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Session 417: MPN and MDS: Targeting red cells and platelets

# Modulation of the immune landscape in lower-risk MDS with imetelstat-induced transfusion independency

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# Conflict of interest

- Research funding from Geron Corp.

# Introduction

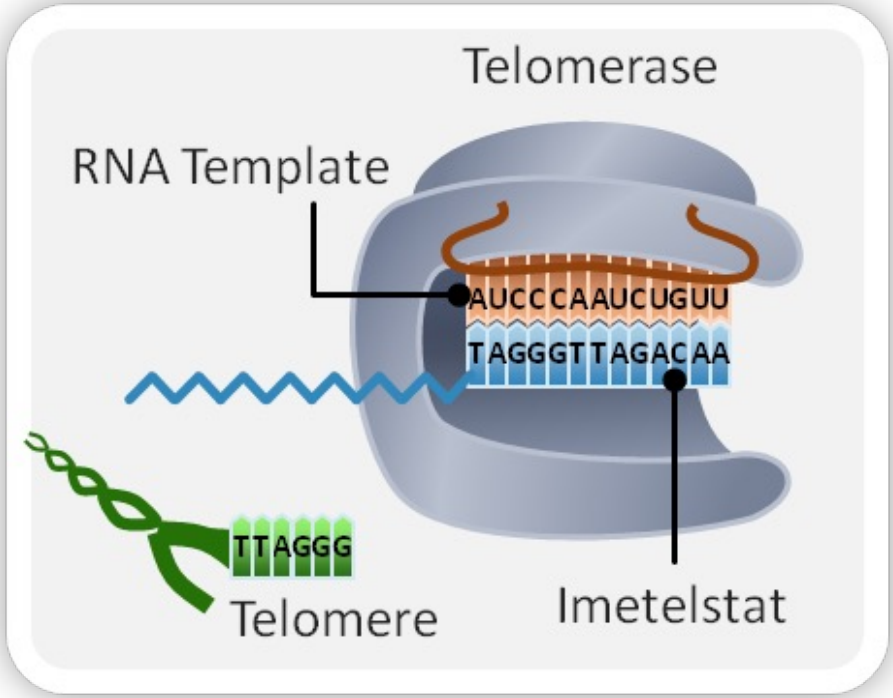
- Around 50% of lower-risk MDS patients are resistant to ESA [1]
- Innate immune signaling and inflammation underlies MDS pathogenesis [2]
- Targeted therapies for MDS-5q or MDS-*SF3B1* are available [3,4]
- Imetelstat, a telomerase inhibitor, [5,6] is in clinical development

Results from IMerge (MDS3001, NCT02598661) :

- Phase II (open-label, single-arm study)
  - 23% of 57 highly transfused LR-MDS achieved 24-wk transfusion independency (TI) with a median duration of 65 wk [7]
  - 65% obtained hematological improvement (HI)-erythroid [7]
  - ≥1 year sustained, continuous TI in 29% of patients with transfusion dependent, non-del(5q) LR-MDS relapsed/refractory to ESAs and lenalidomide/HMA naive [8]
- Phase III (Double blind, randomized, imetelstat vs placebo) [9]

  Imetelstat demonstrated highly statistically significant and clinically meaningful efficacy compared with placebo:
  - 8-week TI= 40% vs 15%,
  - 24-week TI=28% vs 3.3%
  - 1-year TI = 18% vs. 1.7%

Imetelstat, a 13-mer oligonucleotide, is a direct and competitive inhibitor of telomerase activity [4,5]




[1] Park S et al, Blood 2008; [2] Trowbridge & Starczynowski, JEM 2021; [3] List AF et al, N Engl J Med 2005; [4] Fenaux P et al, 2020; [5]Asai A, et al. Cancer Res. 2003; [6]Herbert BS, et al. Oncogene. 2005; [7]Steensma DP et al, J Clin Oncol 2021; [8] Platzbecker U, et al, ASH 2022, Abstract #459; [9] Platzbecker U, et al, EHA 2023, S165

# Study Objectives, Patient Samples and Methods

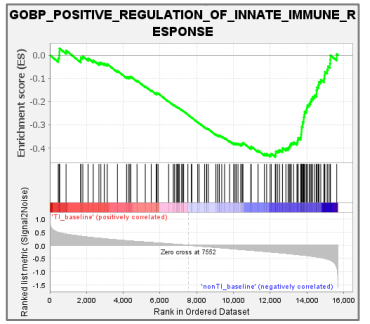
**Objectives: Identify biological pathways associated with the clinical response** in a subset of patients enrolled in the imetelstat MDS3001 phase II clinical trial.

## Patient samples:

- **10 LR-MDS patients:** 6 Transfusion Independence Responder (TIR), 4 Transfusion Independence Non-Responder (TINR) with a median follow-up of 140.7 weeks
- Samples at baseline and 4-7 months post-imetelstat treatment (total 24 samples)

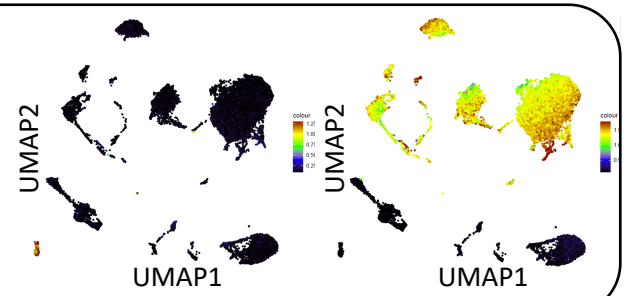
## Methods

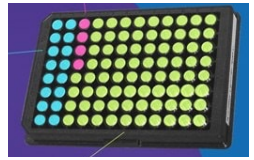
- **BMMNC transcriptomes** were analyzed by RNA-sequencing
- **PBMC immune profiles** were assessed by mass cytometry (CYToF) using the Maxpar® Direct Immune Profiling assay
- **Cytokine profiling** was performed using quantitative multiplex panel of 47 cytokines in PB plasma samples collected from 21 patients (15 TIR, 6 TINR) at 2 to 5 time points.




