



XIX CONGRESSO
NAZIONALE
SIES 2026

**L'Analisi Multiomica a Singola Cellula Rivela
Meccanismi Molecolari e Cellulari Associati alla
Risposta a Ruxolitinib nella Mielofibrosi**

Chiara Carretta

Firenze | 4-6 marzo 2026
Palazzo degli Affari

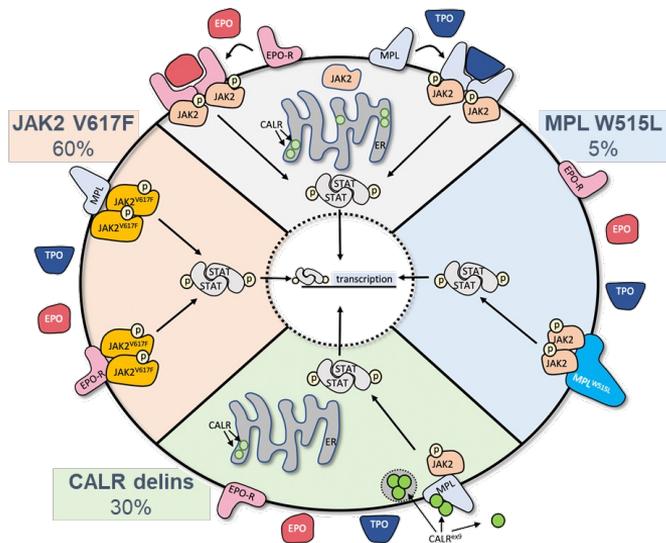


Disclosures of Chiara Carretta

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
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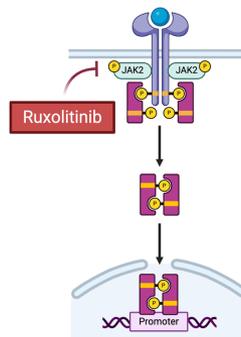


MPN Driver mutations



Schieber, M. et al., Blood Cancer J. 2019

Ruxolitinib treatment

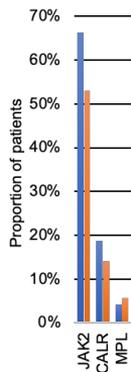


| | |
|--|---|
| <ul style="list-style-type: none"> Reduced spleen/ liver size Improved symptoms Reduced inflammatory signalling | <ul style="list-style-type: none"> Cytopenia (anemia or thrombocytopenia) Reduced immune cell activation, infections No "true" disease modification, disease progression |
|--|---|

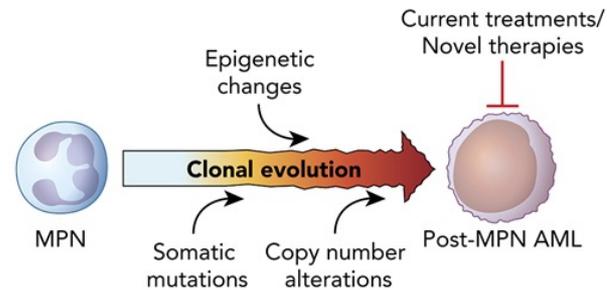
adapted from Verstovsek, S. et al., J Hematol Oncol 2023



