



IMS 2025

Translational Research

יעל כהן

מפגש הקבוצה הישראלית למיאלומה

22.10.2025



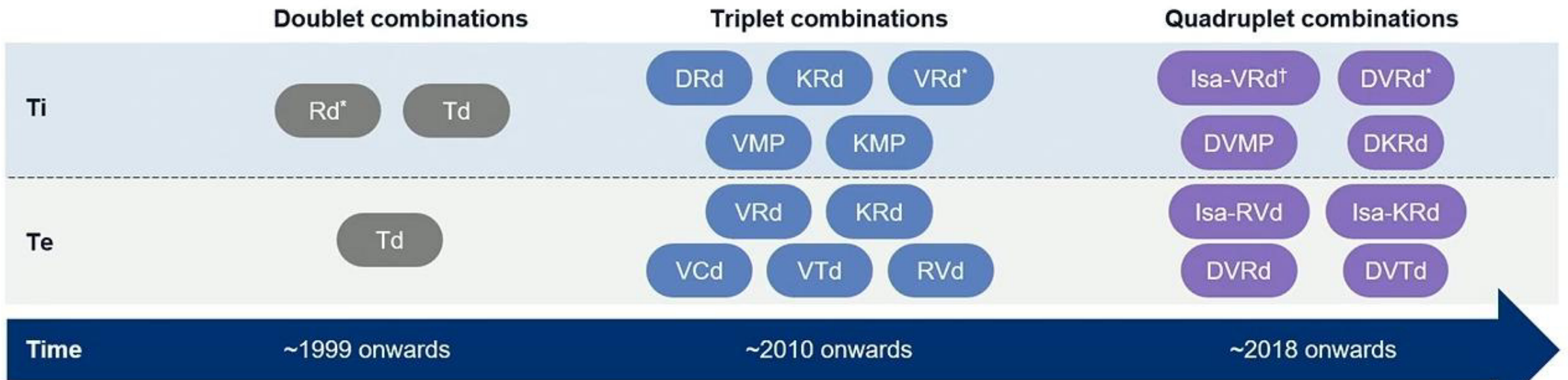
Single-Cell Immune Landscape Associated with Isa-KRD Induction Efficacy in Newly Diagnosed Myeloma

Ludovic Martinet

Cancer Research Center of Toulouse, CHU Toulouse
Intergroupe Francophone du myélome

There will be a time of multiple treatment options

Therapeutic regimens explored in Phase III NDMM trials over time¹⁻⁷

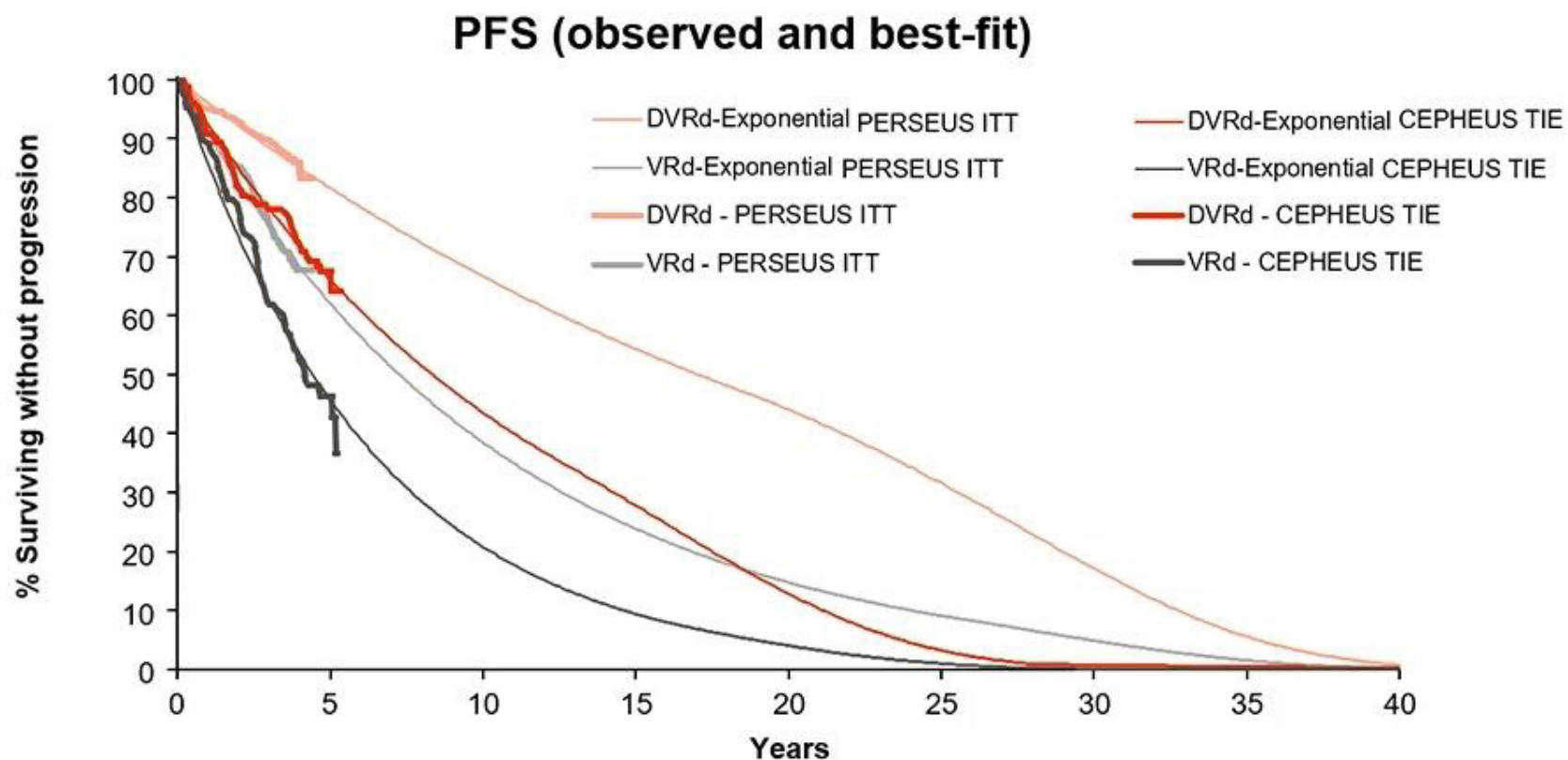


Transplant deferred

CAR-T / TCE

1. Bal S, et al. Am J Hematol 2021;96:367–78; 2. Gay F, et al. ASH 2023; Presentation 4; 3. Mateos MV, et al. ASH 2023; Presentation 209; 4. Mai EK, et al. Leukemia 2015;29:1721–9; 5. Usmani SZ, et al. Nat Med 2025. doi: 10.1038/s41591-024-03485-7. Online ahead of print; 6. Facon T, et al. N Engl J Med 2024;391:1597–609; 7. Leleu X, et al. Nat Med 2024;30:2235–41

There will be a time of median 15y of PFS

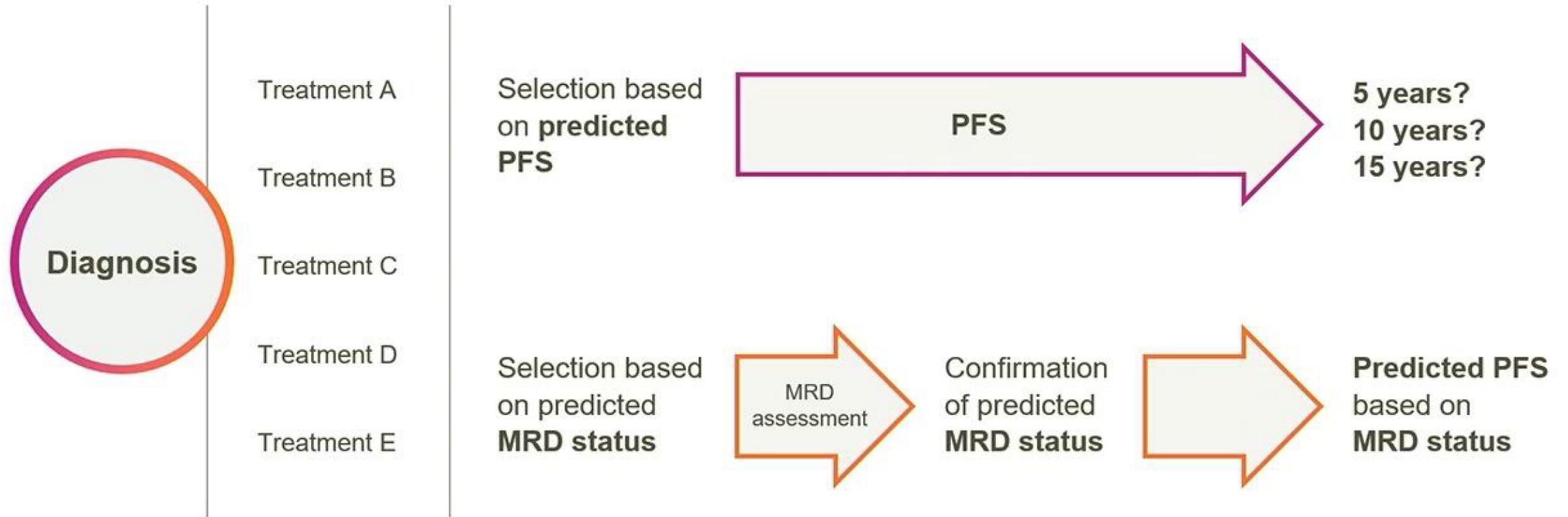


Estimated PFS, DVRd vs VRd

PERSEUS: 205 months (17.1 years) vs 87 months (7.3 years)

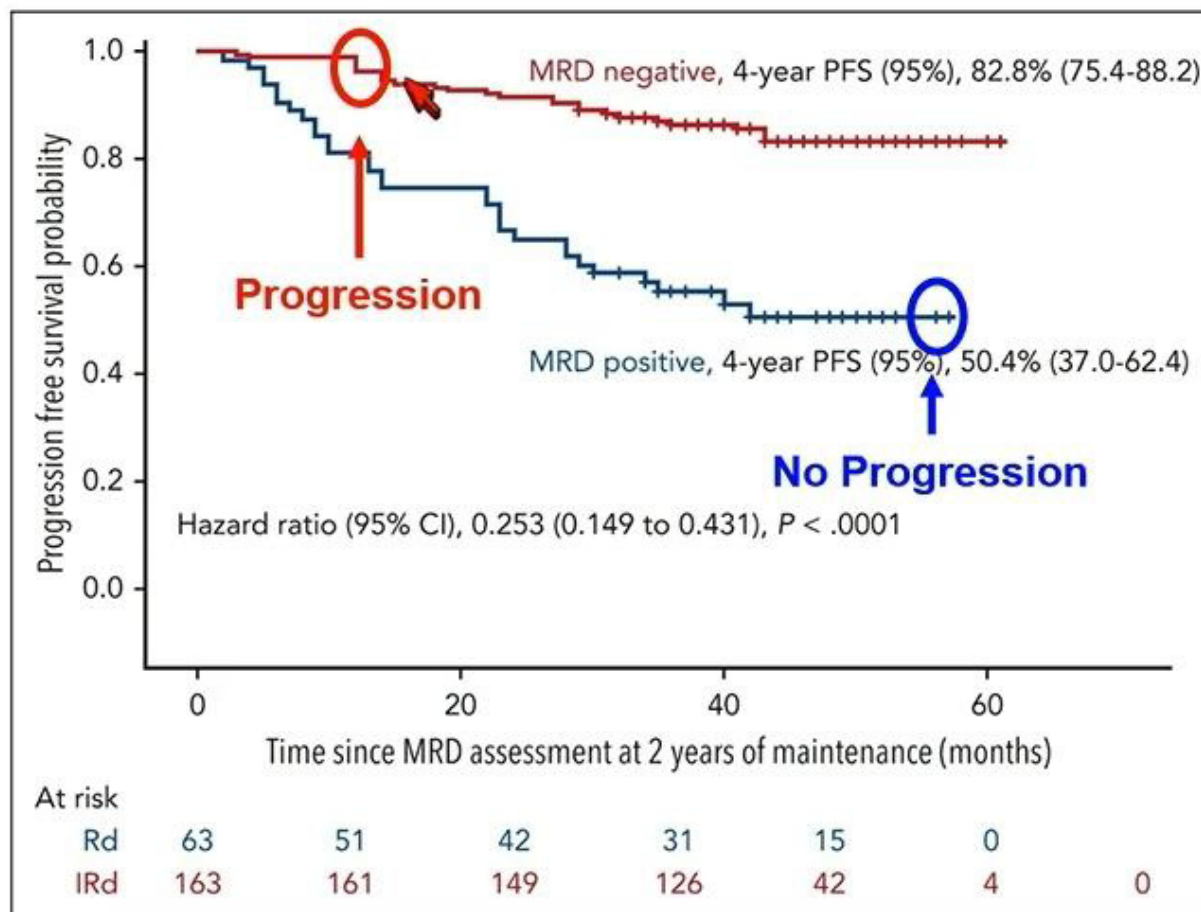
CEPHEUS: 100 months (8.3 years) vs 53 months (4.4 years)

Can we predict MRD outcomes before treatment?



