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# Functional and molecular precision medicine in FLT3- mutated AML

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# Disclosures and affiliations

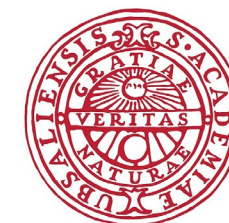
## ❖ Olli Kallioniemi:

- Board member Sartar Therapeutics
- Advisory board: Novo Nordisk Foundation, Data Science Committee
- Grant support and advisory role: Knut and Alice Wallenberg Foundation

## ❖ Sören Lehmann:

- Board member/advisory board: Abbvie, Pfizer, Rarity, Servier

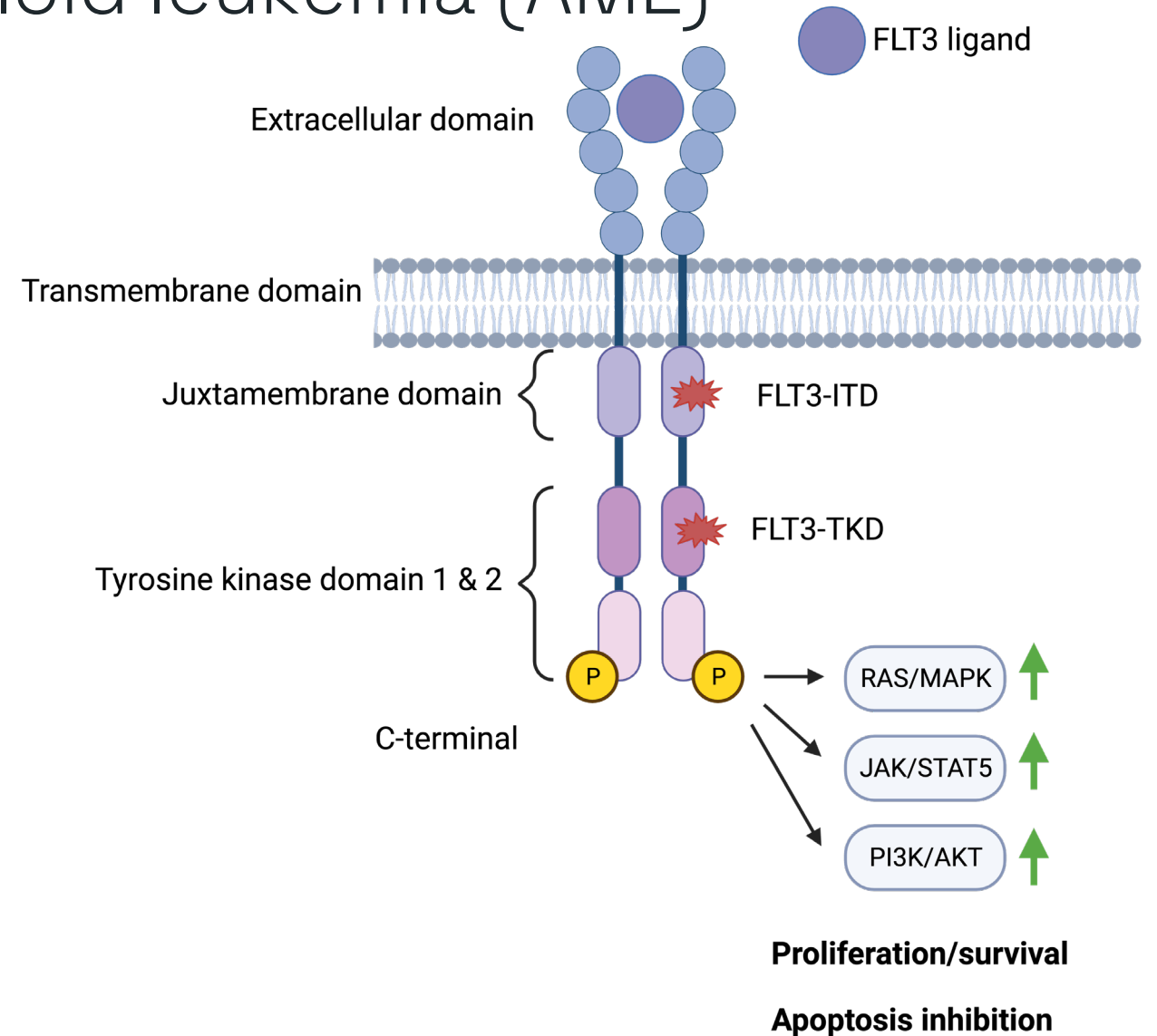
## ❖ Other authors have no disclosures



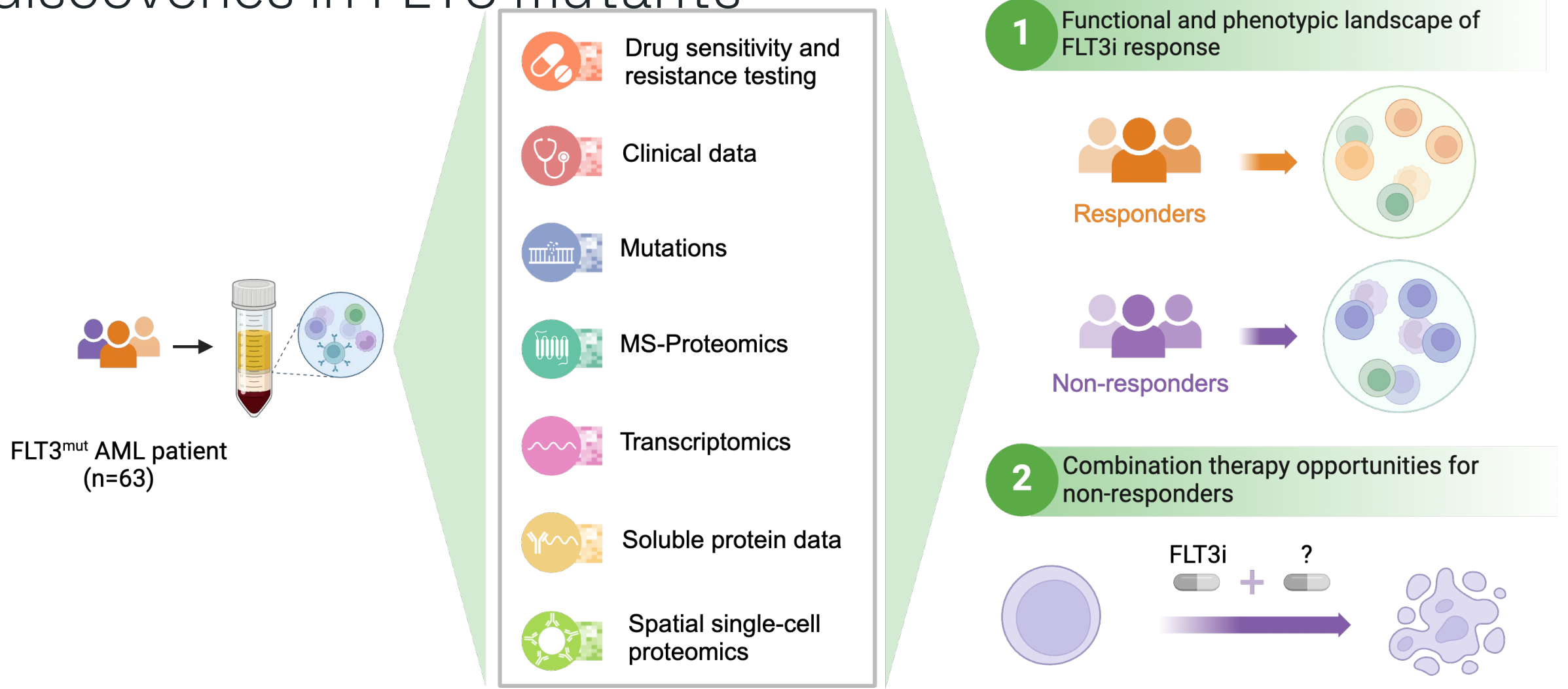
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# FLT3-mutated acute myeloid leukemia (AML)