MPN Clonal Evolution



Rontauoli, S. et al., IJMS, 2022



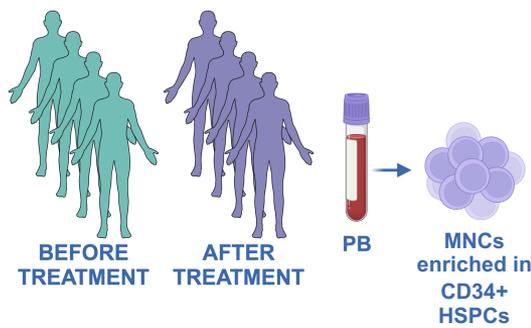
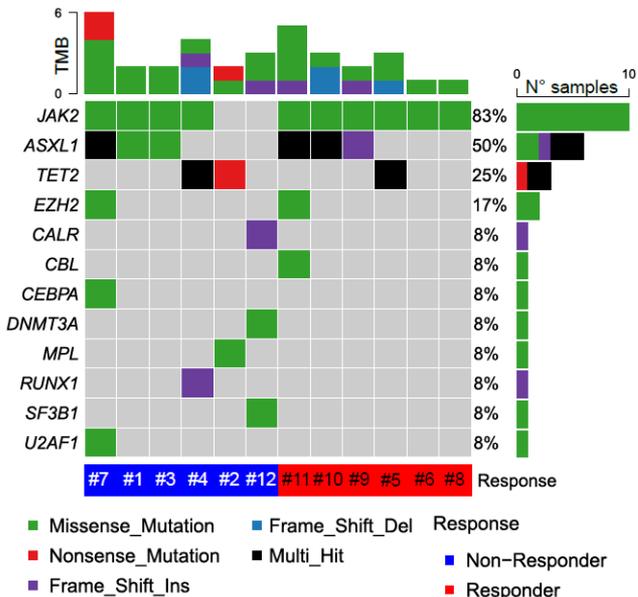
Dunbar, J. et al., Blood. 2020

Molecular Heterogeneity

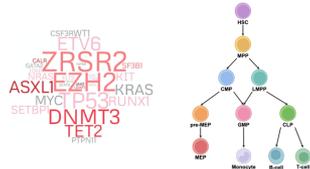




Characterization of the clonal dynamics associated with therapy resistance in MPN

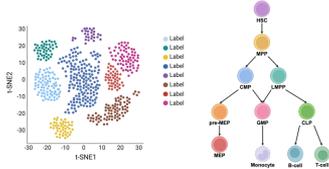


Tapestri



Genomics + Proteomics

10X Chromium

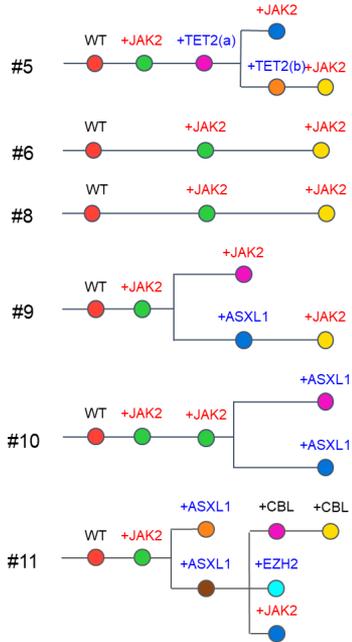


Transcriptomics + Proteomics



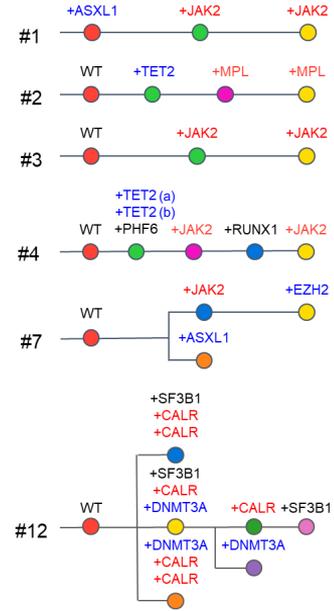
Mutation acquisition order distinguishes JAKi-Responders from Non-Responders