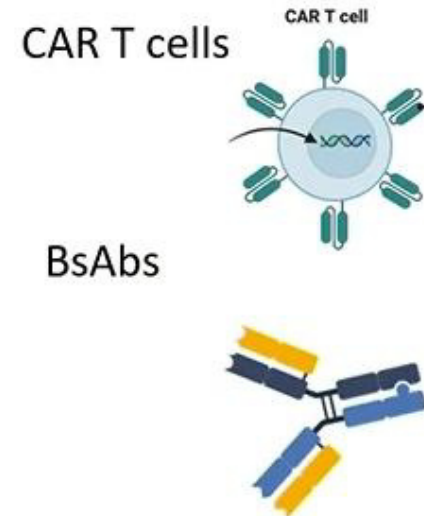
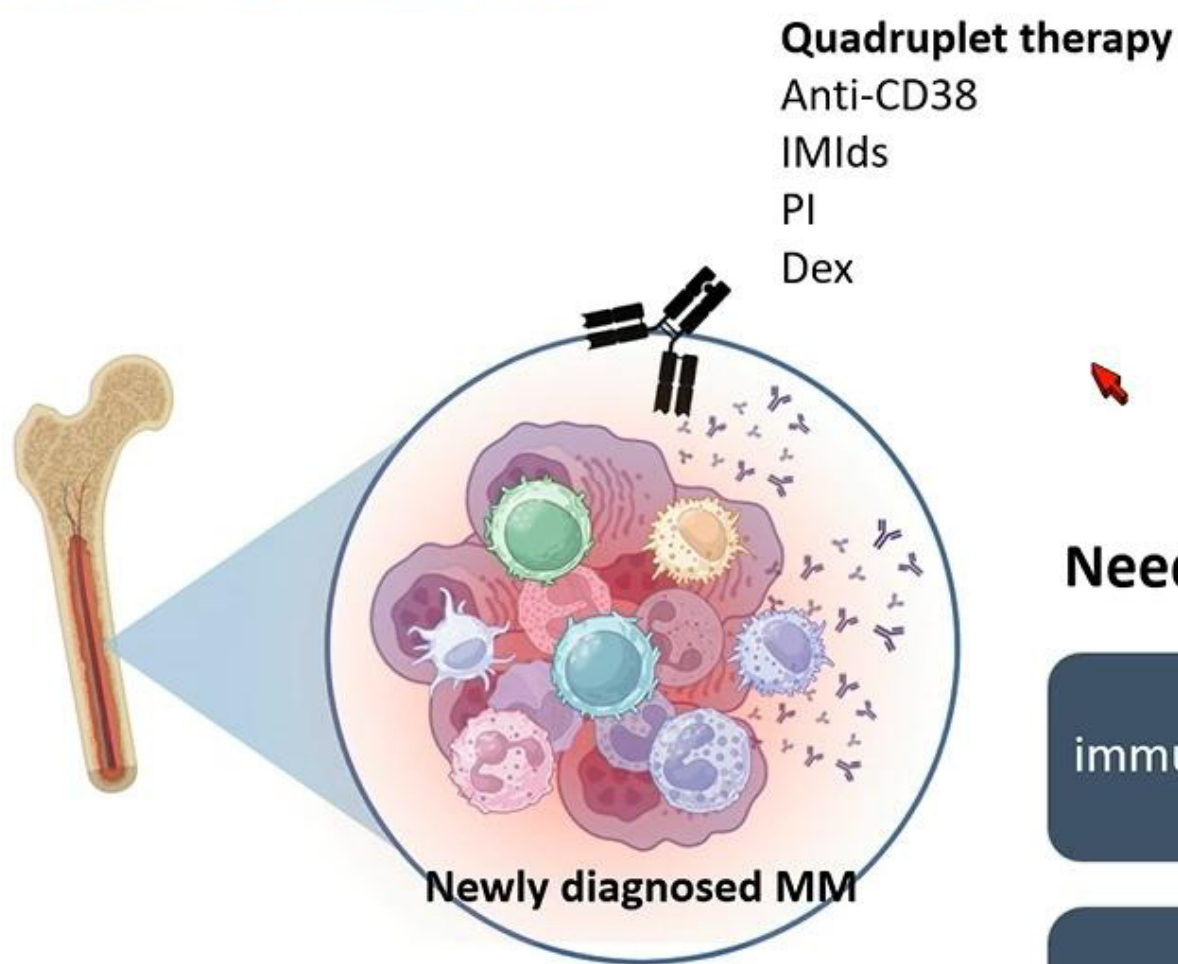
Treatment adaption based on MRD? Promising, but can it be improved by combined MRD & immune monitoring?

Results from GEM2014MAIN



- 
- **The results you will see next may contribute towards individualized induction therapy for improved chances of achieving MRD negativity**
 - **Dr. Martinet and team shed light into immune remodeling during quad induction therapy prior MRD-guided intensification in the IFM MIDAS trial**

MULTIPLE MYELOMA



Need a better understanding :

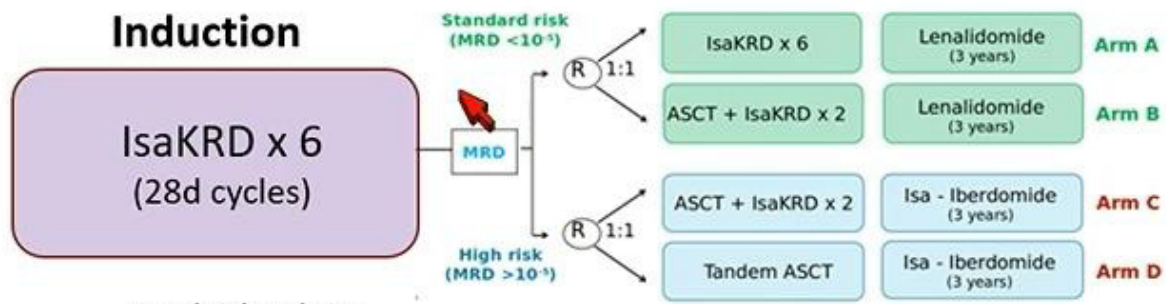
immune determinants of efficacy vs resistance?

The immunological impact of Quadruplet?

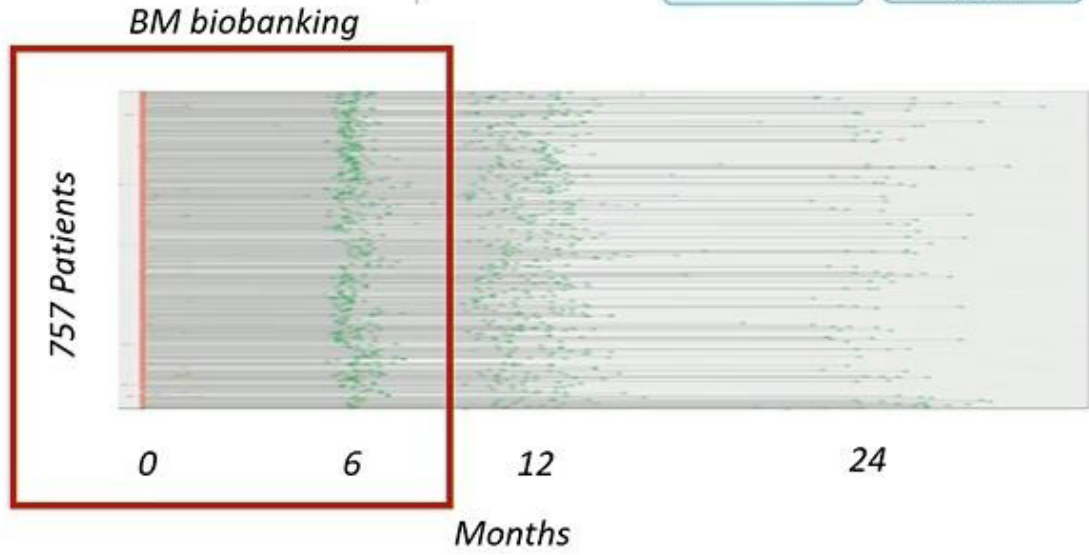
IMMUNE LANDSCAPE ALONG QUADRUPLET THERAPY : THE MIDAS STUDY



= Minimal residual Disease Adapted Strategy

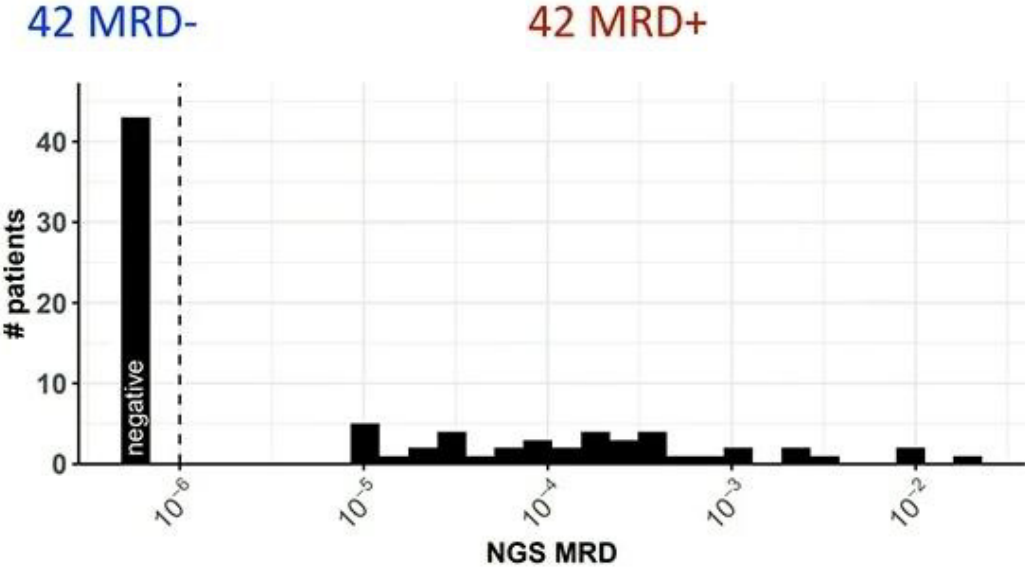
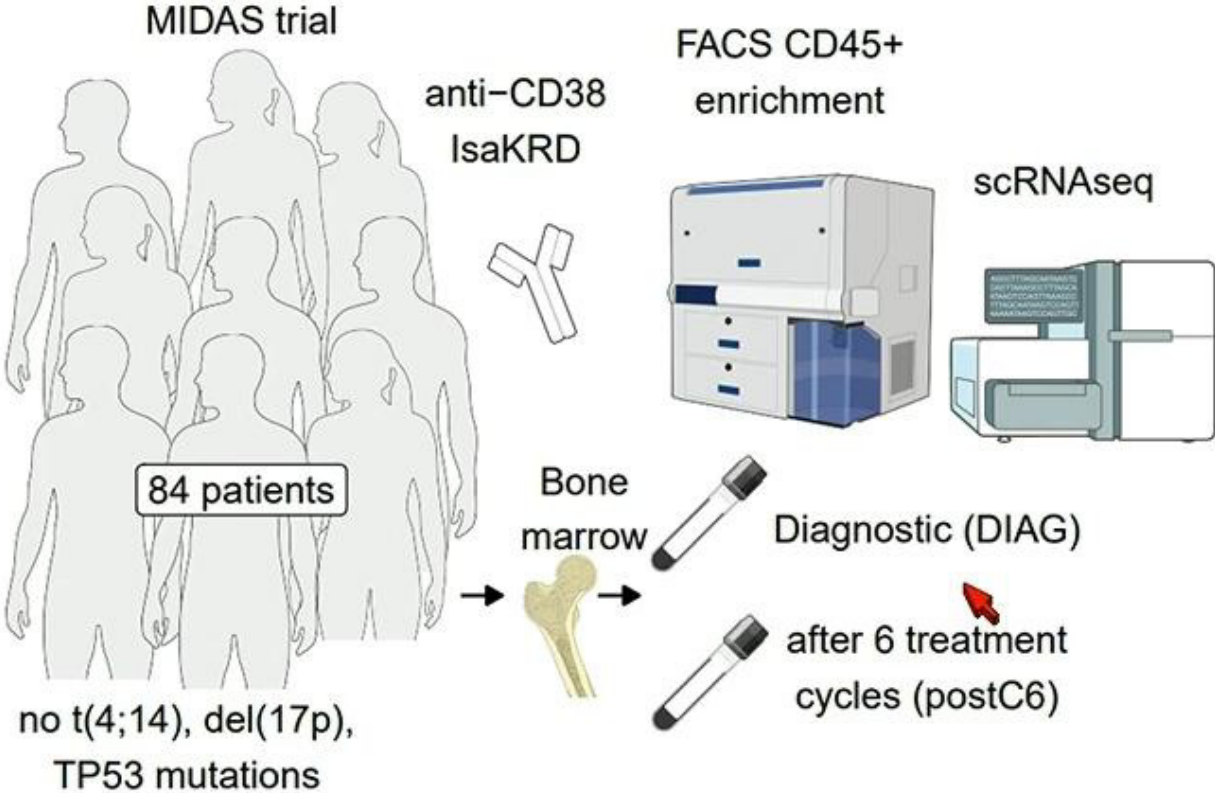


