
Change in SPEP and IF
Alive in last follow-up
Dead



Safety and efficiency of allogenic natural killer cell therapy in relapsed/refractory multiple myeloma and high-risk multiple myeloma patients

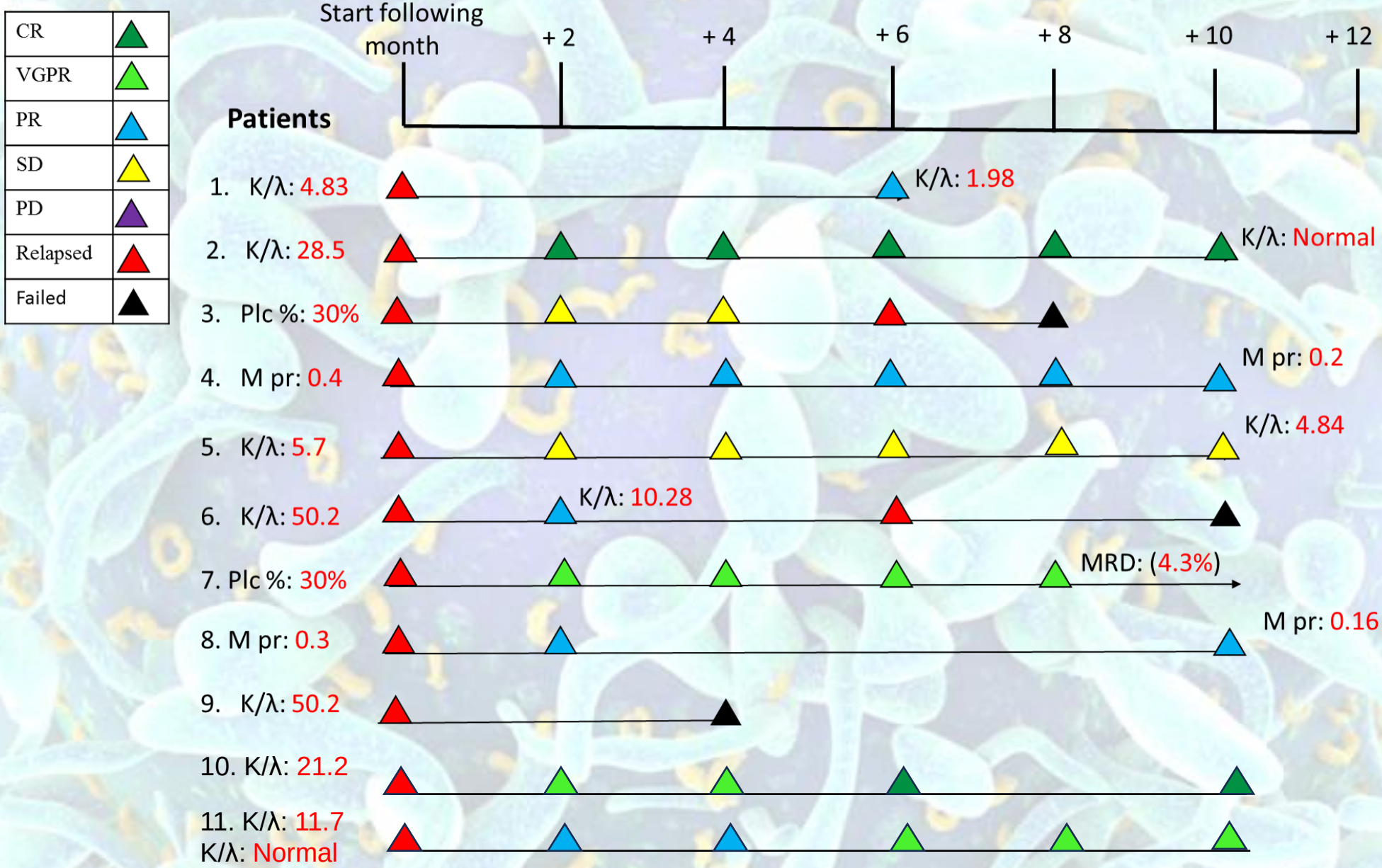


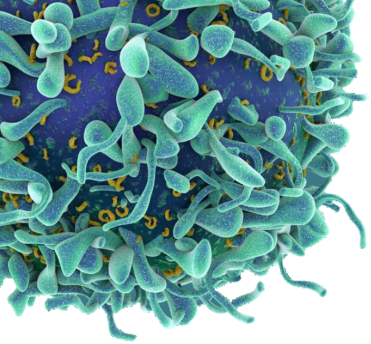
NK cell infusion (escalating dose)