GSEA

Cytoscape

Luminex

# Patients' Baseline Characteristics and Clinical Response

| ID | Age | Gender | WHO | Karyotype | Mutations | IPSS | Treatment duration in cycles | Follow-up (wks) | Longest transfusion free interval (wks) | ≥1-year Transfusion independency |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 78 | M | MDS-RS | 46,XY | *SF3B1*_E622D | Intermediate-1 | 33 | 241,3 | 140,9 | Yes |
| 2 | 62 | F | MDS-MLD | 46,XX,del(5)(q13;q33) | *JAK2*_V617F | Low | 35 | 136,3 | 65,1 | Yes |
| 3 | 60 | F | del(5q) | 46,XX,del(5)(q13;q33) | *TP53*_R248W | Low | 6 | 48,6 | 5 | No |
| 4 | 60 | F | MDS-RS | 46,XX | *SF3B1*_E622D | Low | 18 | 82,4 | 79,3 | Yes |
| 5 | 71 | F | MDS-RS | ND | No mutation | Low | 29 | 223 | 6,9 | No |
| 6 | 69 | F | MDS-RS-MLD | 46,XX | *SF3B1*_K666R | Low | 8 | 144,3 | 3,6 | No |
| 7 | 81 | F | MDS-RS-MLD | 46,XX | *KIT*_M541L<br>*SF3B1*_R625C | Intermediate-1 | 32 | 140,3 | 76,3 | Yes |
| 8 | 60 | F | MDS-RS-MLD | 47,XX,+8 | *SF3B1*_K700E | Intermediate-1 | 26 | 146,3 | 72,7 | Yes |
| 9 | 79 | M | MDS-RS-MLD | 47,XY,+8 | *SF3B1*_K700E | Intermediate-1 | 23 | 128 | 114,7 | Yes |
| 10 | 66 | M | MDS-MLD | 46,XY | *JAK2*_V617F<br>*SRSF2*_P95H | Low | 6 | 141,1 | 3,7 | No |

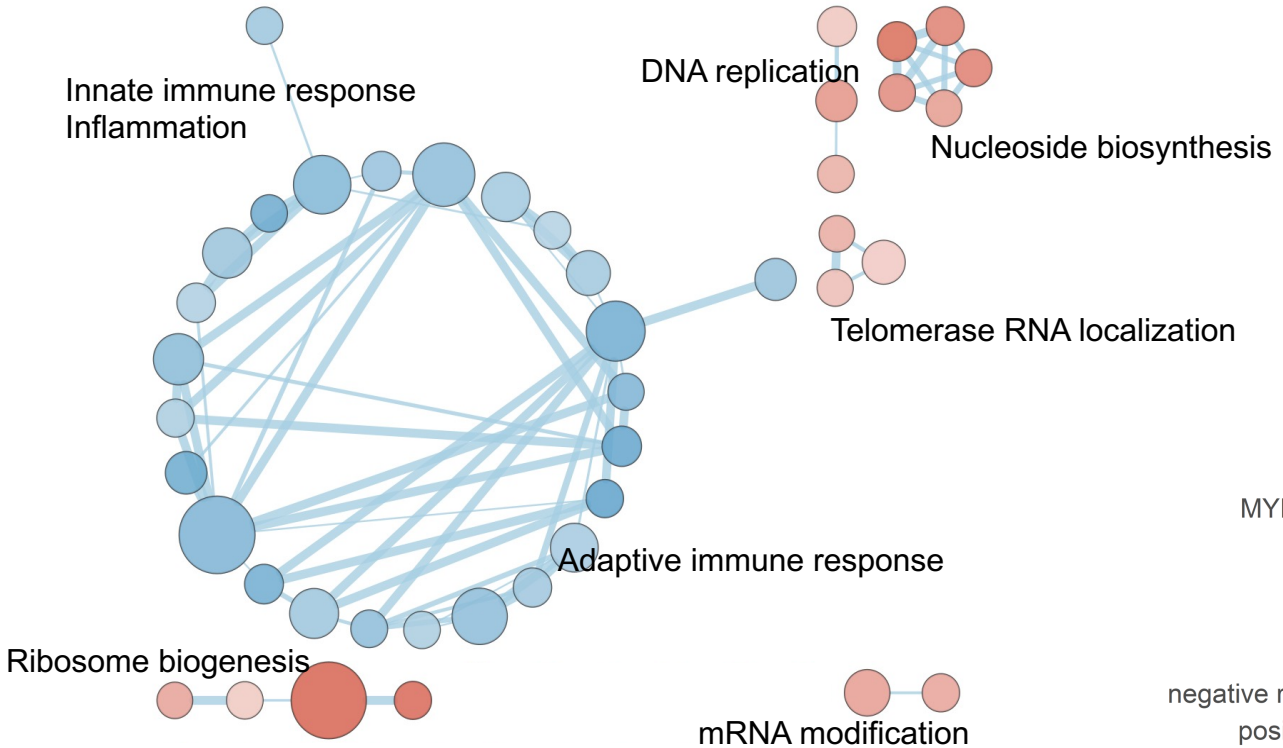
# Low innate immune features and T cell activation at baseline in ≥1 year TI Responders (TIR) Compared to Non-Responders (TINR)