- FMS-like tyrosine kinase 3 (FLT3)
- Mutated in ~30% of AML patients
- Poor prognosis, more likely to relapse
- Midostaurin
- ~40% of FLT3<sup>+</sup> patients do not respond (Stone et al., 2017)



# Study overview - Enabling precision cancer medicine discoveries in FLT3 mutants

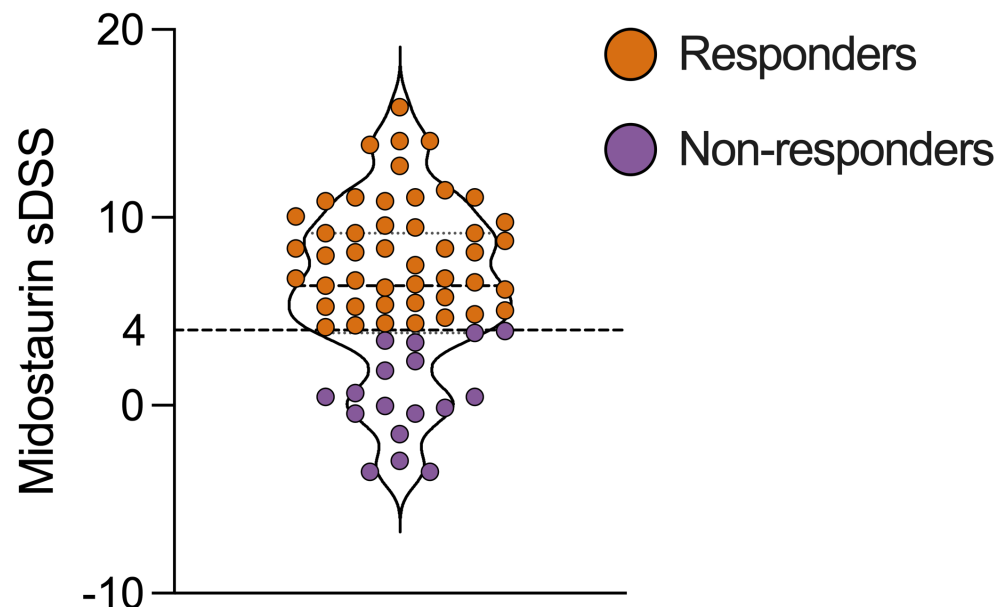


# Clinical outcome of midostaurin treatment is in line with *ex vivo* drug resistance

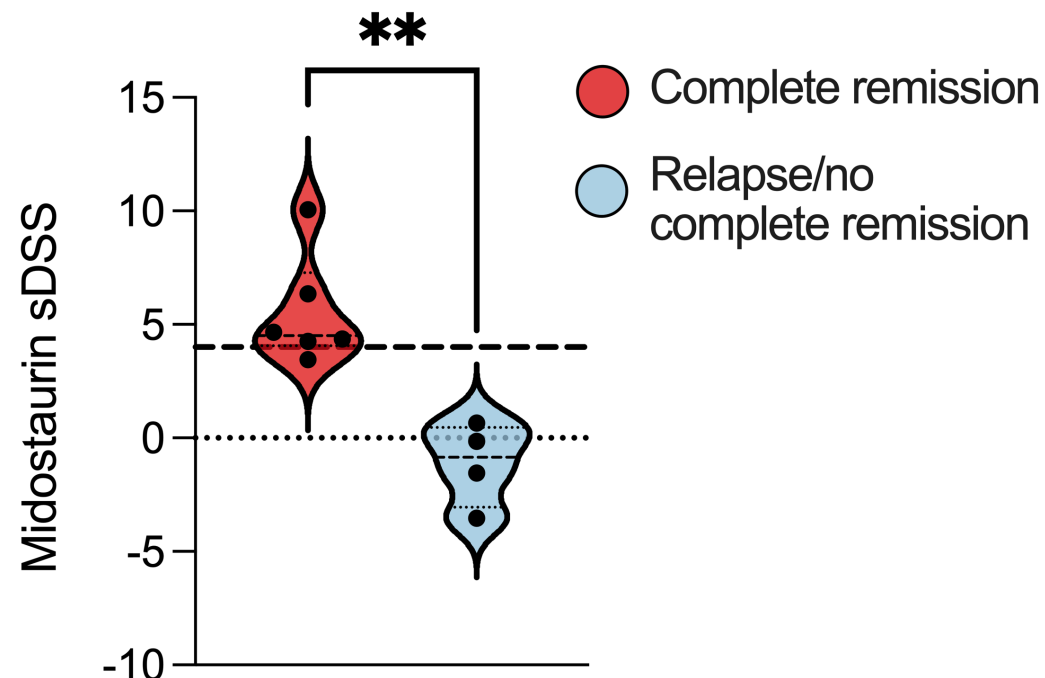
Drug sensitivity and resistance testing



Clinical data





- 63 AML patients with FLT3<sup>mut</sup>
- *ex vivo* selective drug sensitivity score <4 considered resistant