Fludarabin (25 mg/m2)

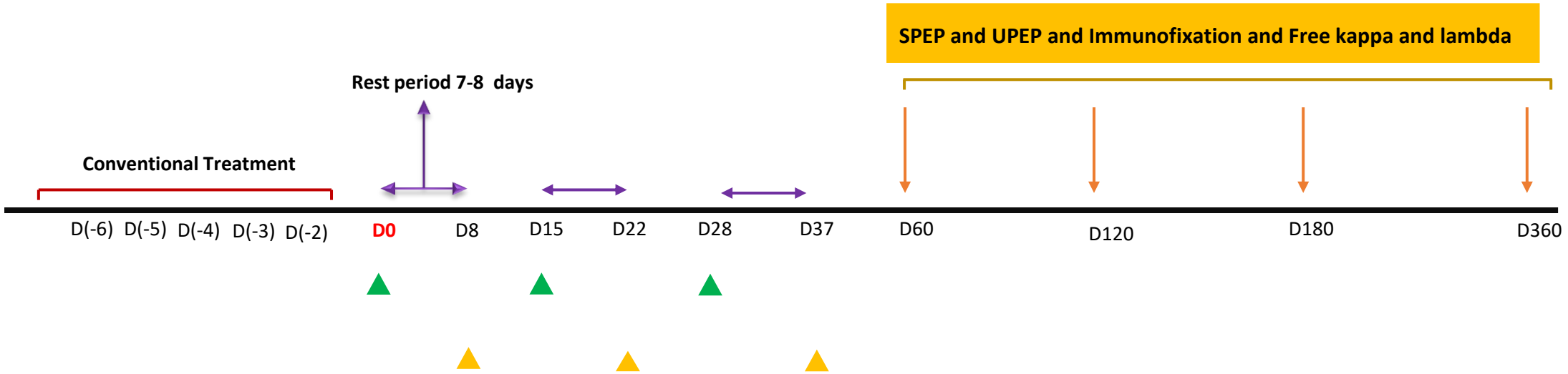
Cyclophosphamide (500 mg)