**Bone marrow MNC transcriptomes in TIR (n=6) *vs* TINR (n=4):**

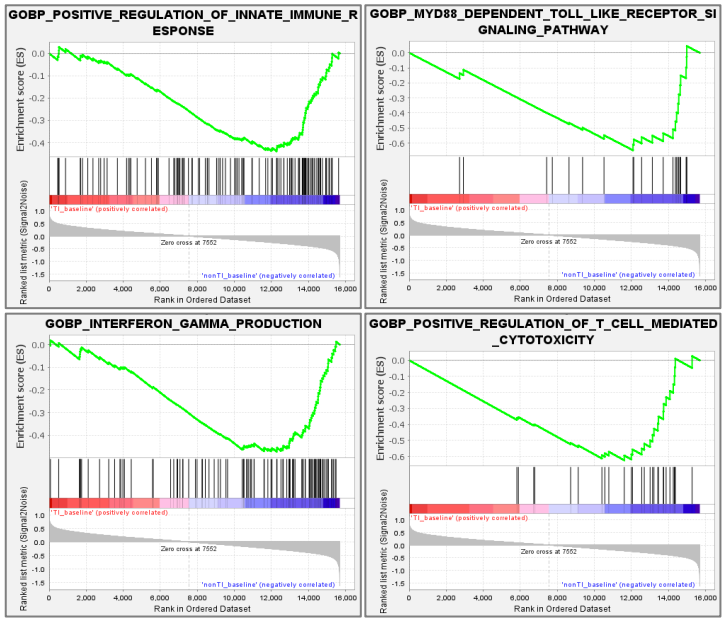
1185 differentially expressed genes ($P$ = 0.05; $\log_2$(FC) = I1I)

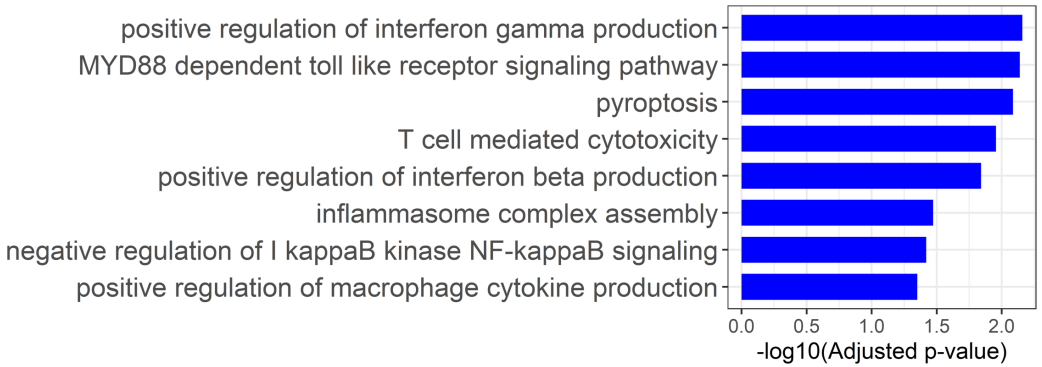
1150 down (blue) & 35 up-regulated (red)