Perrot, Touzeau et al. Blood. 2025
Perrot, Touzeau et al. NEJM 2025

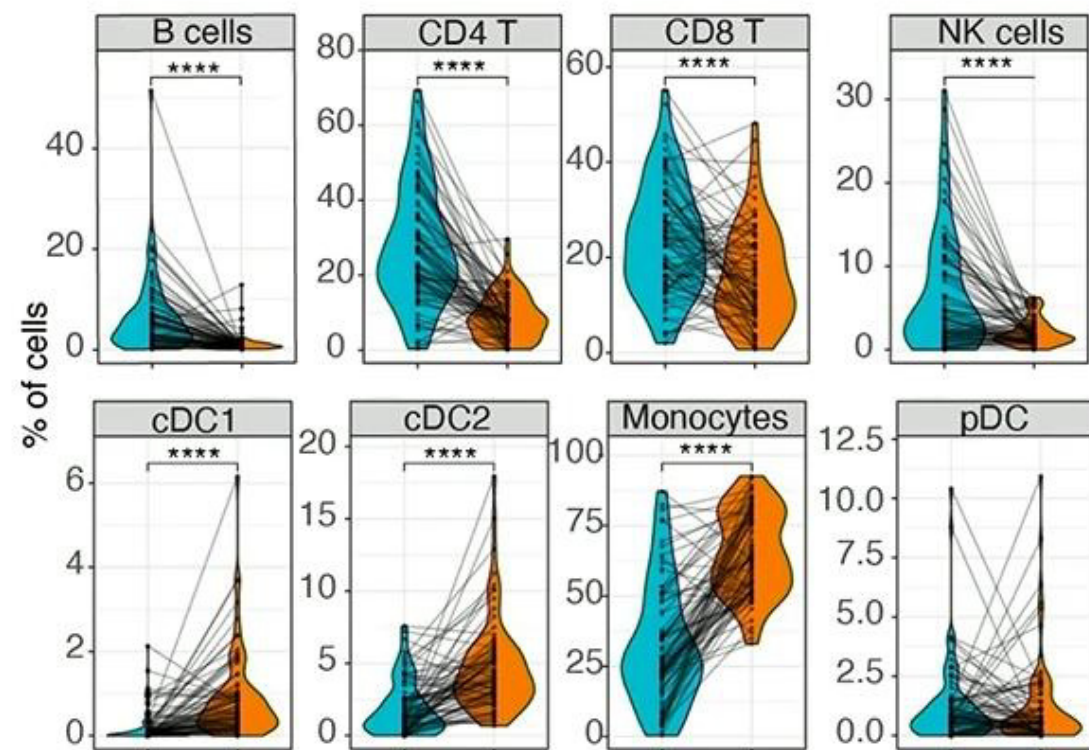
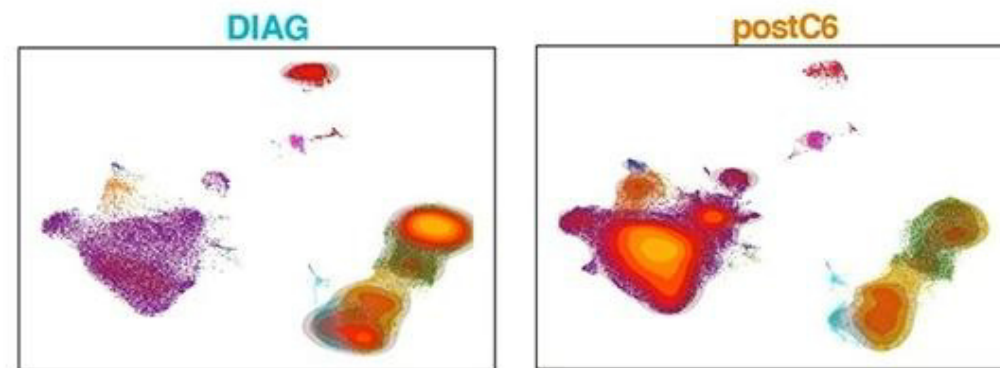
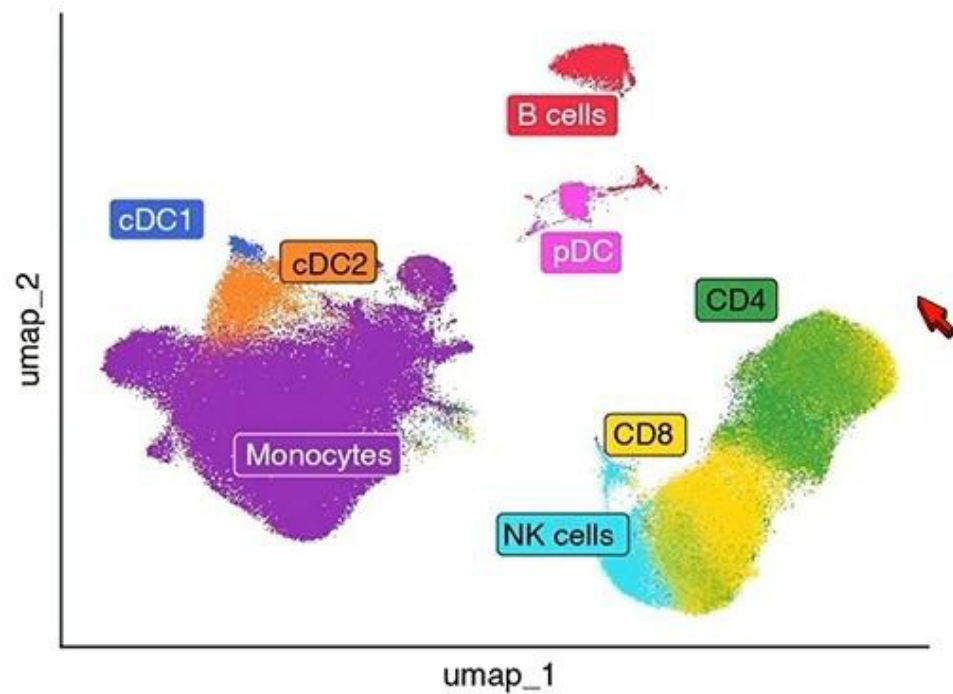


SCRNASEQ ALONG ISAKRD INDUCTION

- 10x SCRNAseq GEX and 5' TCR seq

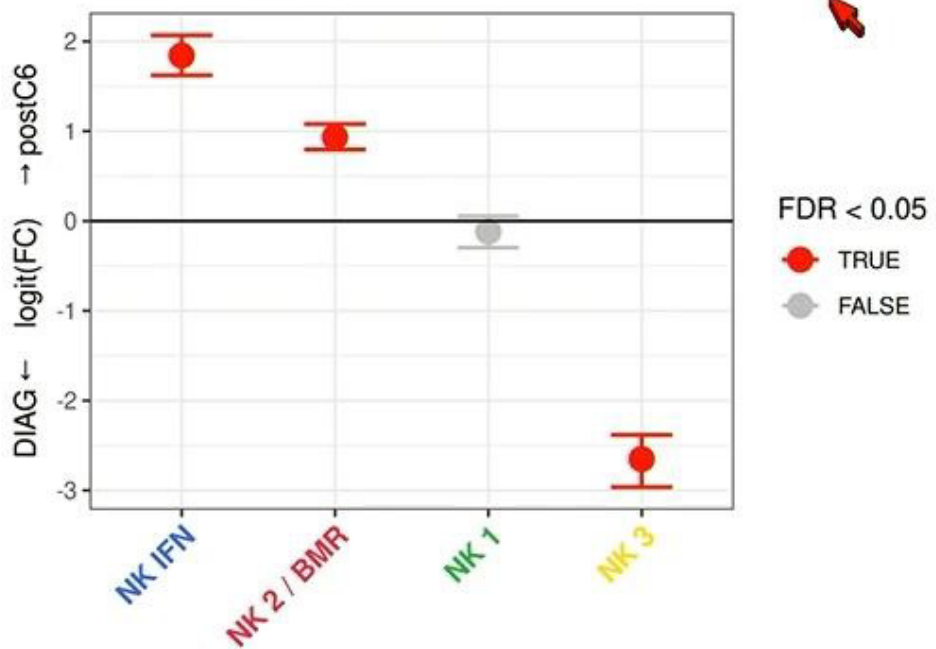
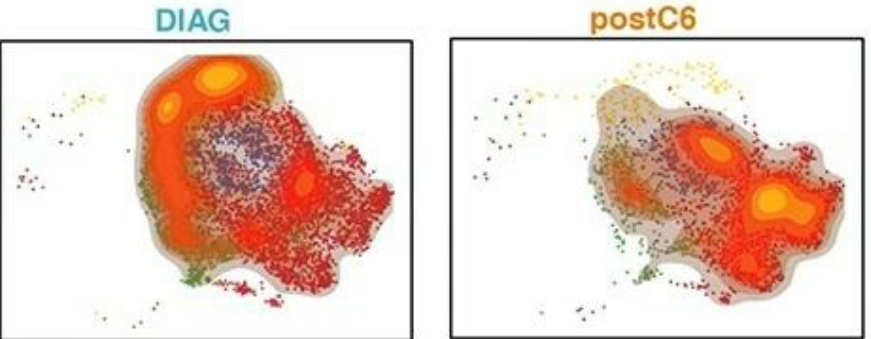
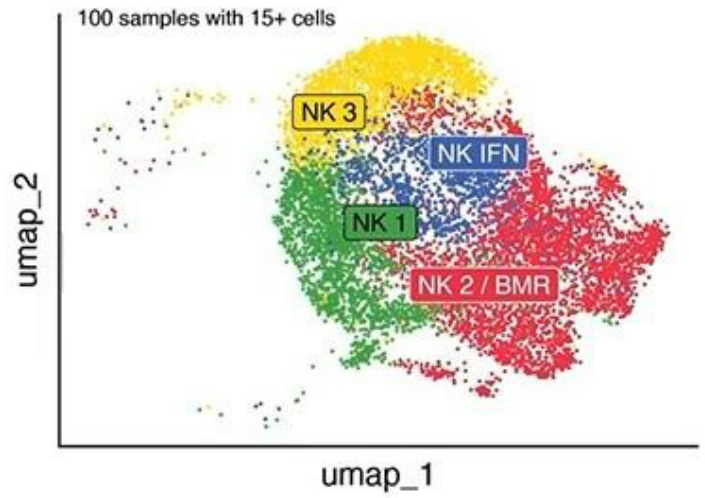