NK therapy in High Risk Multiple Myeloma patients



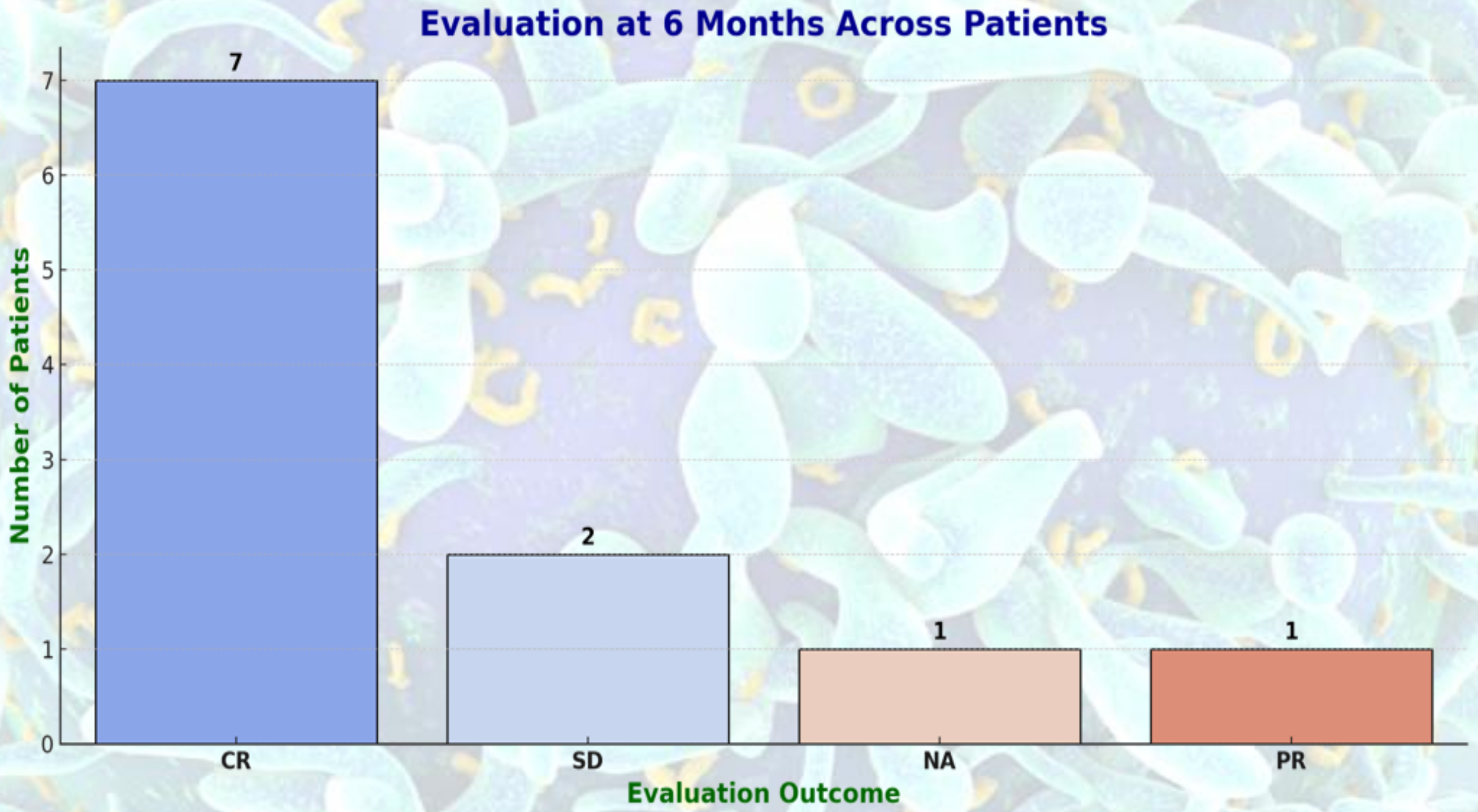


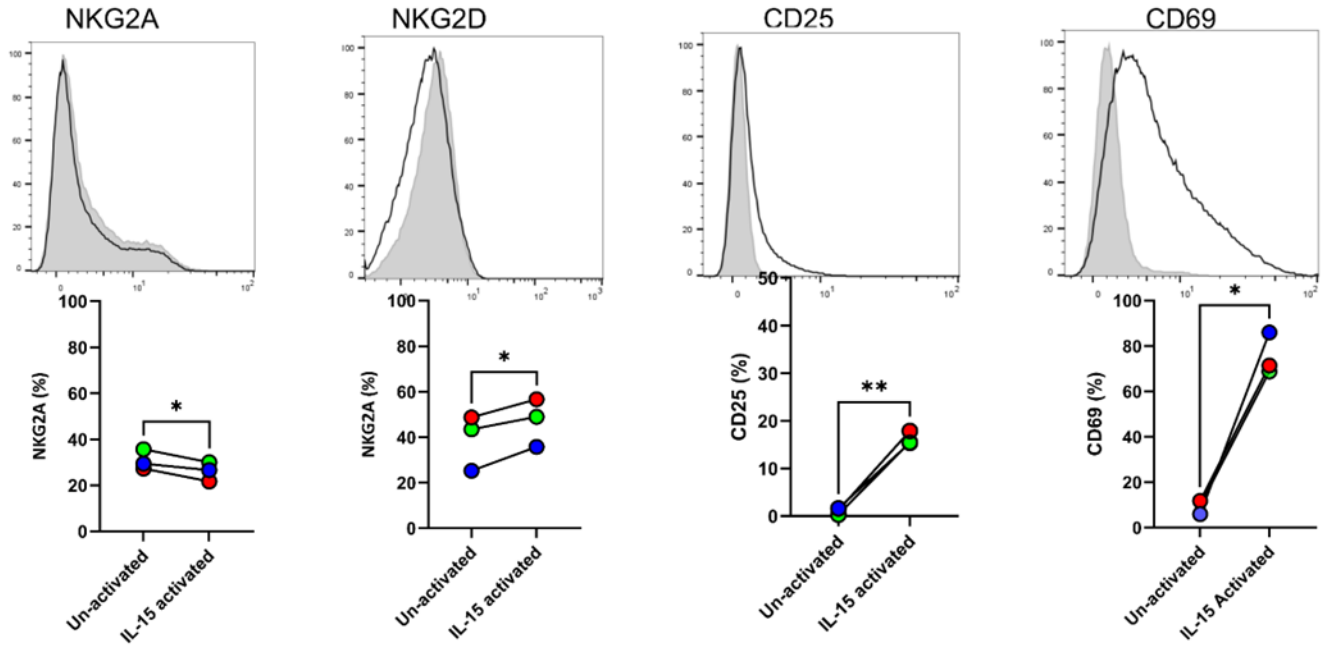
Efficacy of allogeneic natural killer cell therapy in combination with medicinal treatment relapsed/refractory multiple myeloma and high-risk multiple myeloma patients