## Cytoscape




## Gene set enrichment



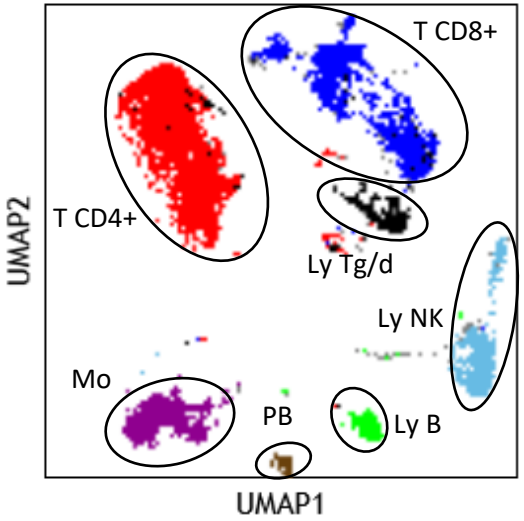



# High heterogeneity of immune cells repartition at baseline

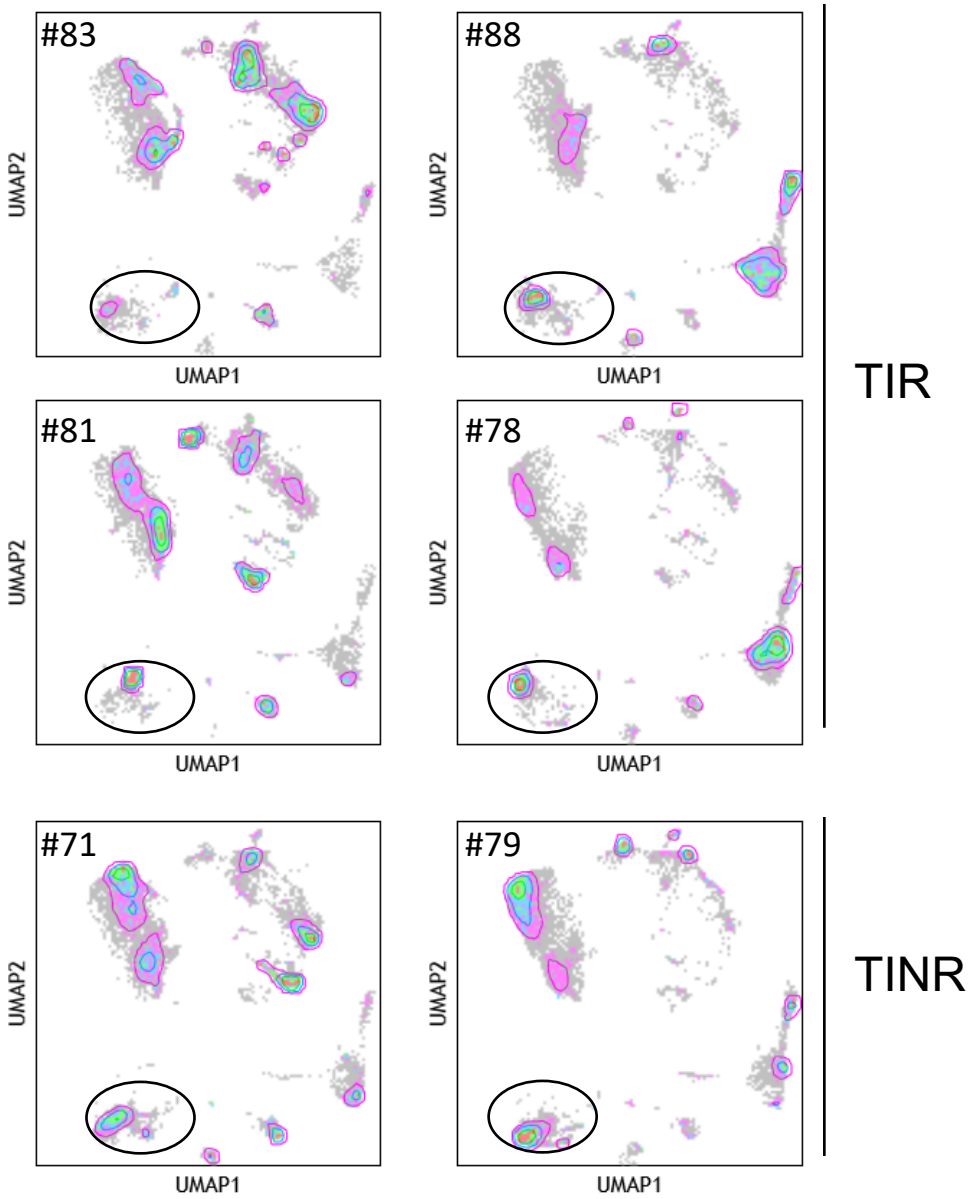
Blood samples at baseline (n=9)


Maxpar® Direct Immune Profiling assay (CyTOF)

<u>Unsupervised analysis in TIR (n=6) *vs* TINR (n=3)</u>




- High heterogeneity between samples in both TIR and TINR
- No differences of B, T and NK cell proportion
- **Difference in monocytes repartition**

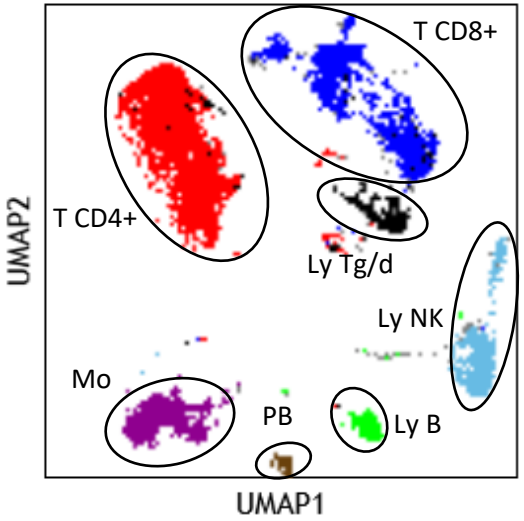


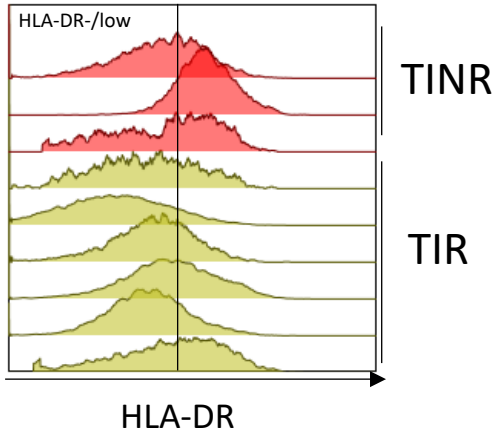
# Low inflammatory features and immune suppression in TIR at baseline

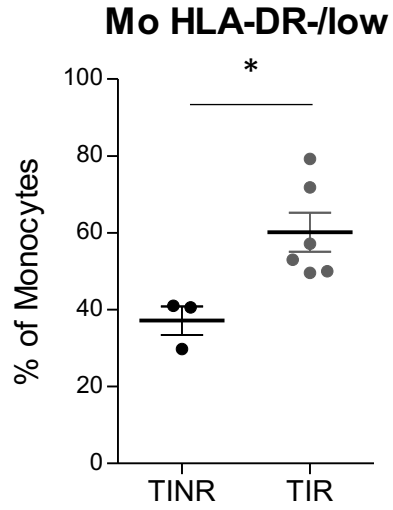
Blood samples at baseline (n=9)


Maxpar® Direct Immune Profiling assay (CyTOF)

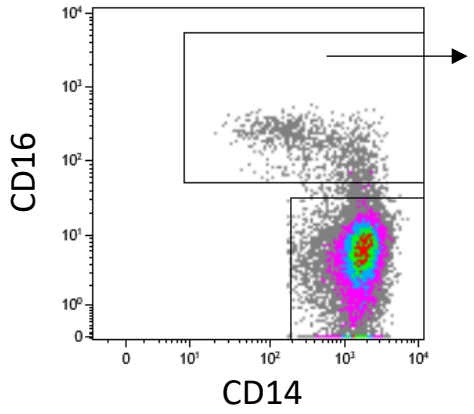
<u>Unsupervised analysis in TIR (n=6) *vs* TINR (n=3)</u>