ISA-KRD INDUCES PROFOUND IMMUNE REMODELING

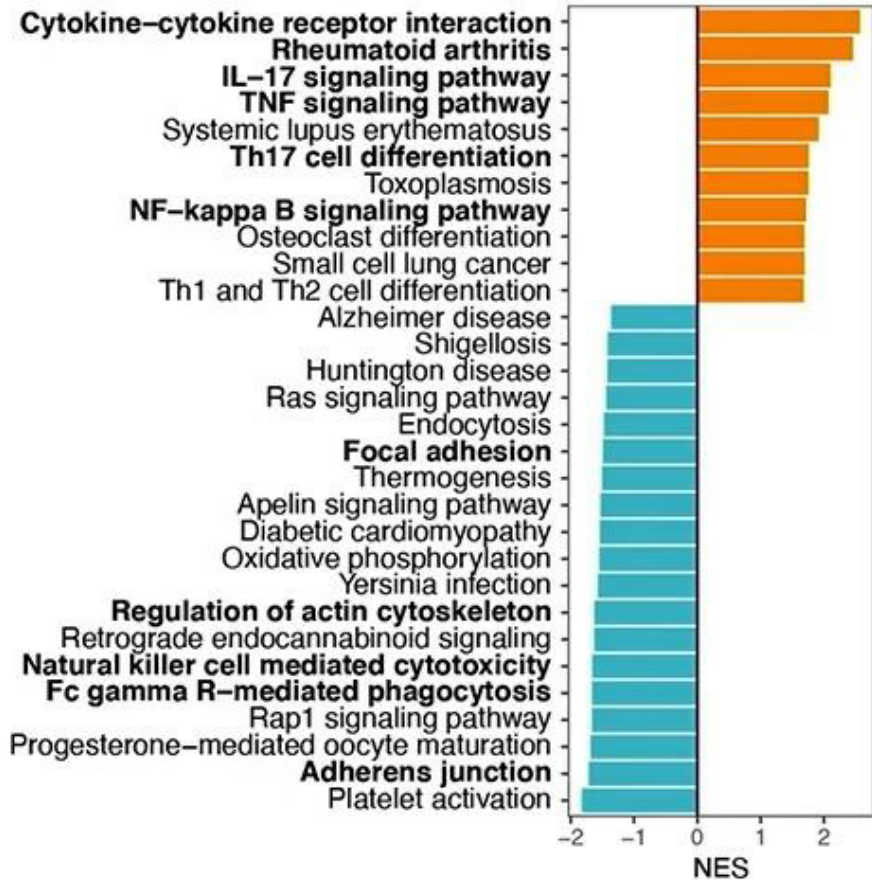
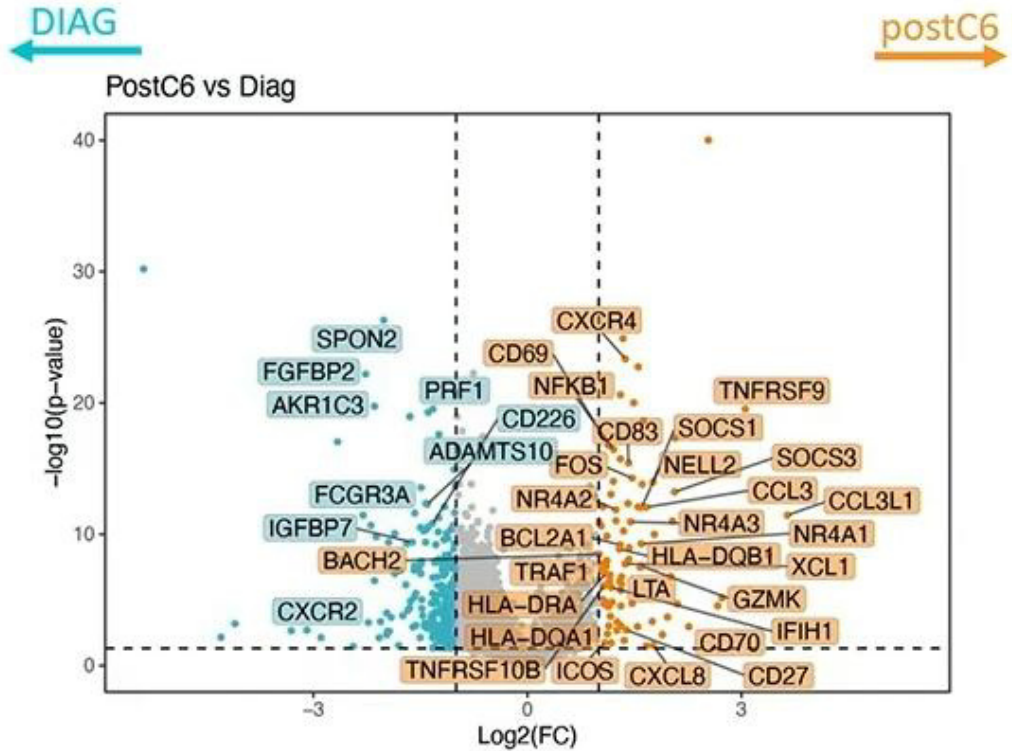


timepoint
DIAG
postC6

CHANGES IN NK CELL LANDSCAPE INDUCED BY ISA-KRD

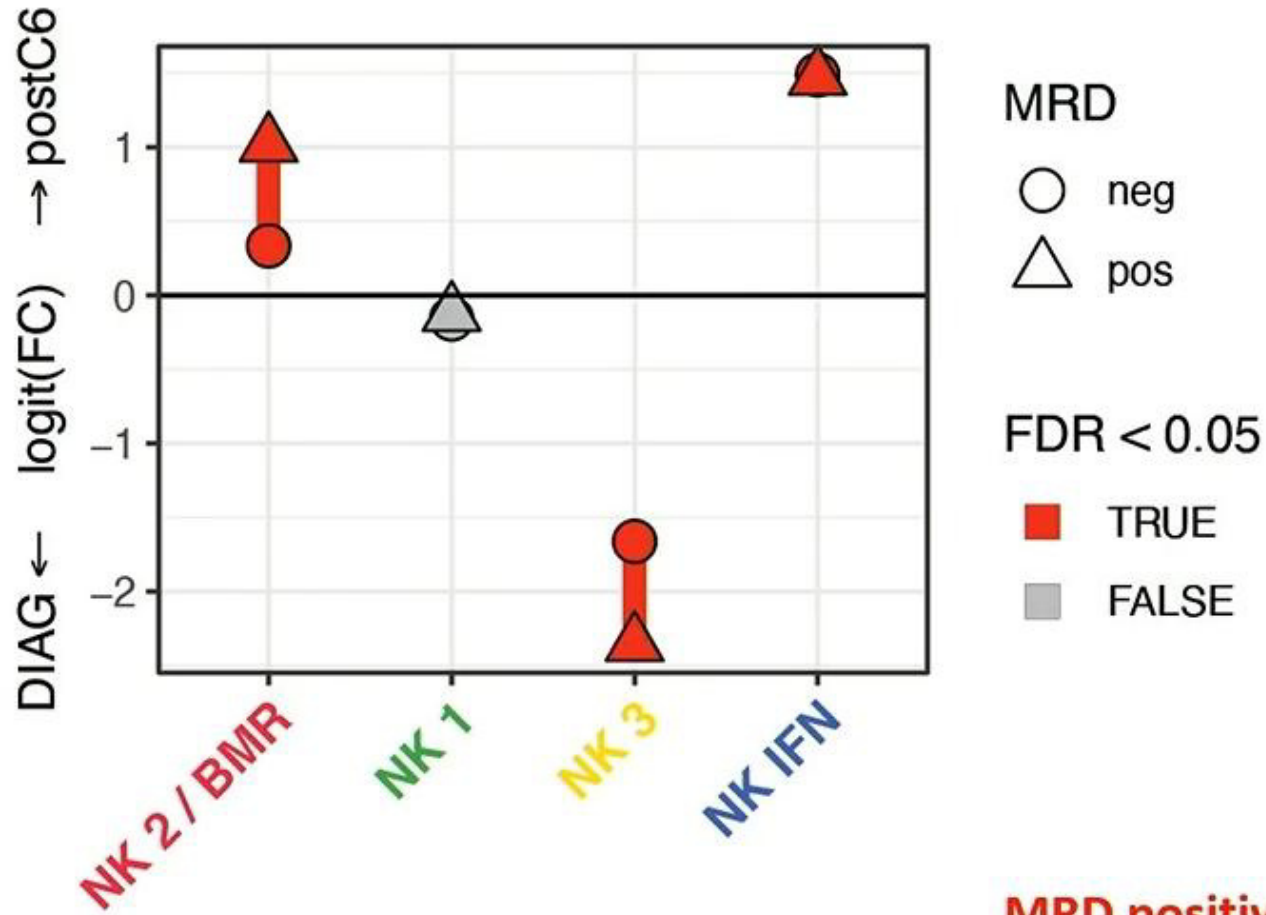


CHANGES IN NK CELL TRANSCRIPTOME UPON ISA-KRD



↑ Inflammation of NK
 ↓ cytotoxicity and adhesion

ISA-KRD NK ALTERATION IS LINKED TO MRD STATUS

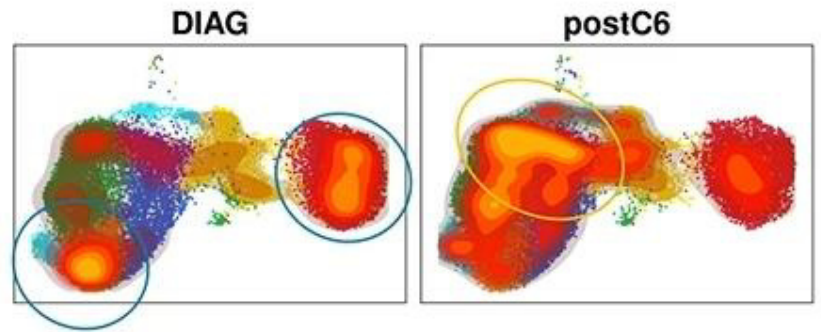
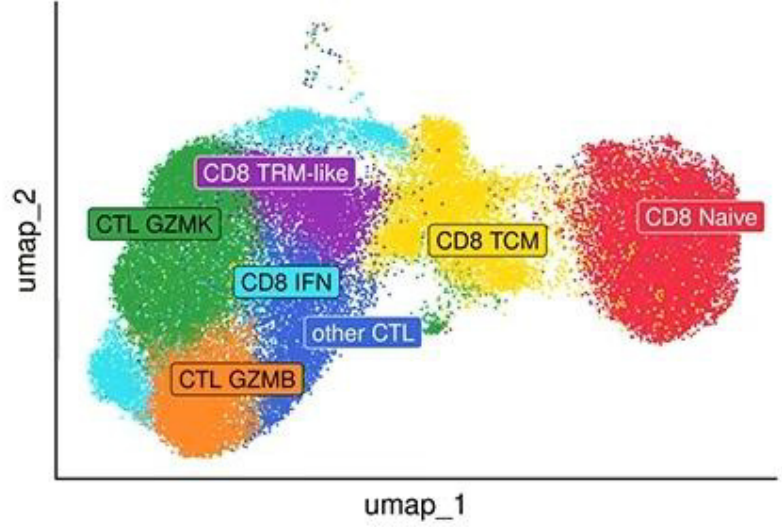