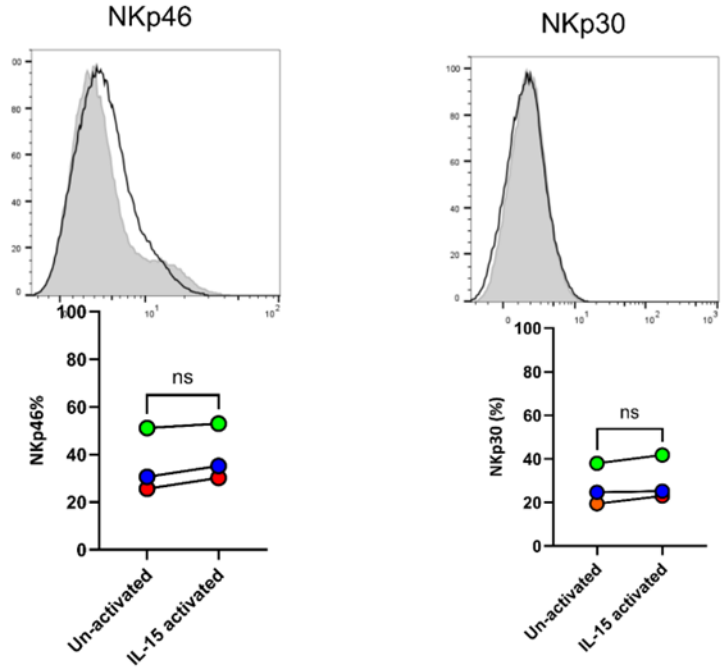


NK cell infusion (escalating dose)

Daratomomab


Evaluation at 6 Months Across Patients
Number of Patients
0
1
2
3
4
5
6
7
7
2
1
1
CR
SD
NA
PR
Evaluation Outcome