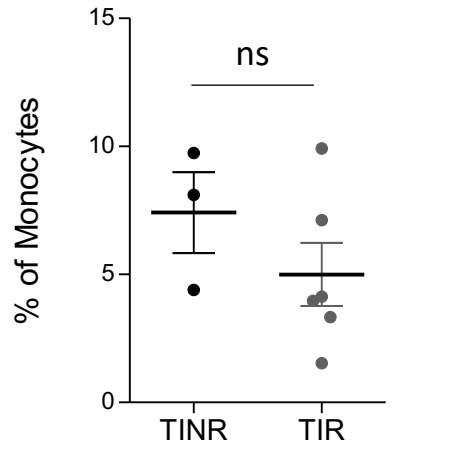



- High heterogeneity between samples in both TIR and TINR
- No differences of B, T and NK cell proportion
- **Difference in monocytes repartition**

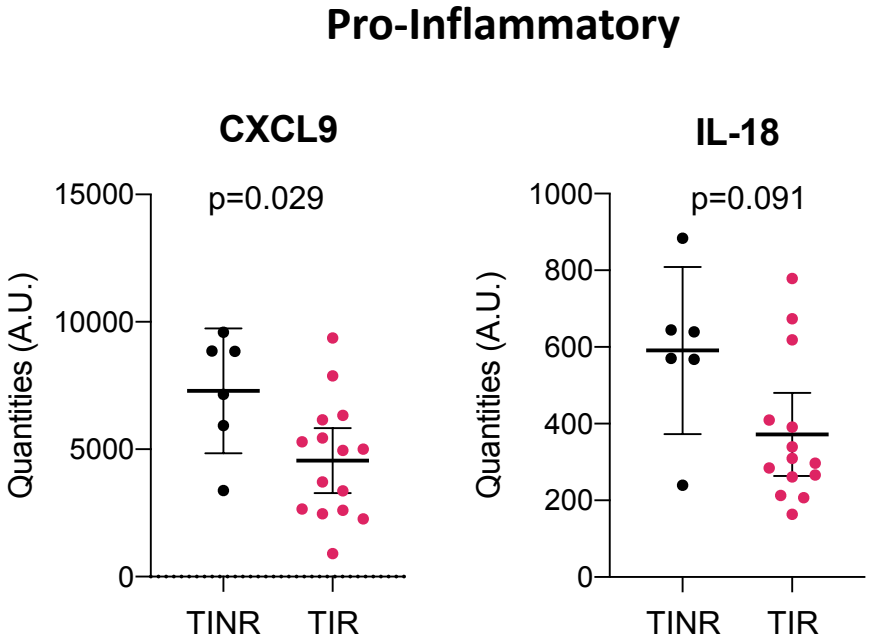


# Low inflammatory features in TIR at baseline demonstrated by relative low levels of CXCL9 and IL-18

**Cytokine profiling** (Milliplex® kit) in PB plasma samples collected at baseline

Analysis in TIR (n=15) *vs* TINR (n=6)




- **No difference at baseline for plasmatic amounts of IFNγ, IL-4, IL-5, IL-6**

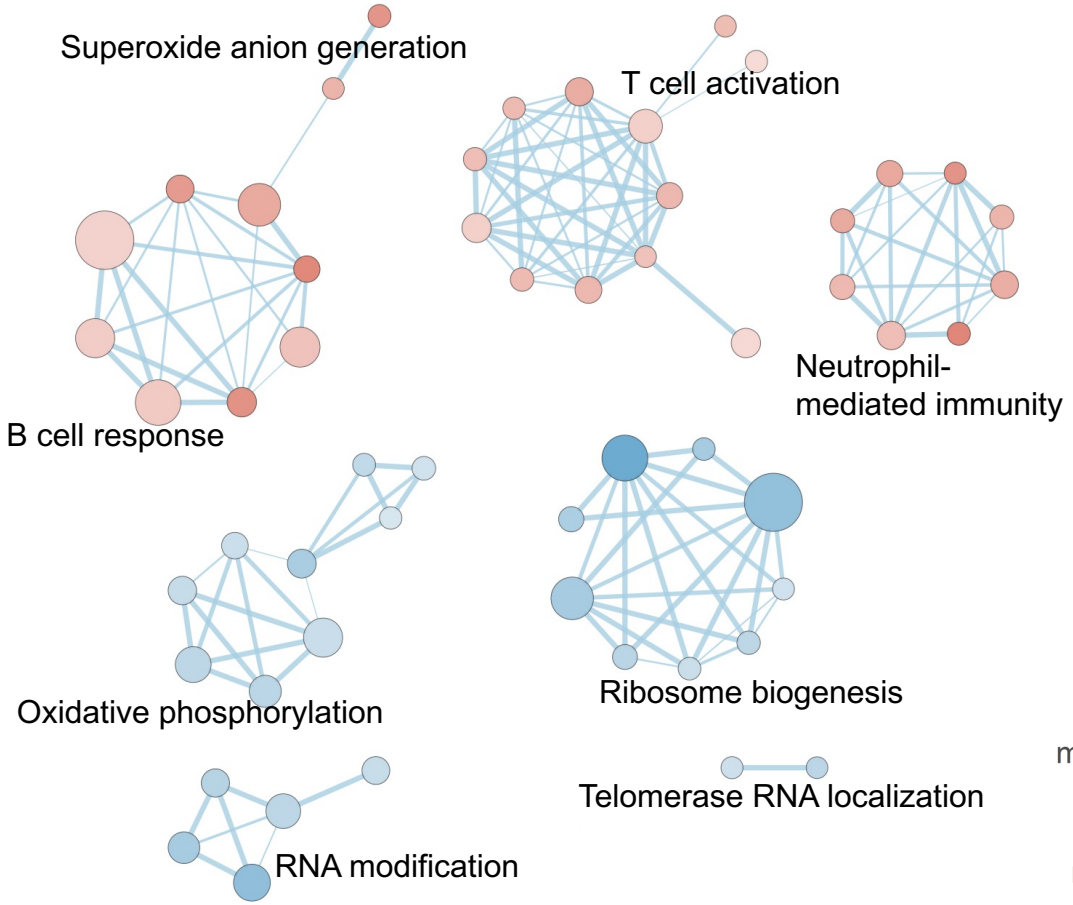
- **Some monocyte-derived chemokine or interleukin are less expressed in TIR**