MRD positive :

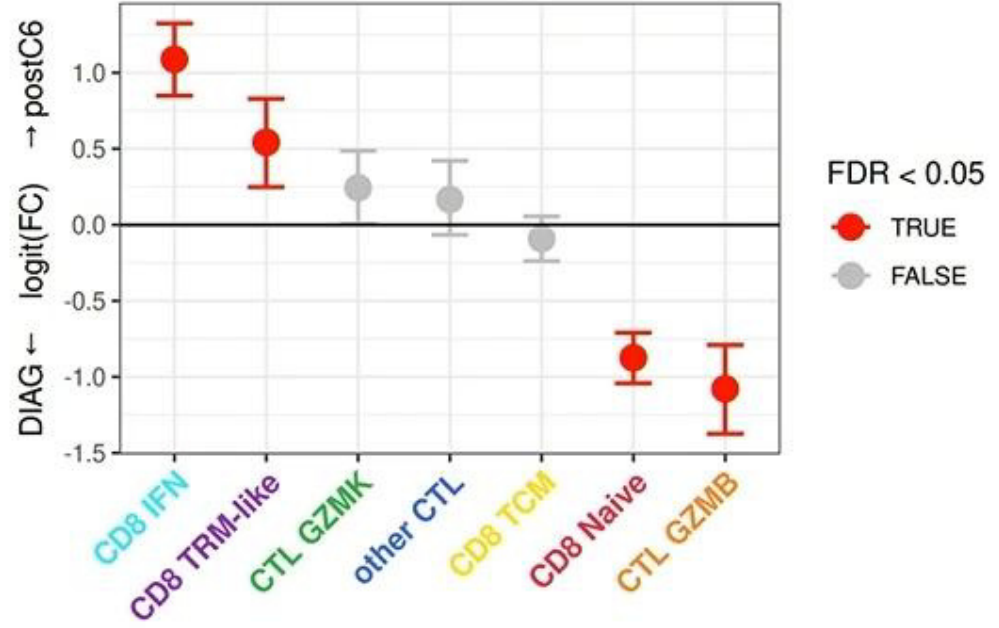
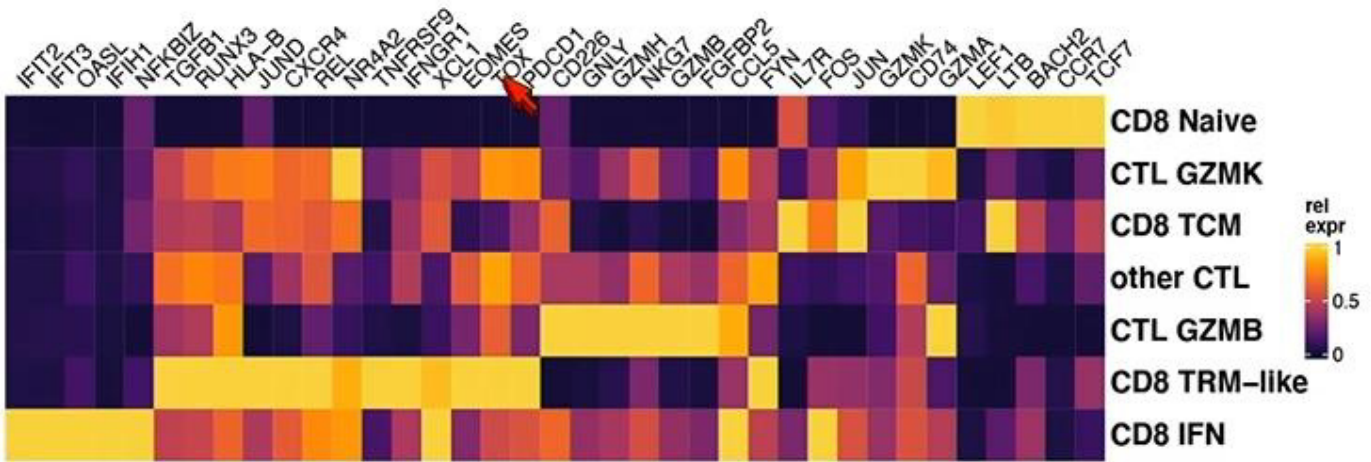
↓ cytotoxic NK

↑ inflammed BM Resident NKs

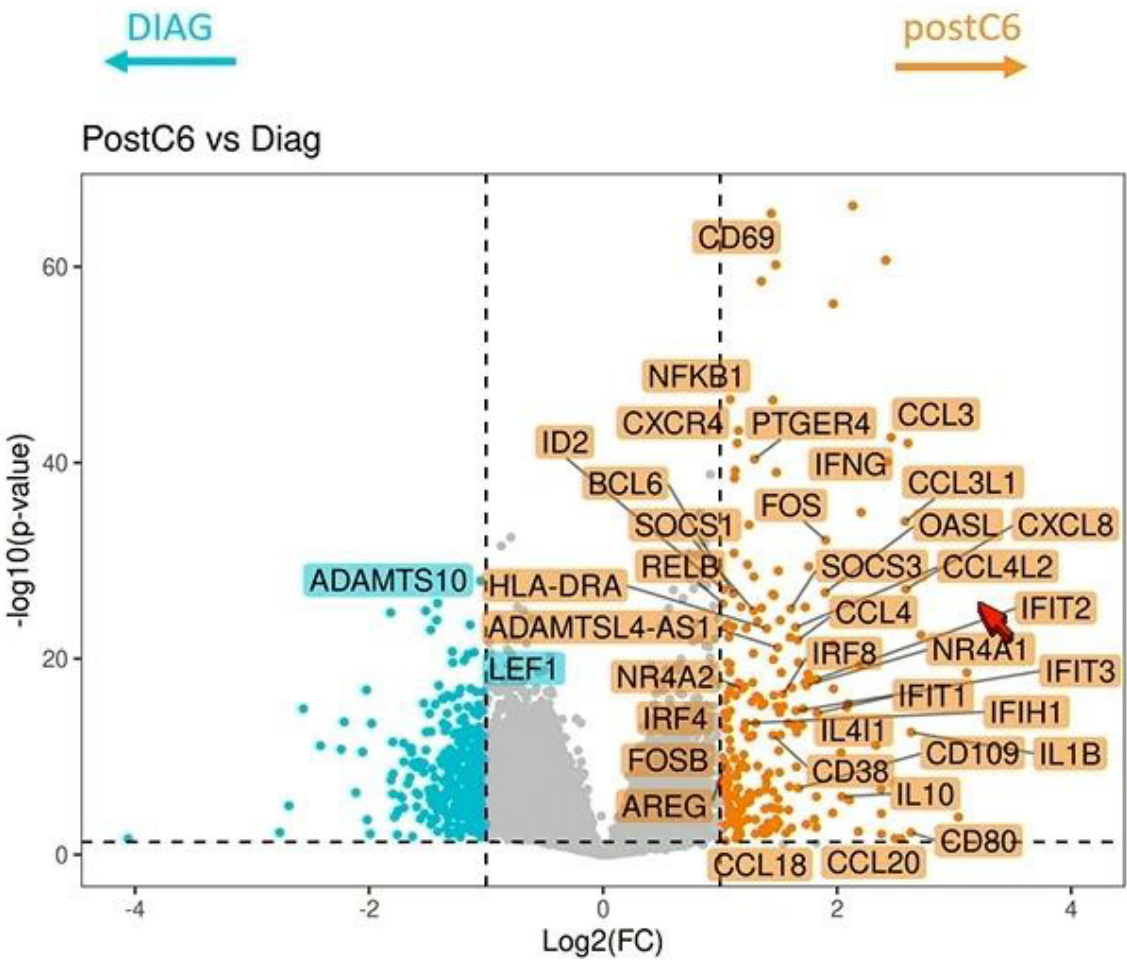
CHANGES IN T CELL LANDSCAPE INDUCED BY ISA-KRD



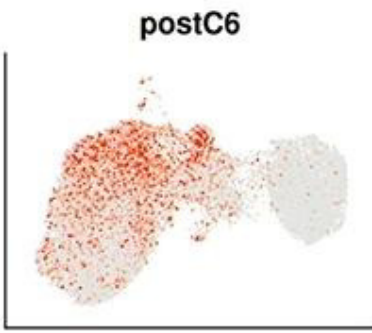
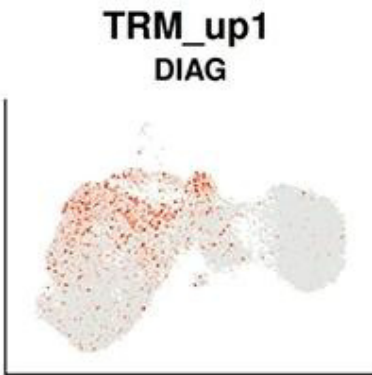
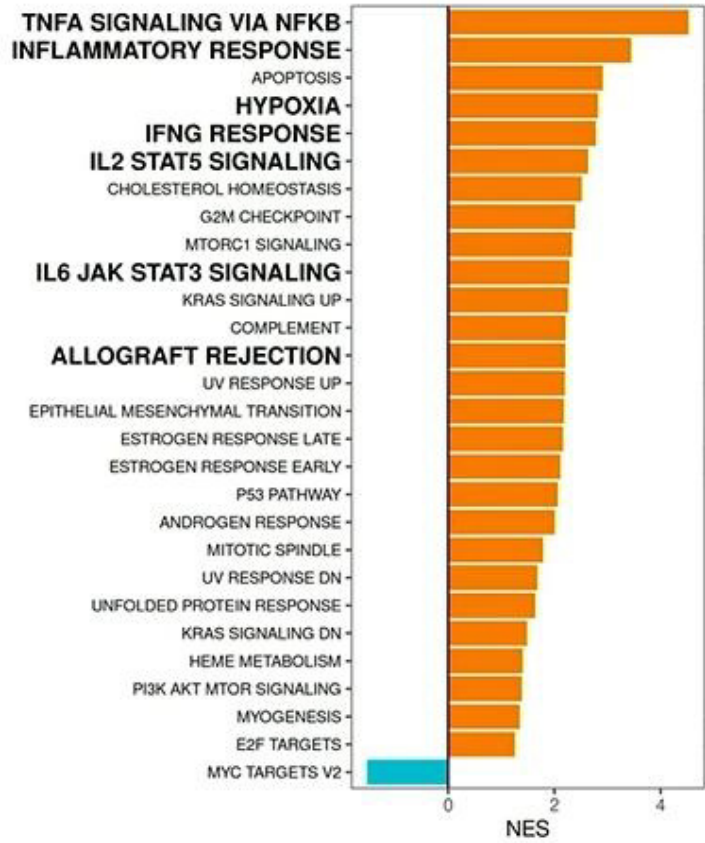
↓ Cytotoxic and Naïve CD8
 ↑ IFN and resident memory CD8