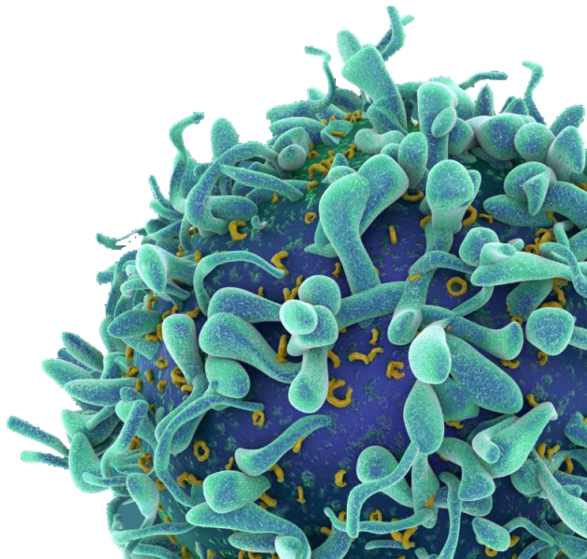
Un-activated

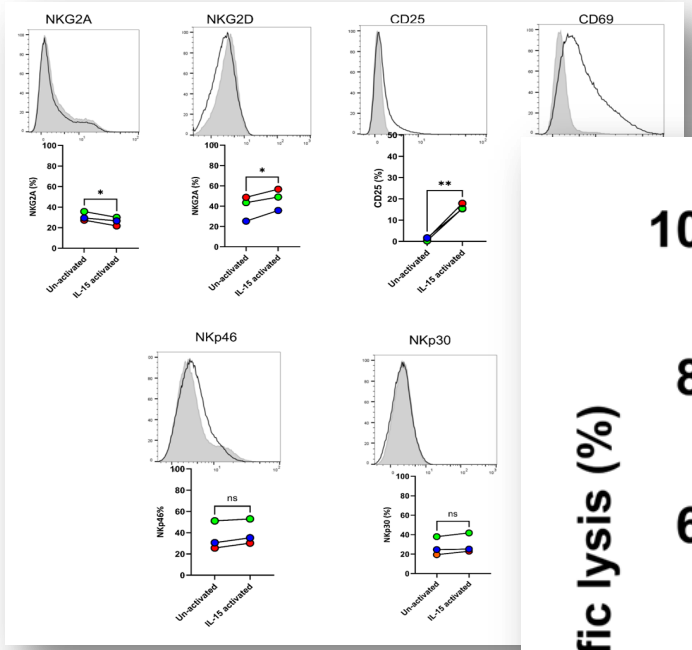
IL-15-activated

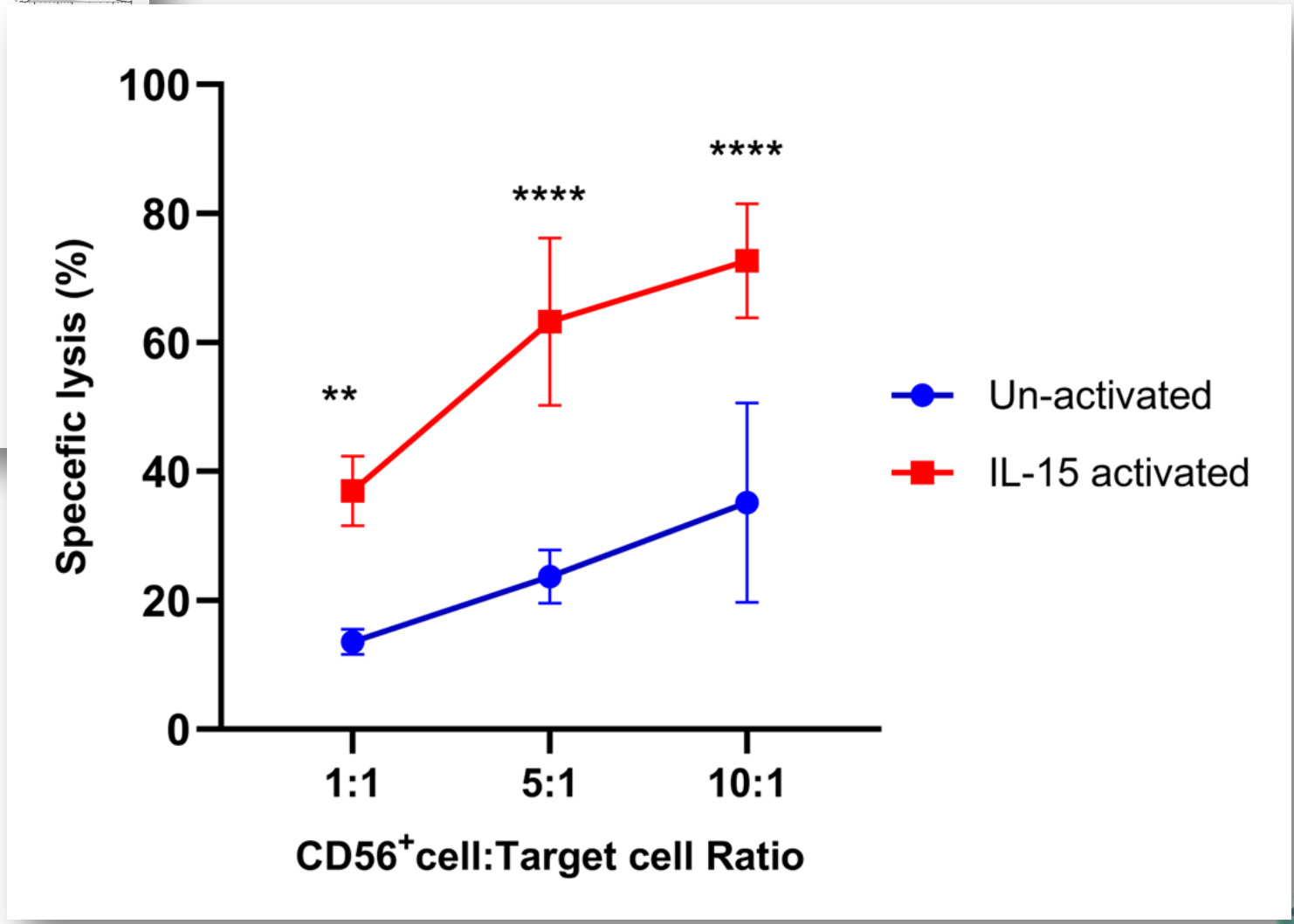
Donor 1

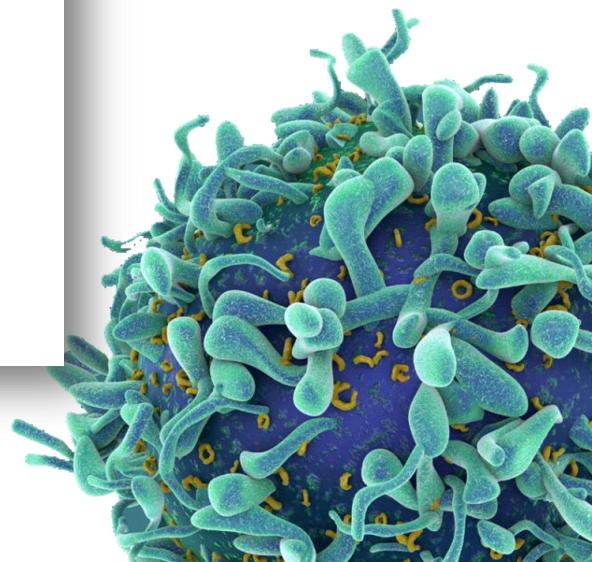
Donor 2

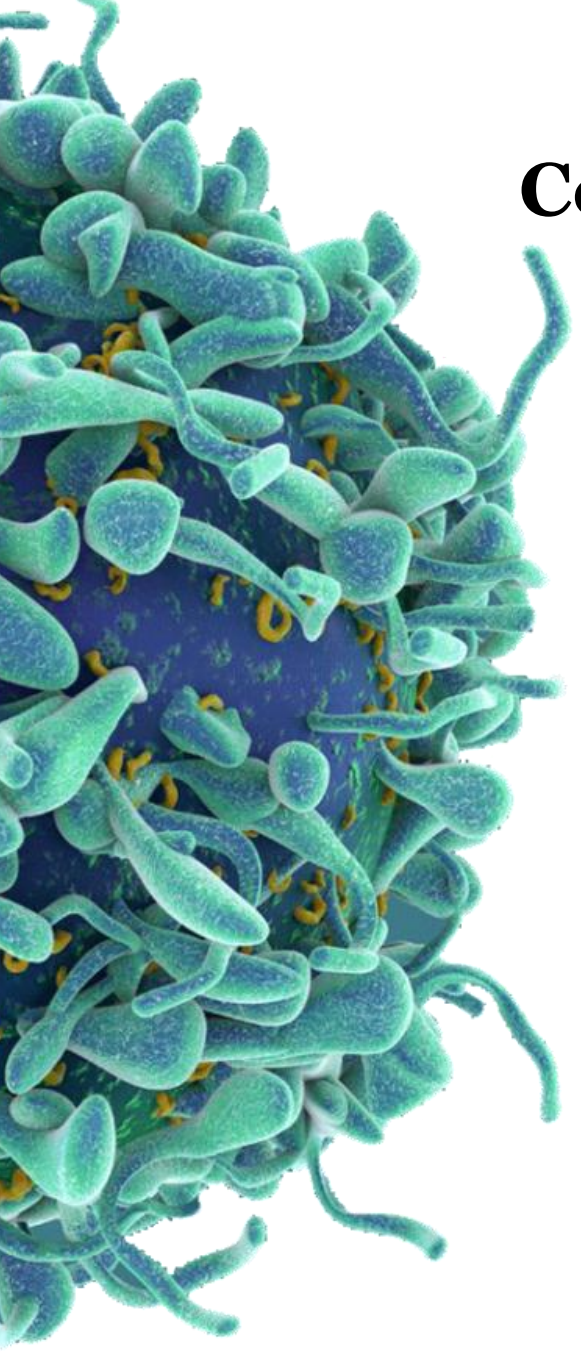
Donor 3




NKG2A
NKG2D
CD25
CD69
NKG2A (%)
NKG2A (%)
CD25 (%)
*
*
**
Un-activated
IL-15 activated
NKp46
NKp30
Nkp46%
Nkp30 [%]
ns
ns


Specefic lysis (%)
100
80
60
40
20
0
**
****
****
1:1
5:1
10:1
CD56+cell:Target cell Ratio
Un-activated
IL-15 activated