JAKi Responders



Driver only
 or
 Driver + Epigenetic

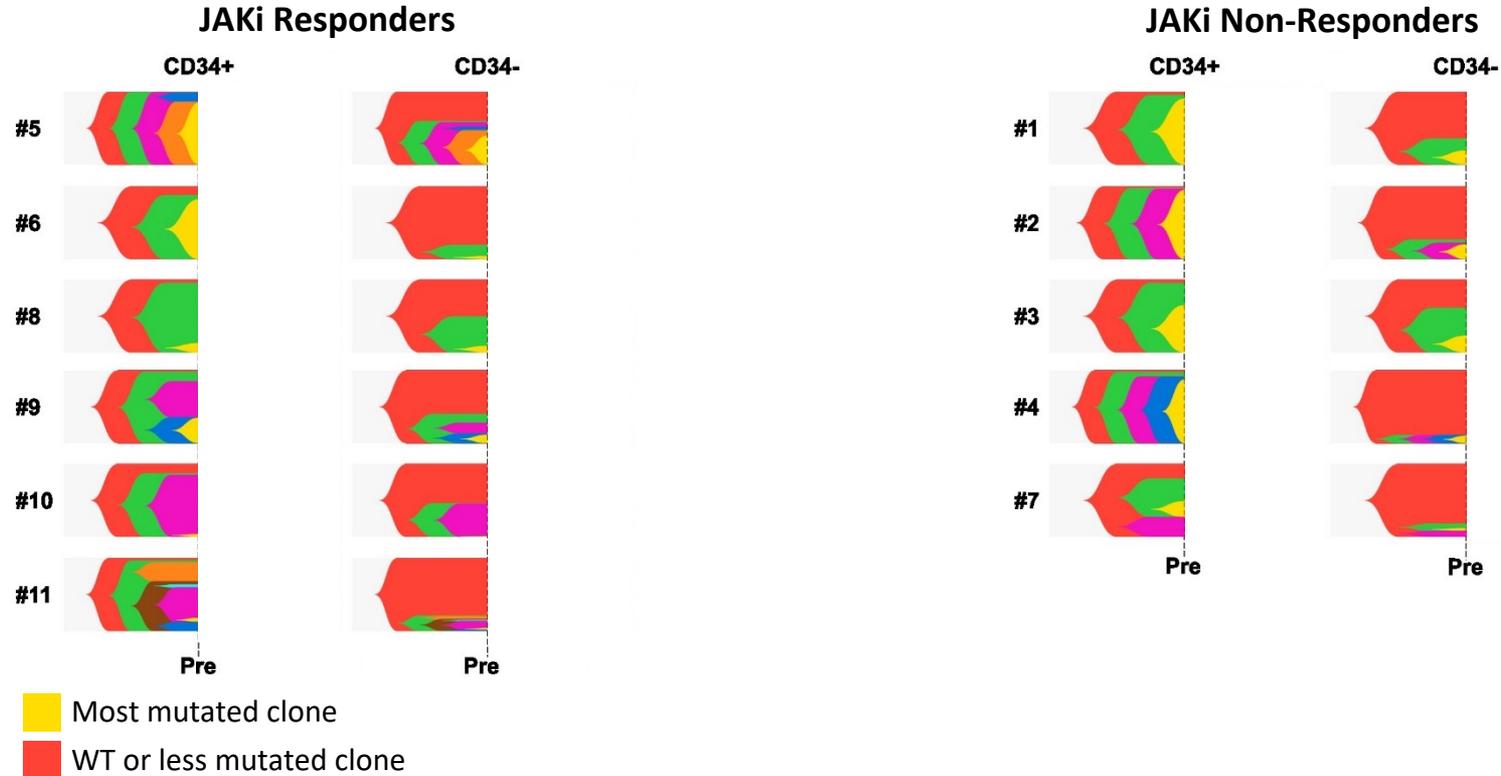
JAKi Non-Responders



Epigenetic + Driver

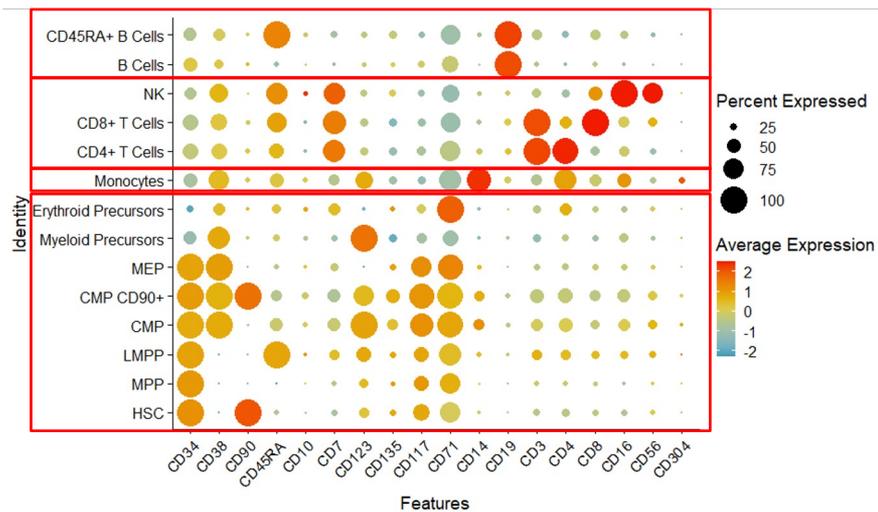


The most mutated clone dramatically expands in Non-Responders despite JAK inhibition