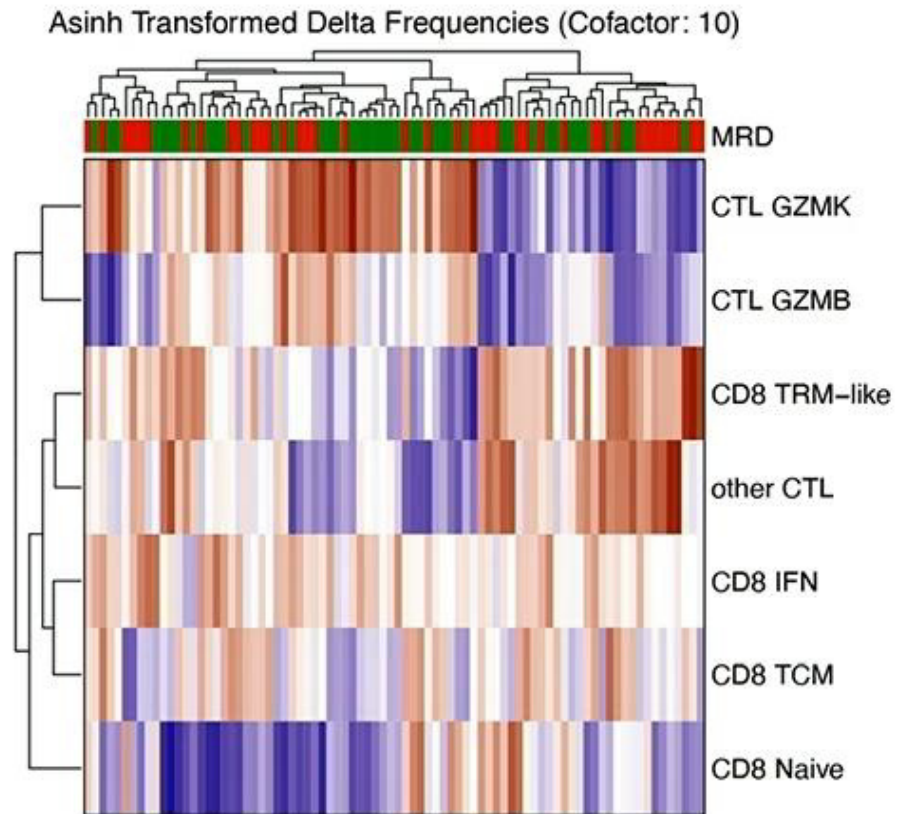
CD8 – TRANSCRIPTOMIC VARIATION INDUCED BY ISAKRD



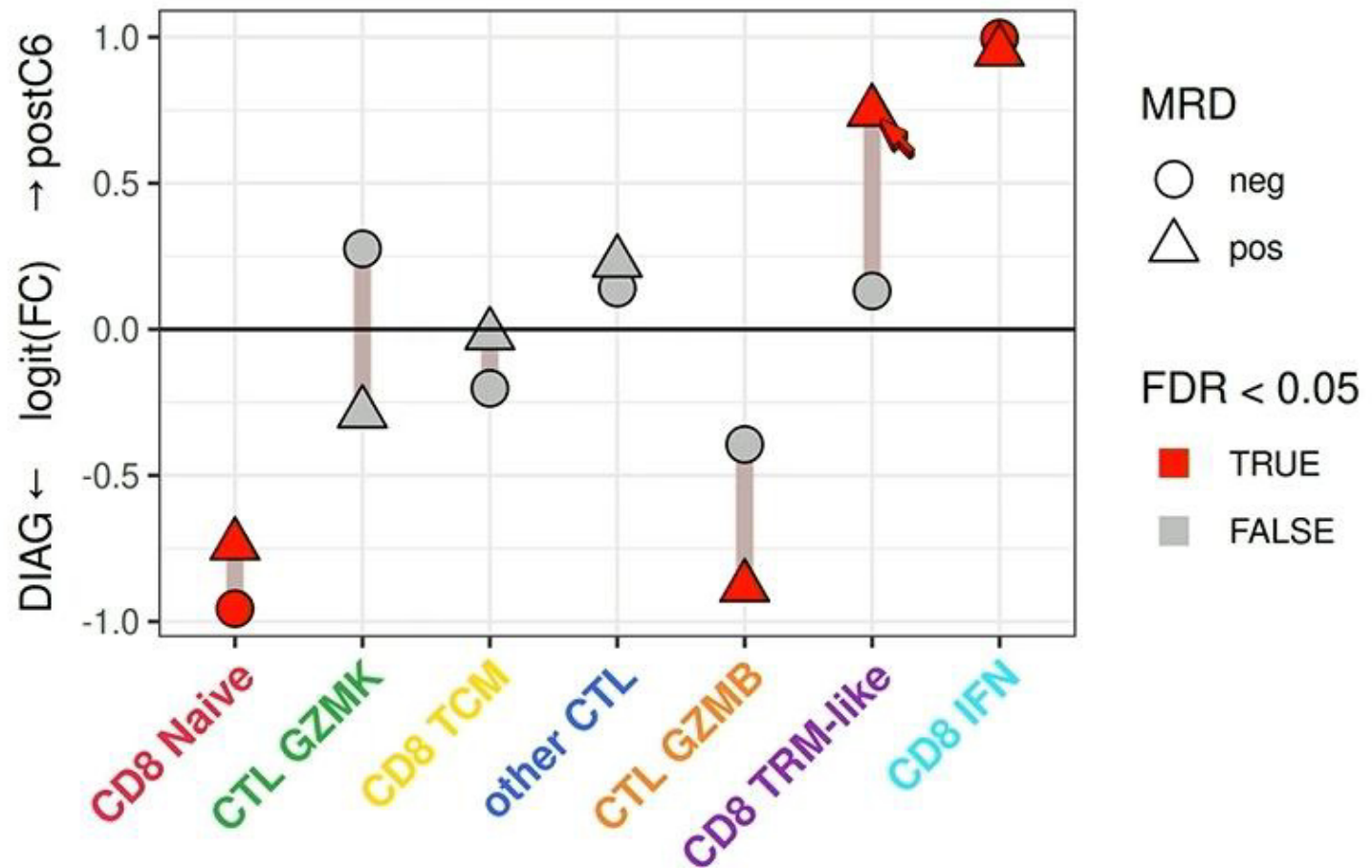
Gene Set Enrichment Analysis (HALLMARK)



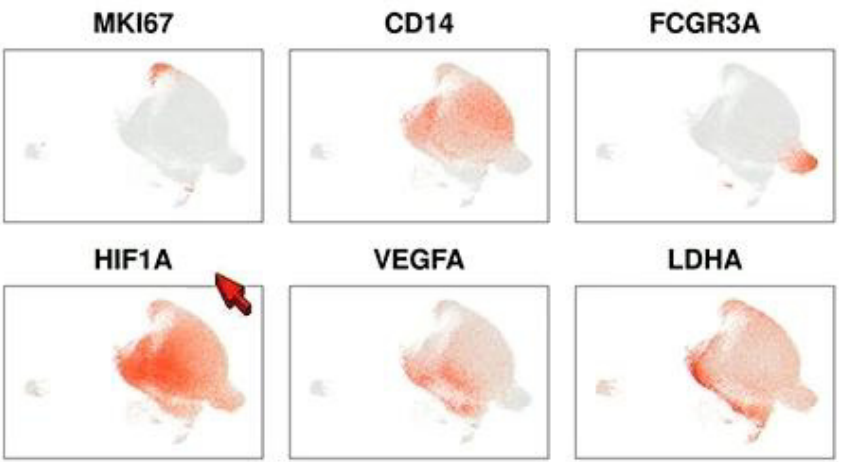
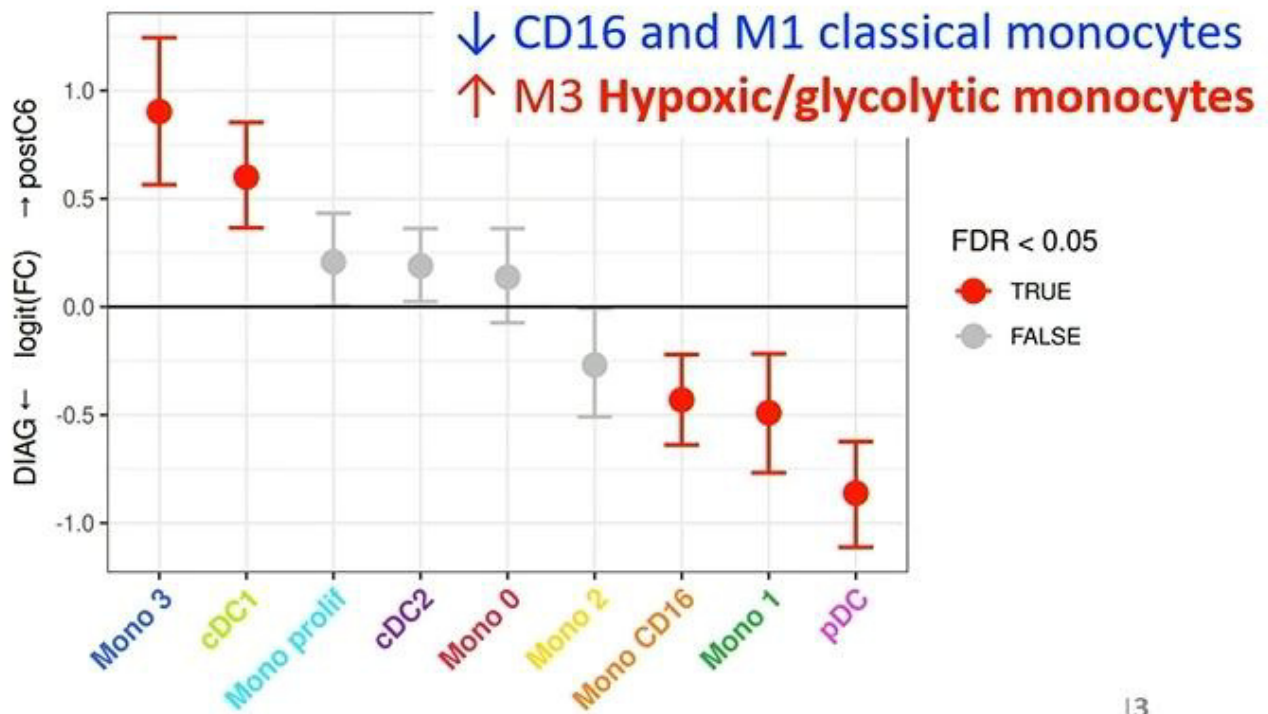
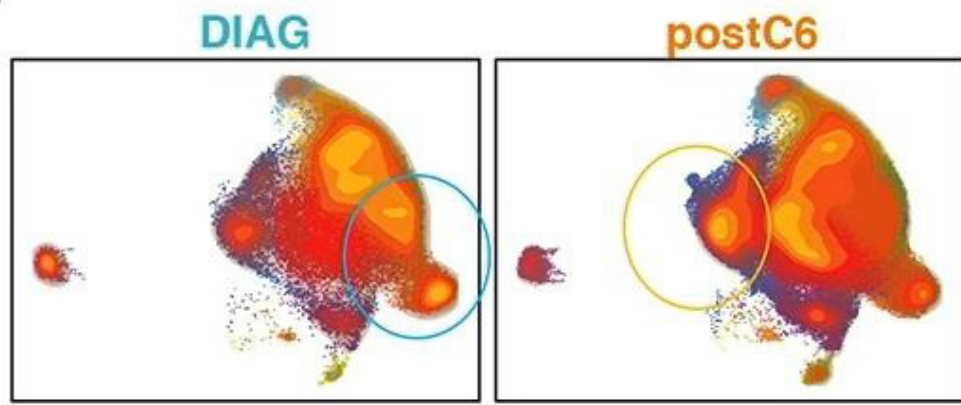
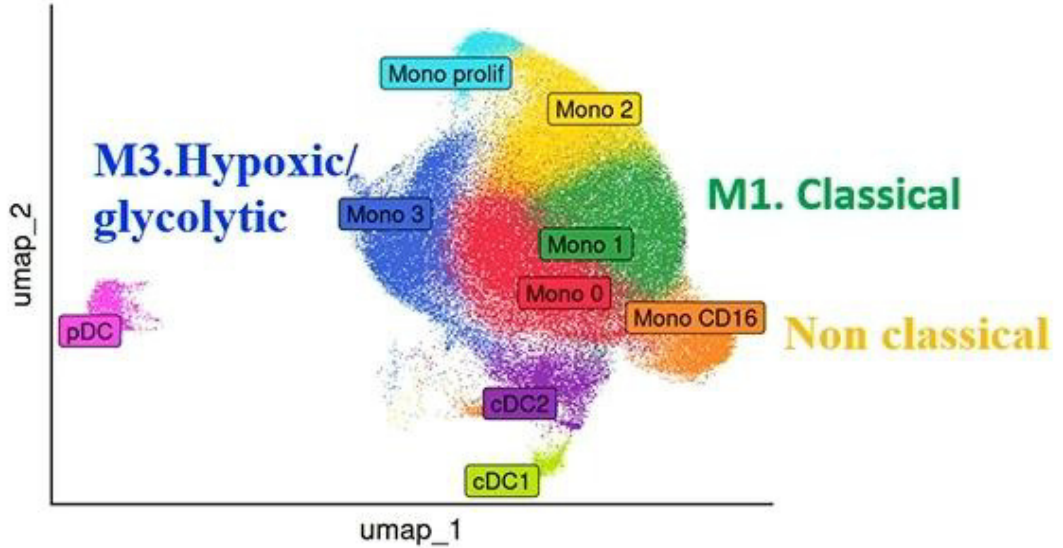
LT CD8 – LINK WITH MRD