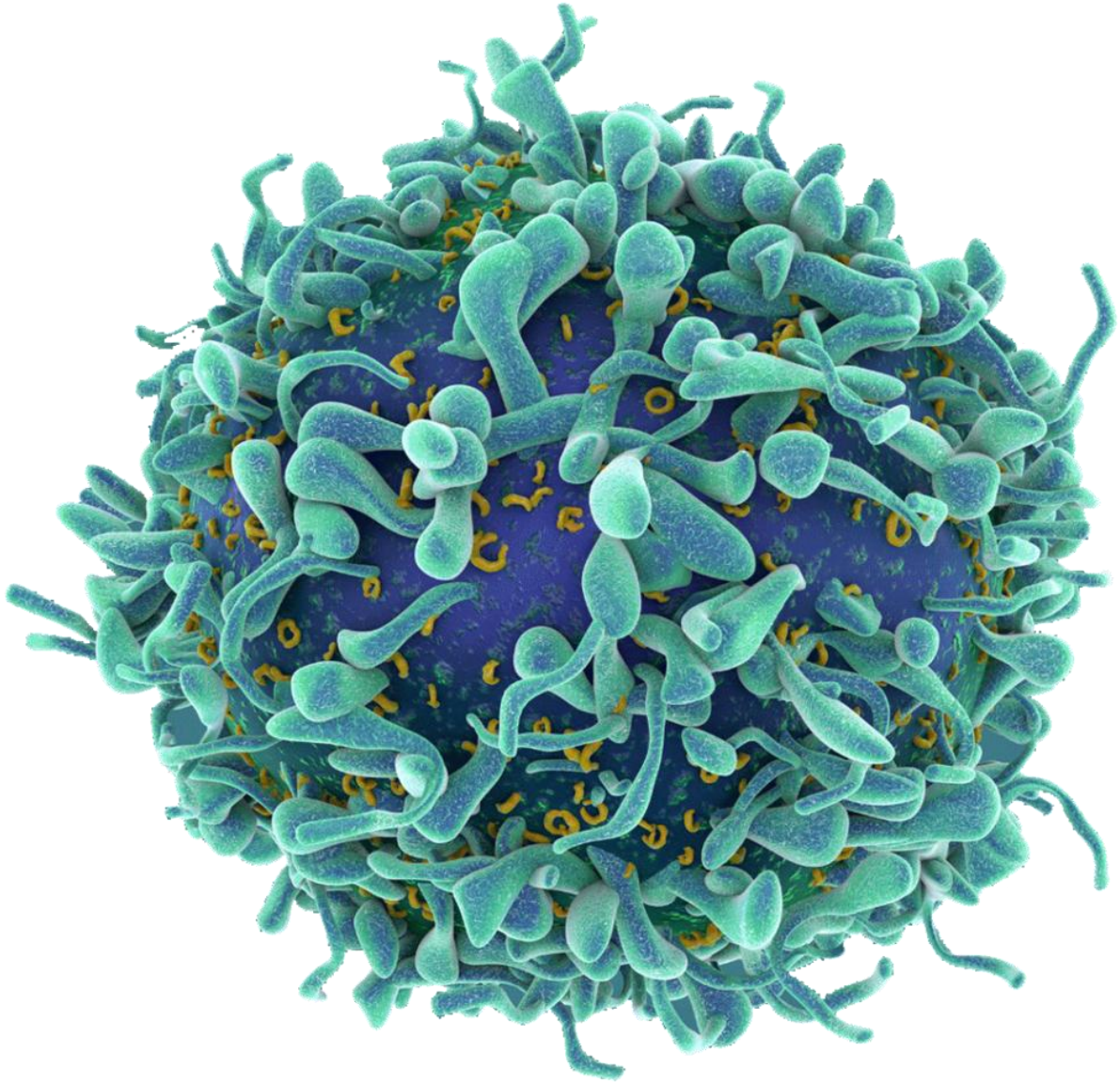


Conclusion

Insights into the control of NK cell function may usher in a new era of NK cell therapy and may offer the prospect of developing effective NK cell therapy for myeloma and other malignancies.

Allogenic NK cells seem safe, plus LEN showed clinical efficacy in MM.

Combination therapy of activated NK cells with immunomodulatory drugs (IMiDs) lenalidomide and pomalidomide , PIs, and monoclonsl antibodies can increase the efficacy.



Thanks for your attention…