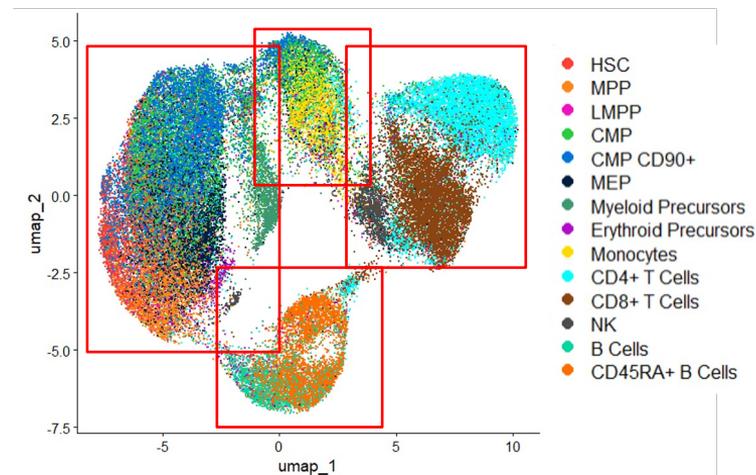




Single-Cell Proteomics Resolves HSPCs and Their Differentiated Subpopulations



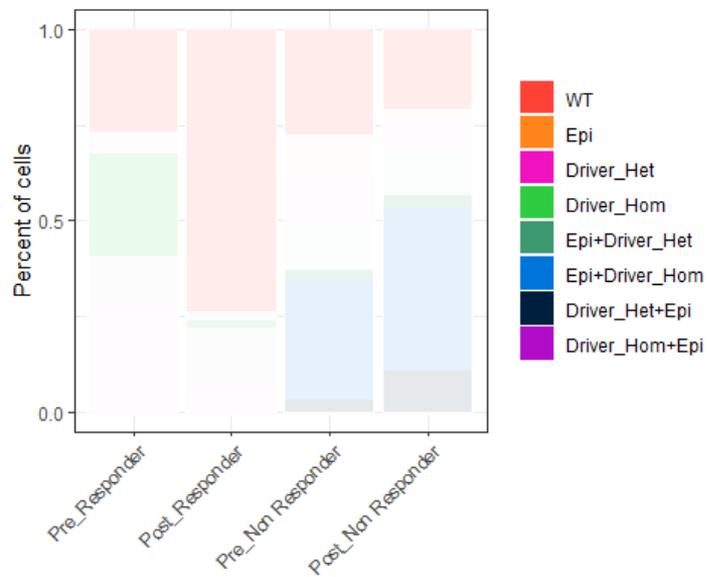
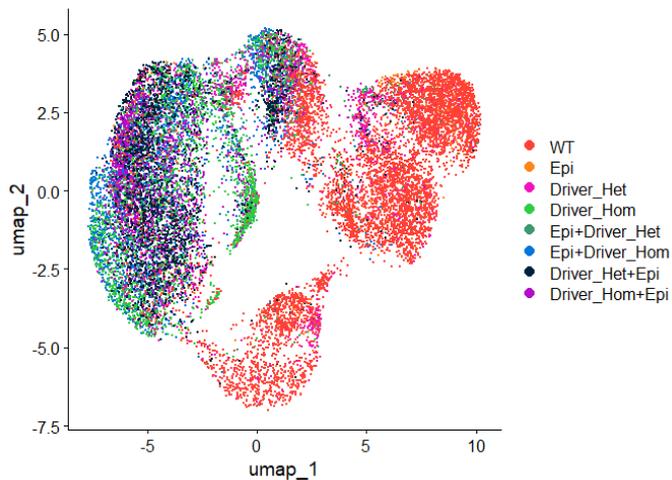
Proteomic classification