MRD positive :
 ↓ Cytotoxic CD8
 ↑ resident memory CD8

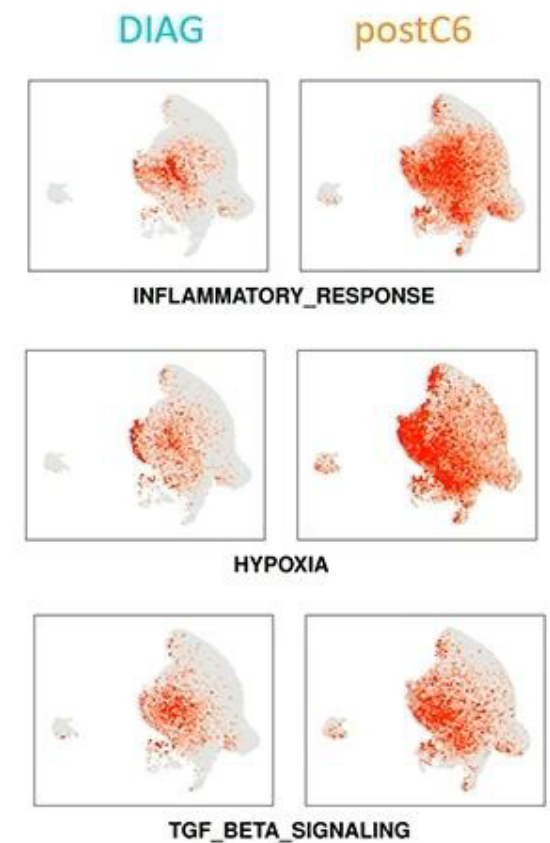
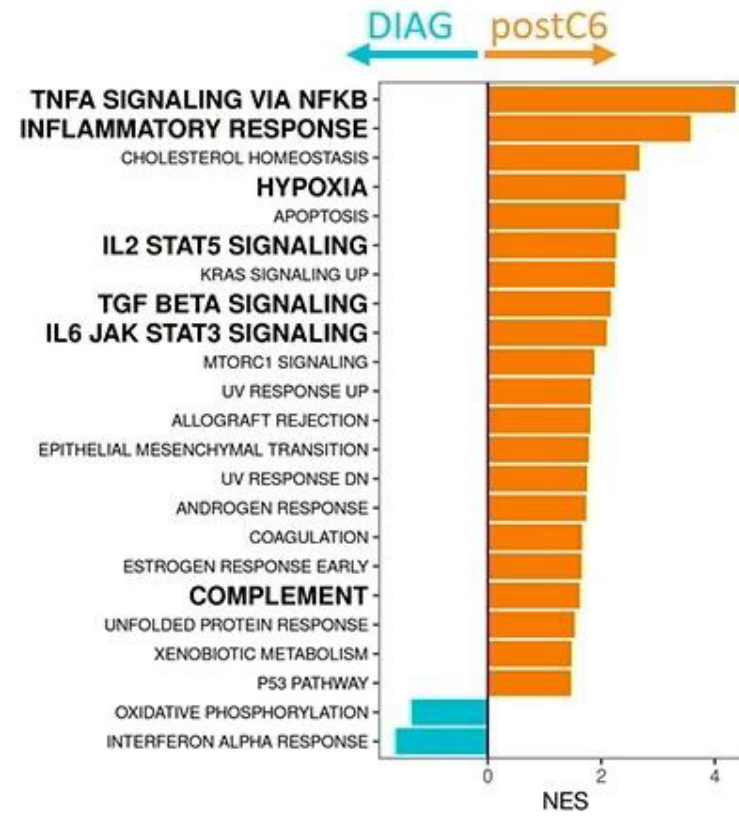
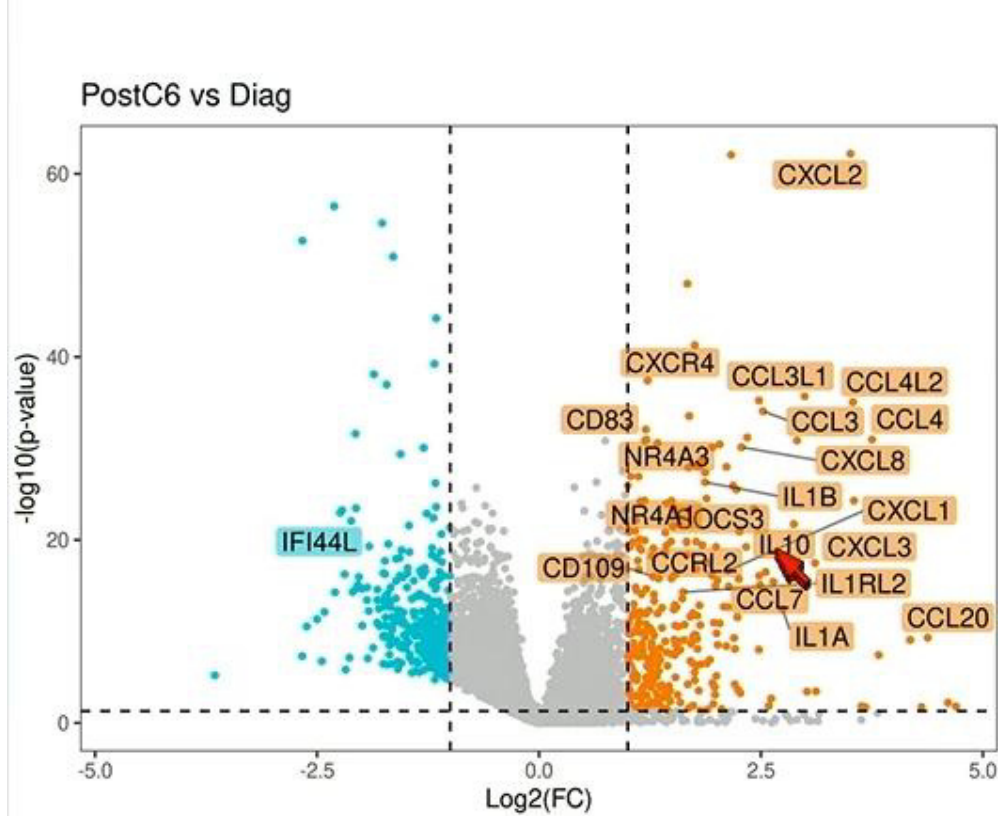


CHANGES IN MYELOID LANDSCAPE INDUCED BY ISA-KRD

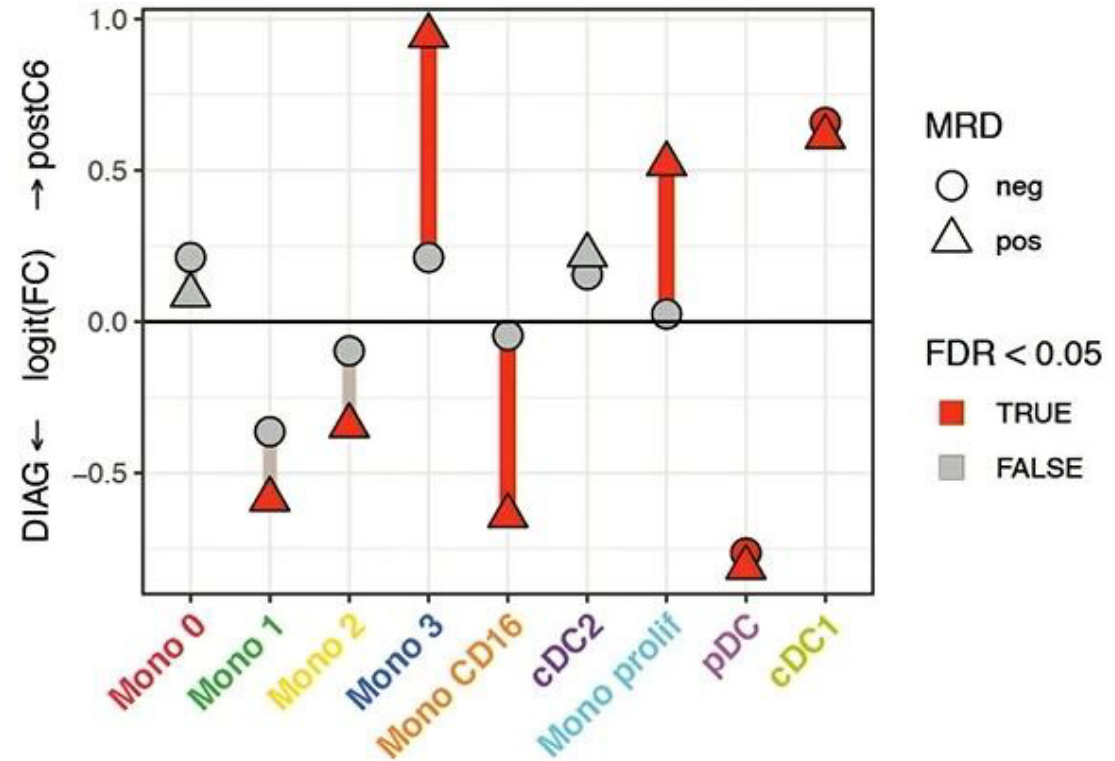
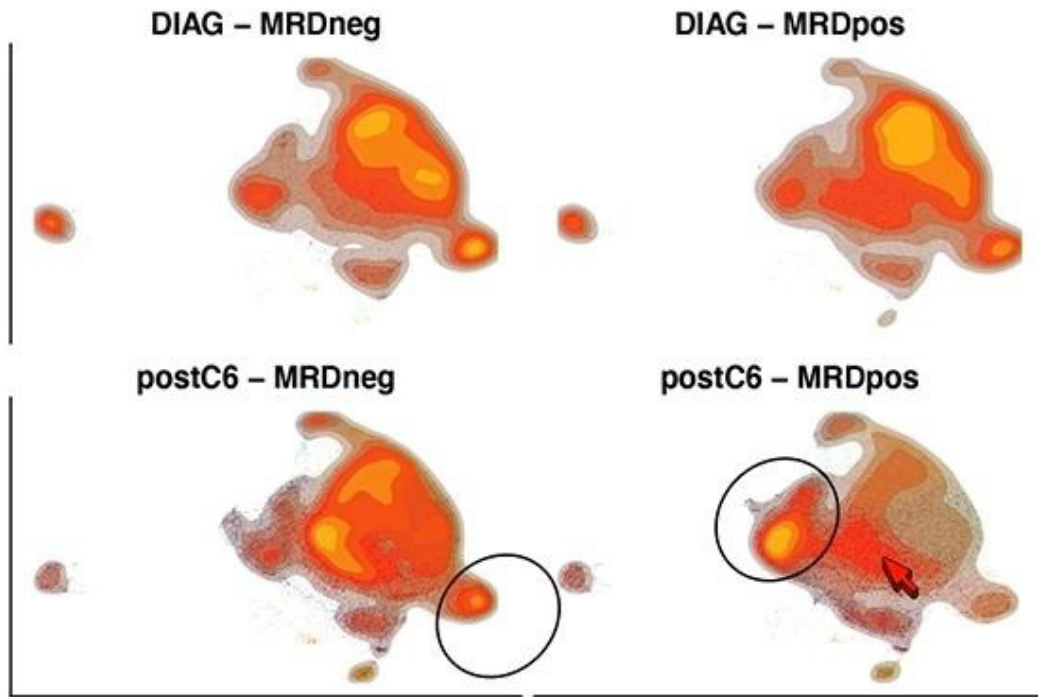