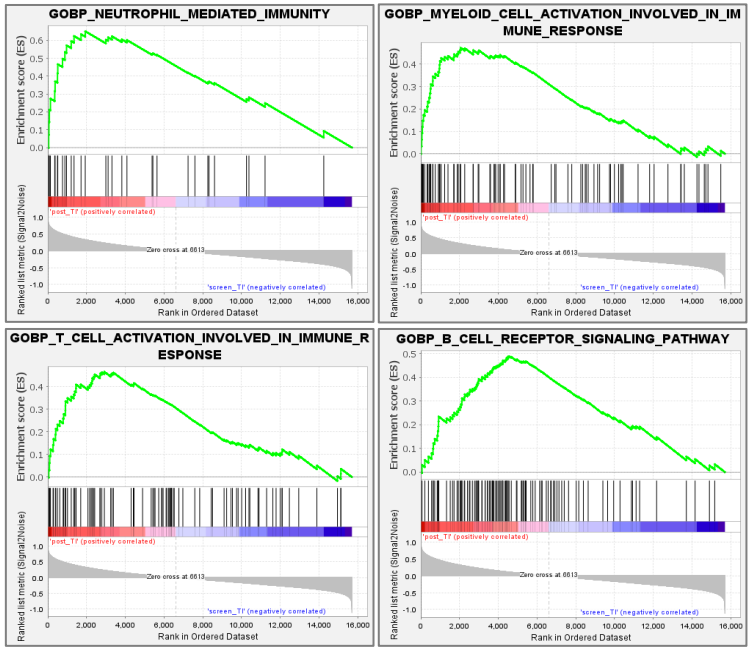
# Immune cell activation associates with the response to Imetelstat

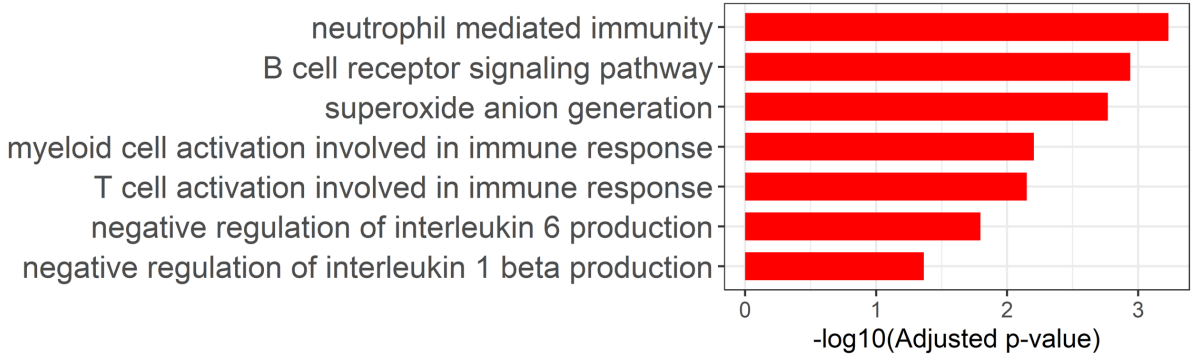
**Bone marrow MNC transcriptomes in TIR (n=6) post treatment *vs* baseline:**

127 differentially expressed genes ($P$ = 0.05; $\log_2$(FC) = I1I)

37 down (blue) & 90 up-regulated (red)