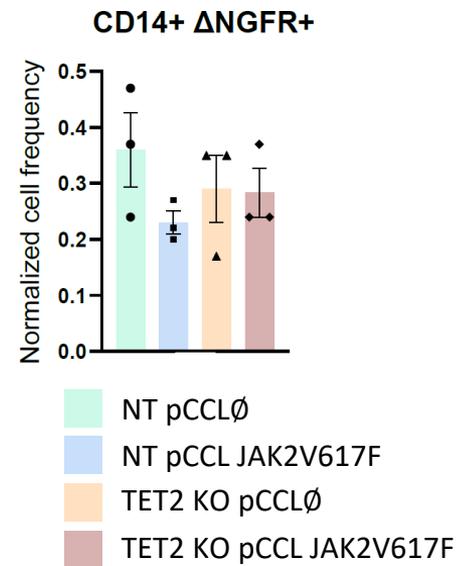
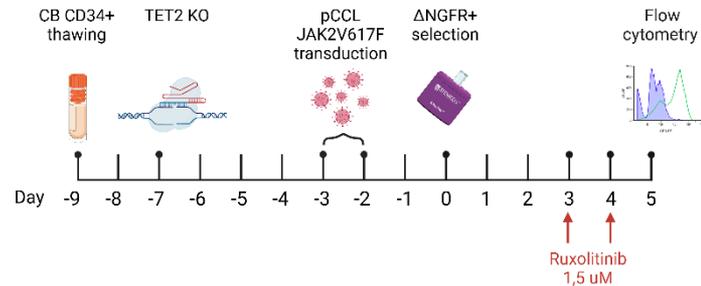
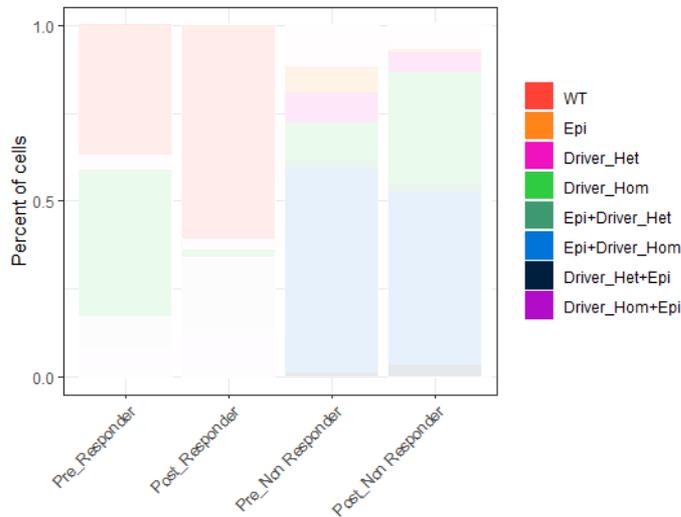
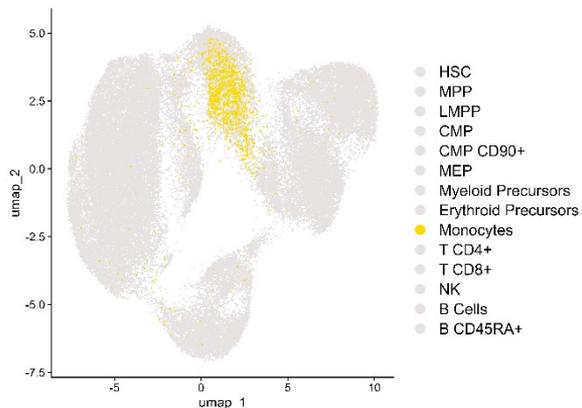
MPN driver homozygous clones are the most sensitive to JAKi treatment