TRANSCRIPTOMIC VARIATION INDUCED BY ISAKRD

Gene Set Enrichment Analysis (HALLMARK)



ISA-KRD MONOCYTE CHANGES ARE LINKED TO MRD STATUS

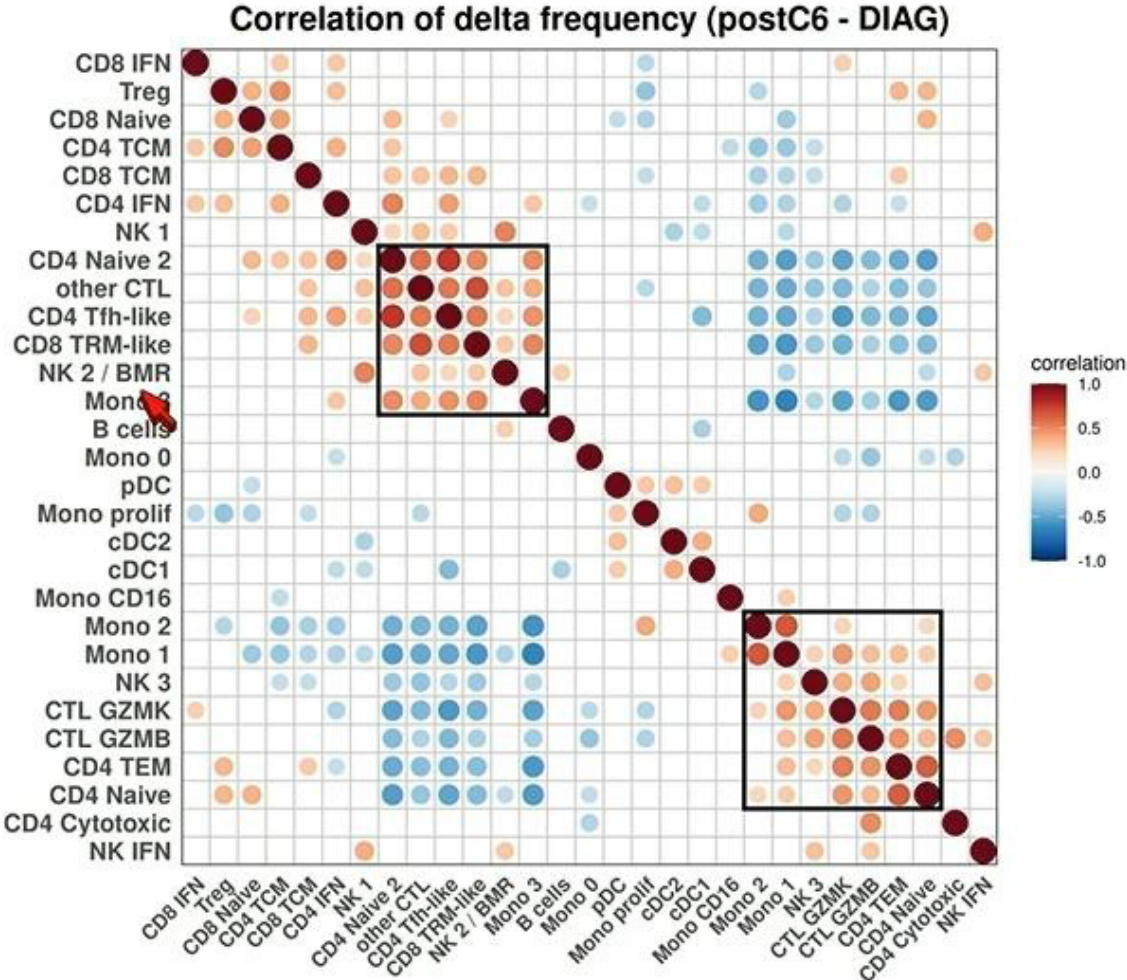
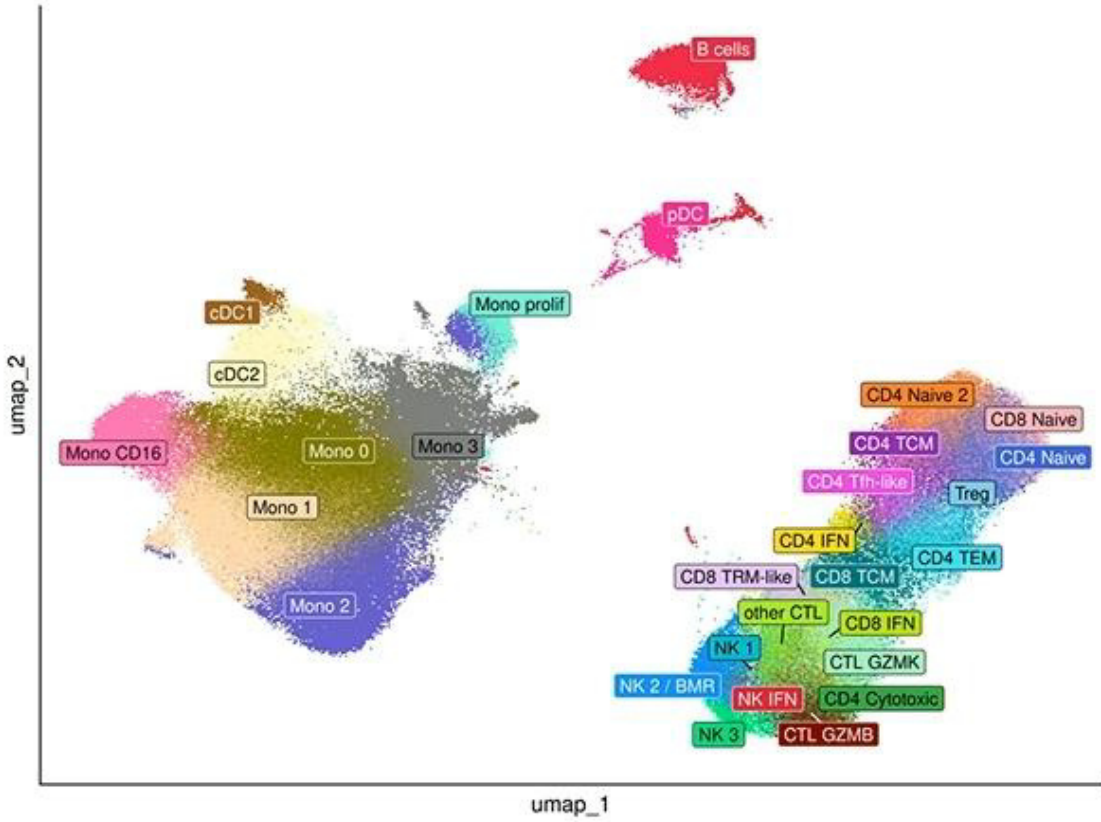


MRD+ :

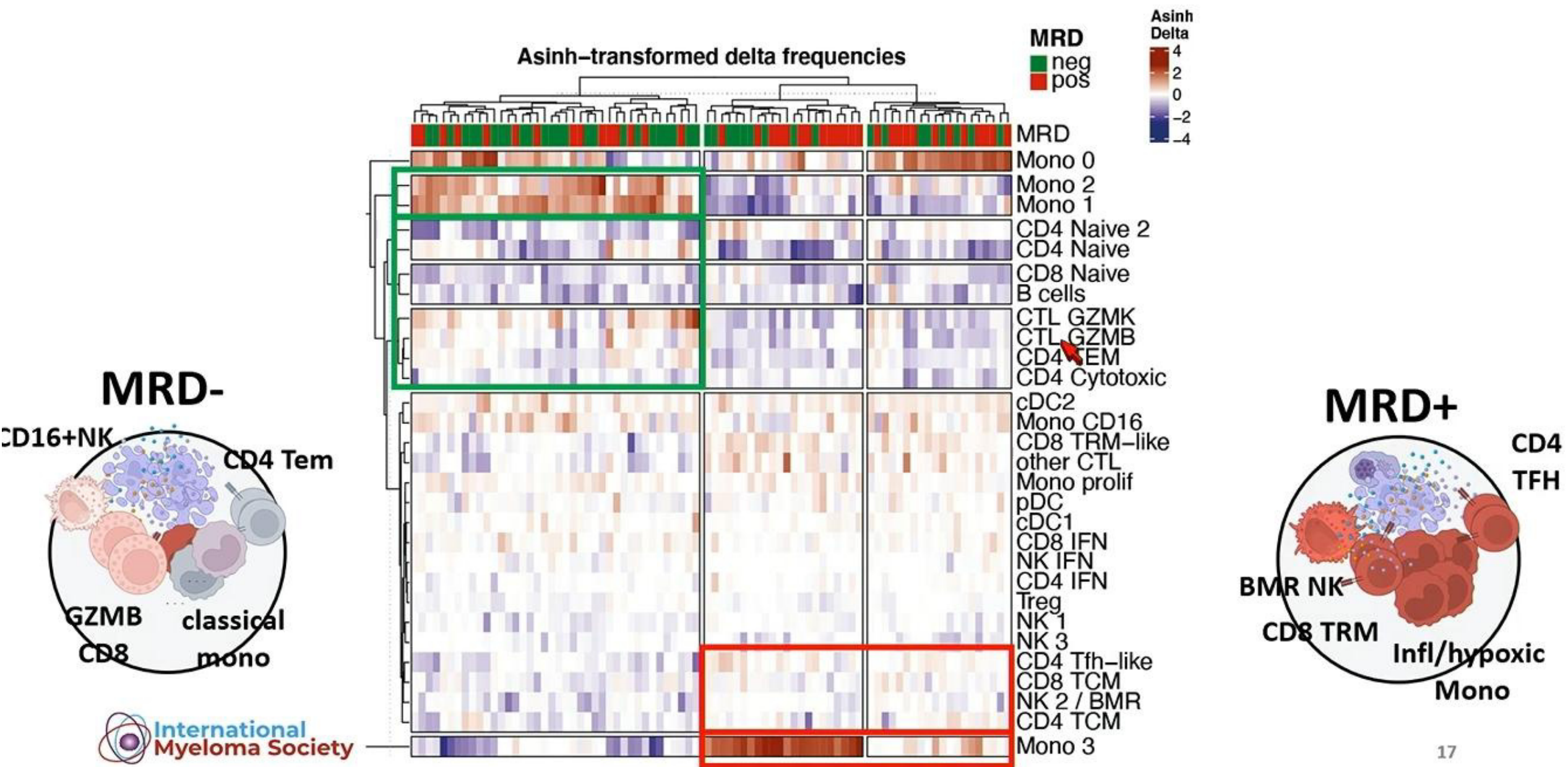
↓ CD16 monocytes

↑ Hypoxia/suppressive and proliferating monocytes

COORDINATED IMMUNE REMODELING UPON ISAKRD



COORDINATED IMMUNE REMODELING ASSOCIATED WITH MRD



My Summary, take home, and follow-up questions...



(=take with grain of salt..)

- המחקר בדק תבניות של TME לפני ואחרי אינדוקציה עם Isa-KRD במחקר MIDAS, תוך שימוש ב scRNAseq ובחן גם קשר ל MRD
- זהו שינויים ב TME תחת האינדוקציה – ב compartments של תאי T, NK ומיאלואידים – בכיוון של exhaustion & inflammation
- השינויים היו במתאם גבוה בין שלושת המדורים
- נצפו הבדלים בין חולים שהשיגו MRD שלילי לאלו שנותרו חיוביים
 - בשליליים – פחות תשישות חיסונית ופחות inflammation
 - לא היו הבדלים ב baseline לניבוי MRD
- **שאלות –**
 - מה המשמעות מבחינת מעבר לאימונתרפיה?
 - "ביצה ותרנגולת" – האם עמידות המיאלומה משפיעה על TME / להפך / הדדי... ?