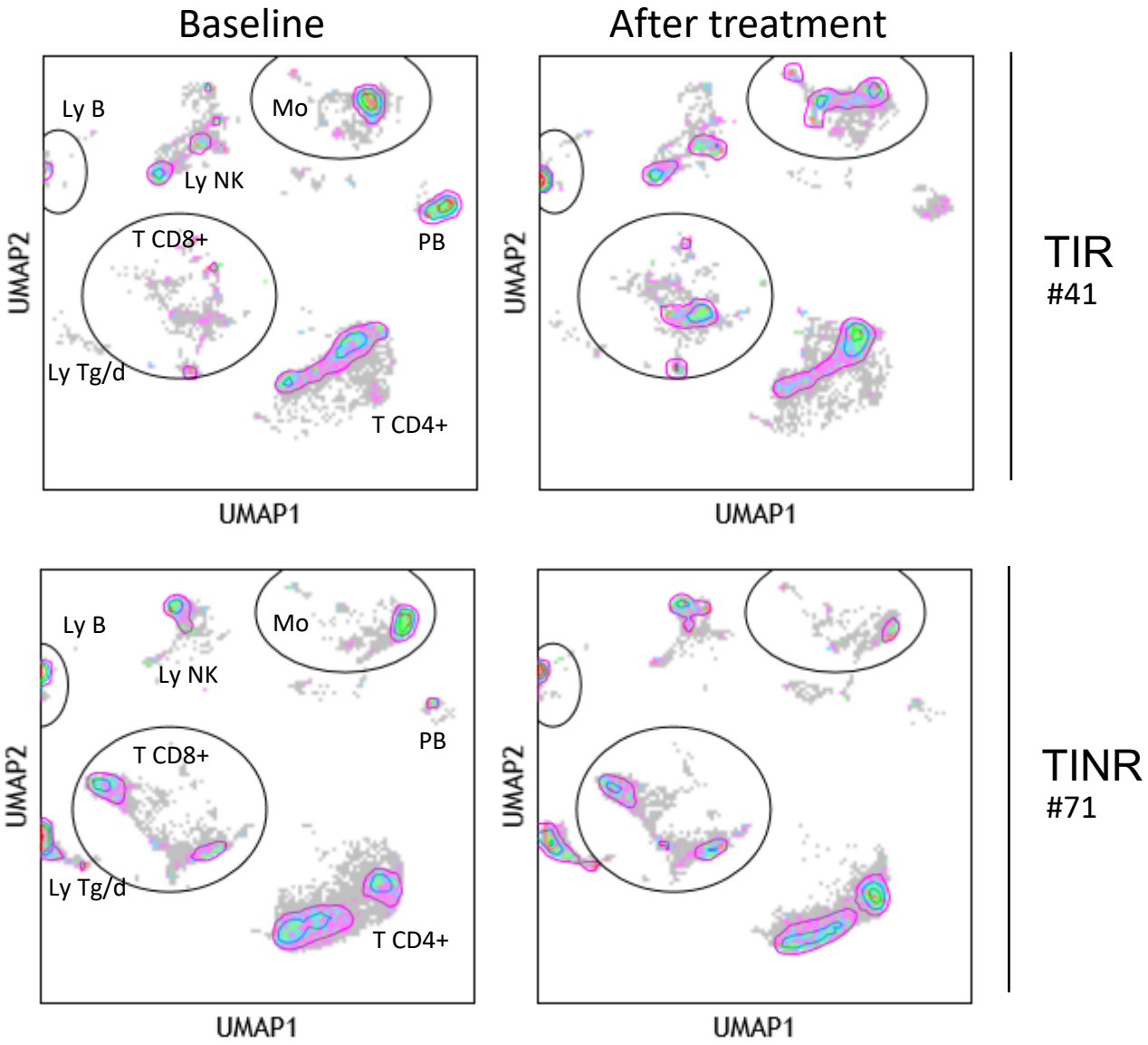



# Imetelstat induces modification of immune cells repartition in TIR

Blood samples at baseline and after treatment (n=9)


Maxpar® Direct Immune Profiling assay (CyTOF)

Unsupervised analysis in baseline *vs* post treatment for TIR (n=6) and TINR (n=3)



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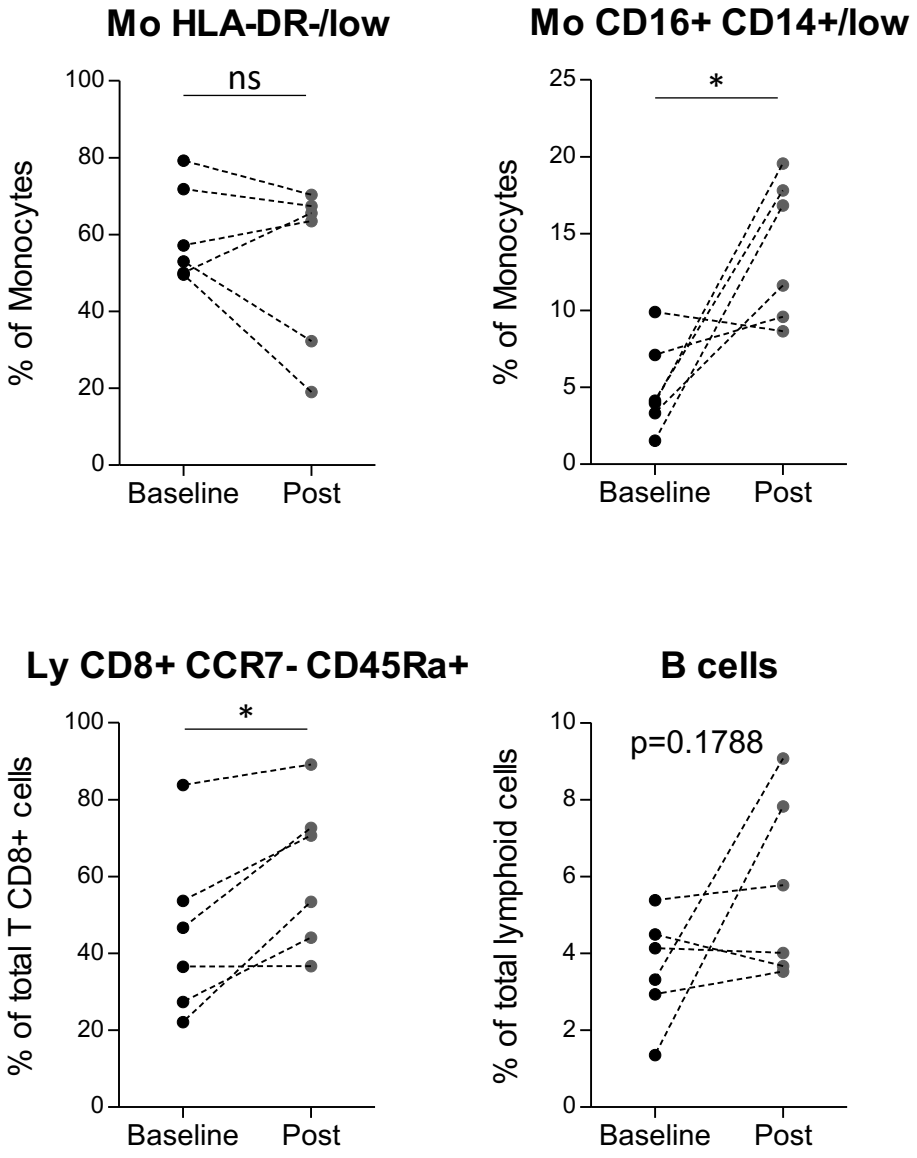
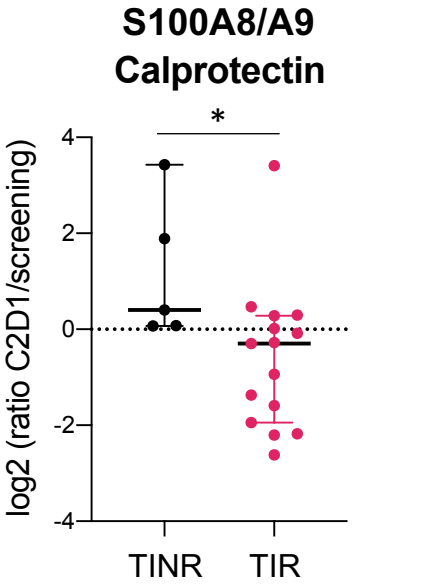