Genomic classification



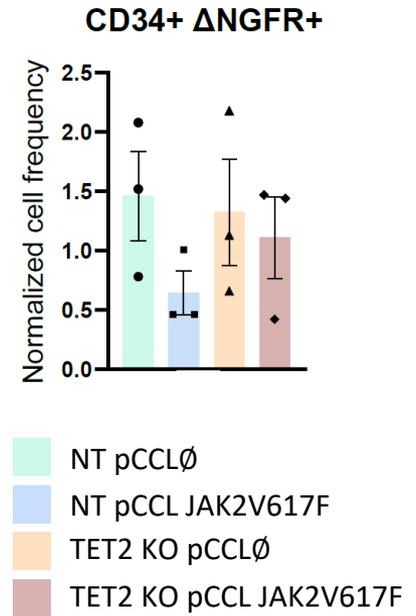
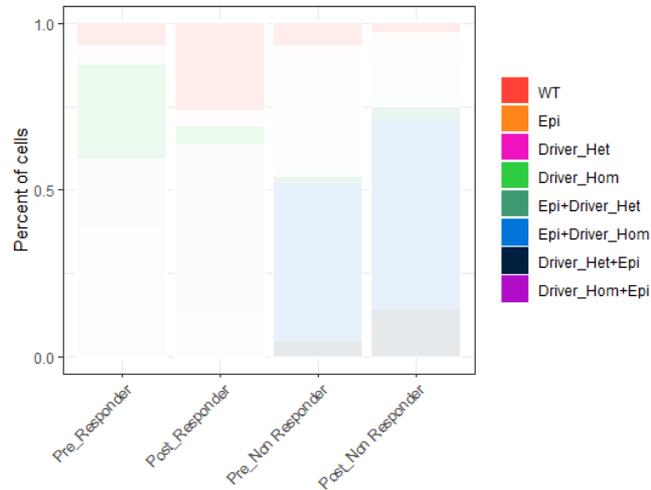
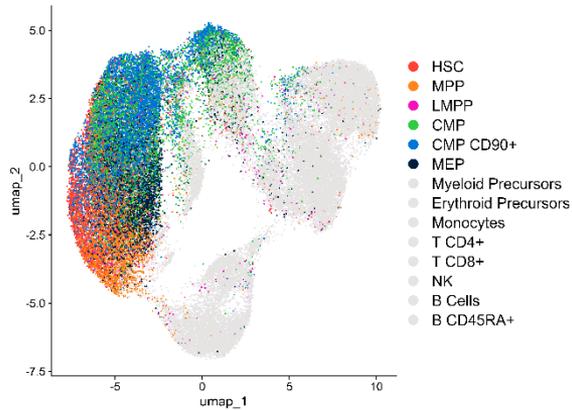