**<u>In TIR (n=6) :</u>**

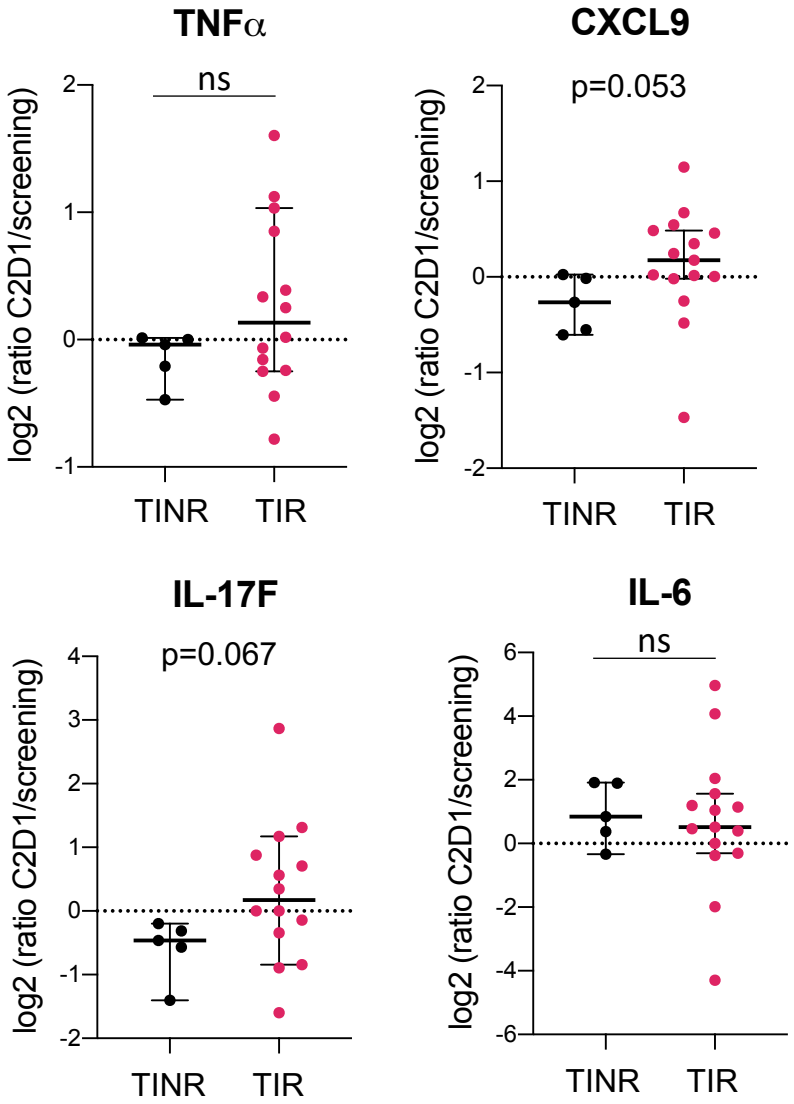
- Modification of repartition of monocytes subpopulations with decreased of HLA-DR-/low monocytes
- Increased of CD8+ terminal effector T cells
- Increased of B cells

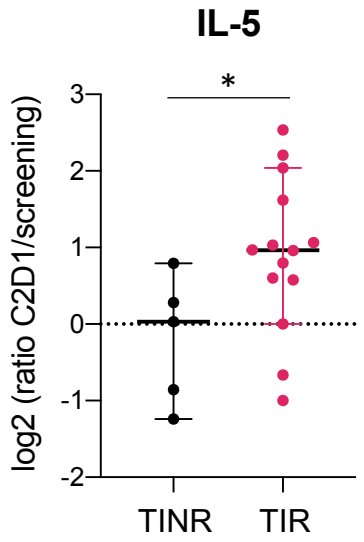
# Early modulation of immunosuppressive S100A8/A9 and pro-inflammatory cytokines after 2 cycles of imetelstat treatment




**Immune suppression**

**Pro-Inflammatory**




**B cells Stimulation**

# Conclusion

- **At baseline TIR** are characterized by **immune suppression, low innate immune features and T cell activation** attested in blood by :
  - Increase proportion of immunosuppressive monocytes (HLA-DR-/low)
  - Lower level of some pro-inflammatory chemokines (IL-18 and CXCL9)
  - Lower level of pro-inflammatory monocytes (CD16+)

- **Imetelstat treatment induces in TIR an immune cell activation** attested in blood by remodeling of:
  - immune cell repartition (monocytes, T CD8+ cells and B cells)
  - pro-inflammatory and immunosuppressive cytokines

**Future studies will be necessary to**

- Determine the contribution of immunomodulation to the erythroid response
- Validate theranostic and predictive biomarkers of response to imetelstat treatment

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