WT monocytes are expanded in Responder patients



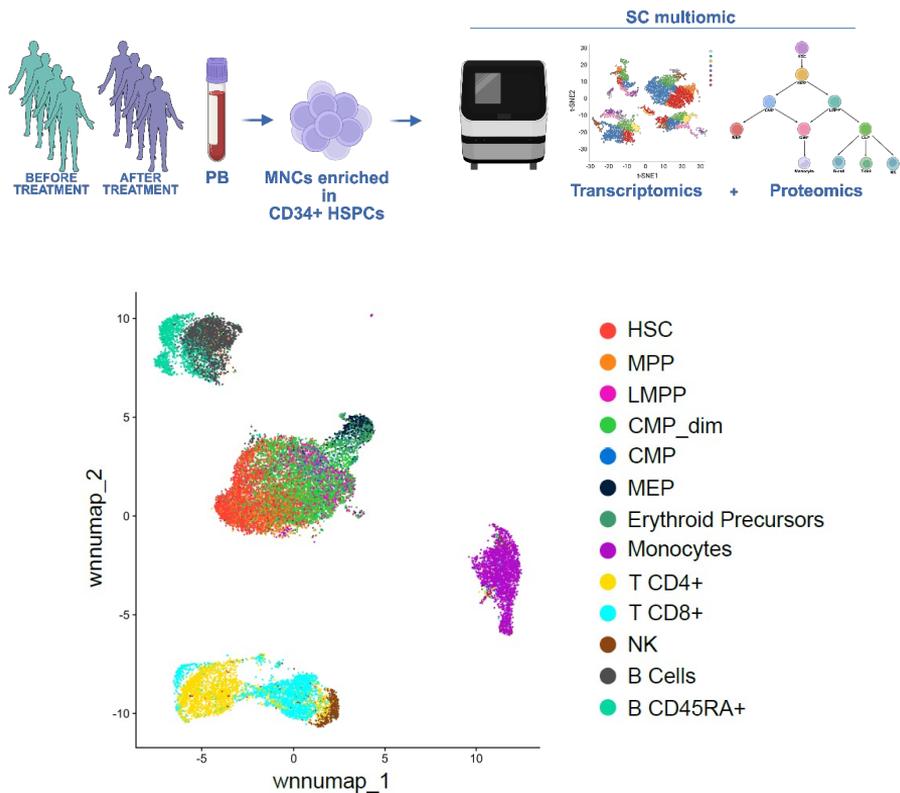


JAKi treatment does not eradicate co-mutated clones in HSPC compartment

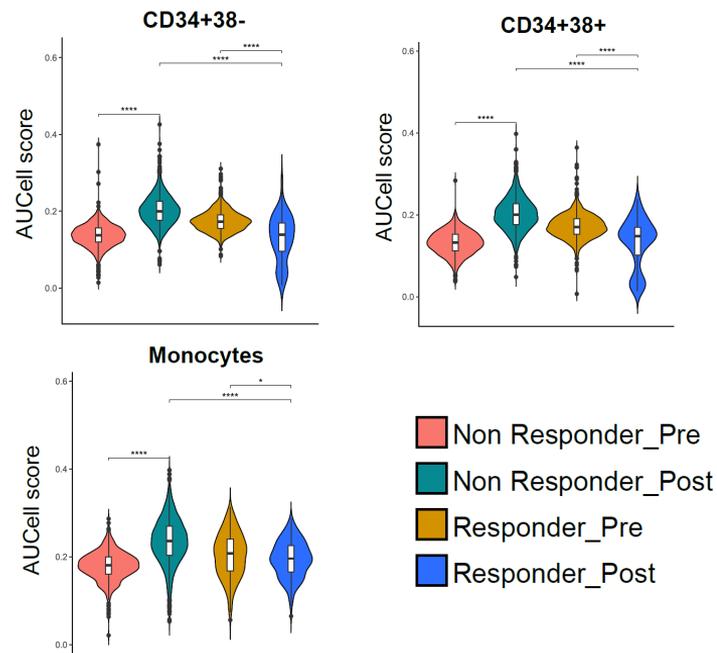




JAK/STAT signaling activation was increased in Non-Responder cells after JAKi treatment



Interferon signaling predicted activation





Conclusions

- **MPN driver mutation is a secondary event in JAKi Non-Responder patients**, preceded by hits in epigenetic modifiers, mainly *TET2* and *ASXL1*.
- JAKi response is associated with a **reduction in MPN driver homozygous cells** and an expansion of WT cells.
- In both Responder and Non-Responders, **the frequency of co-mutated HSPCs is unaffected** by JAK inhibition.
- In Non-Responder patients, **JAK/STAT signaling is activated despite JAKi treatment**, suggesting that inflammation might contribute to MPN clones' persistence.



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