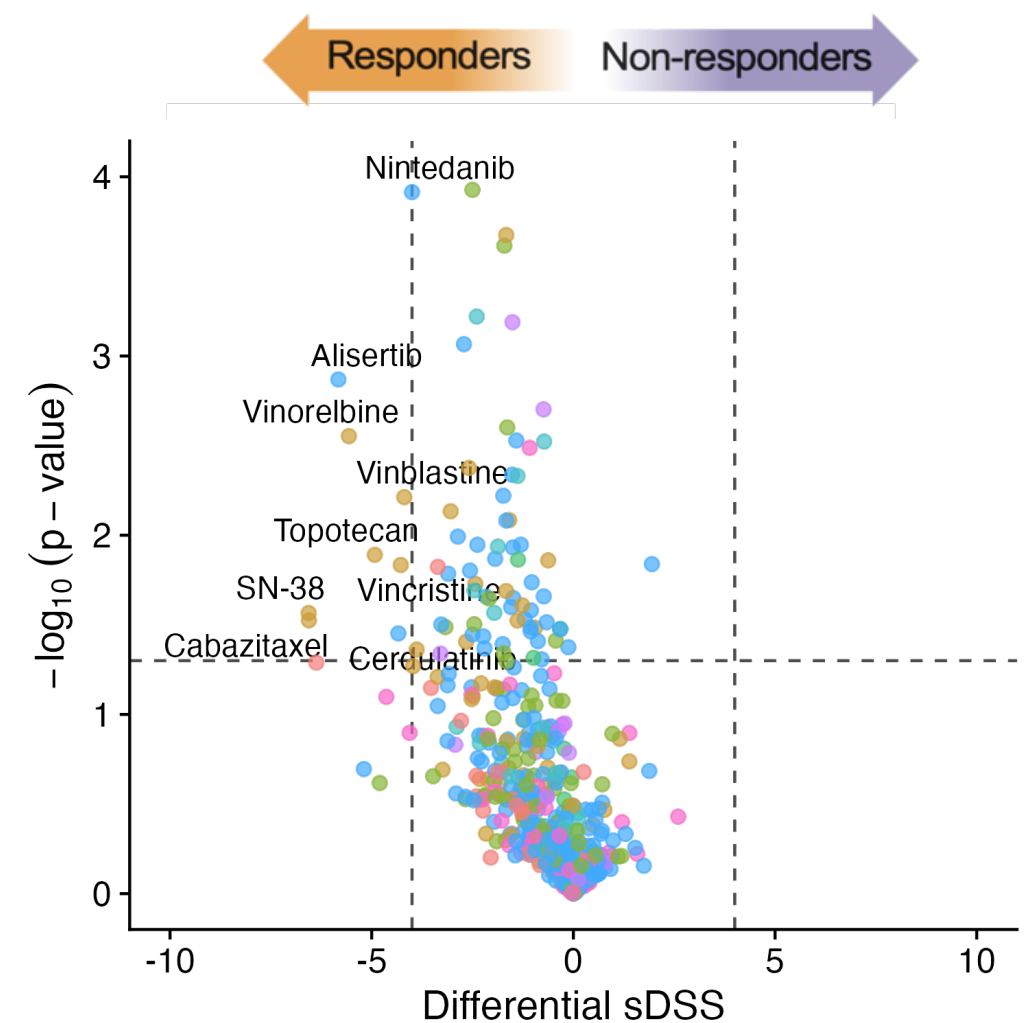
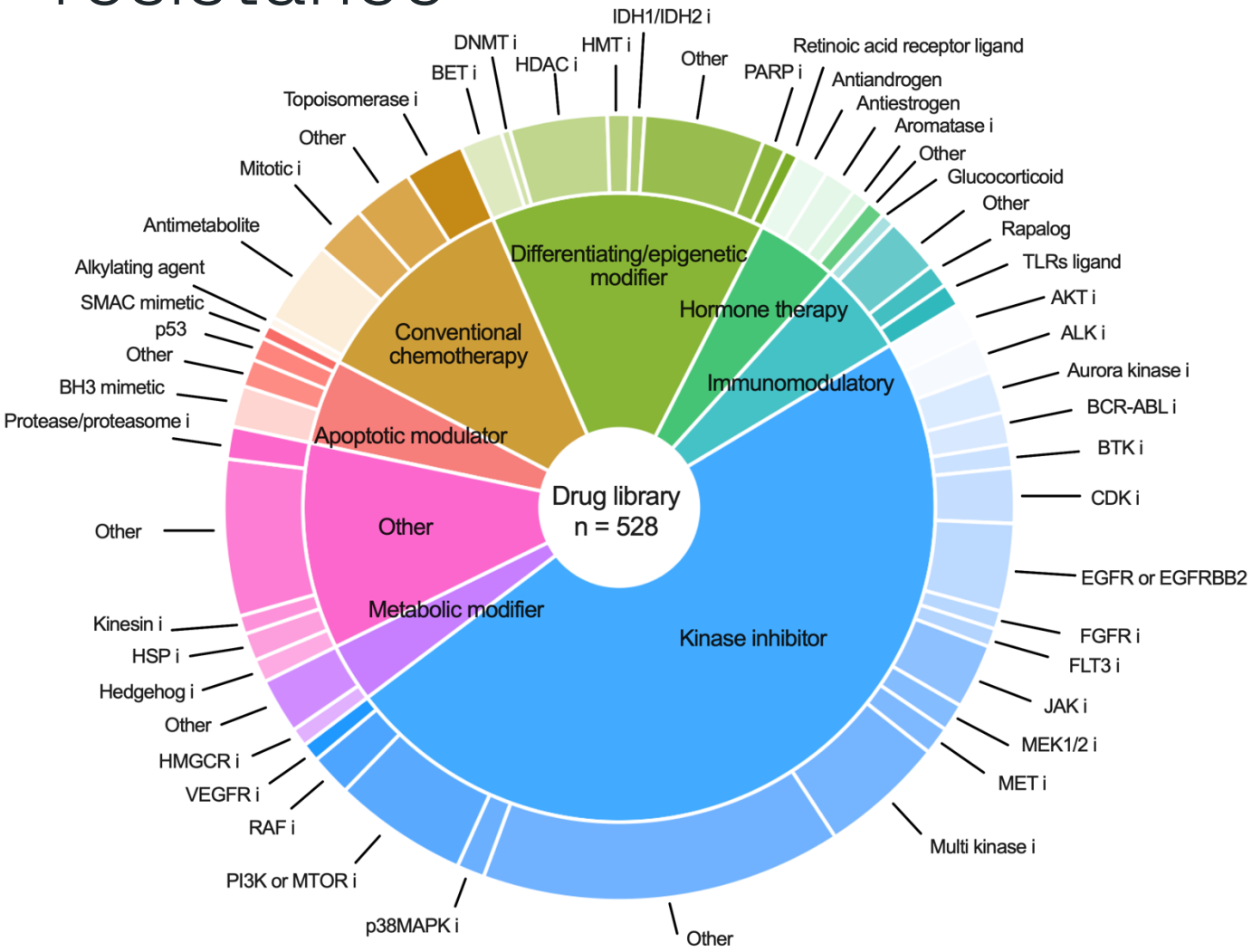


- Patients receiving midostaurin (n=10) more likely to relapse if lower sDSS

# Non-responders associate with overall drug resistance

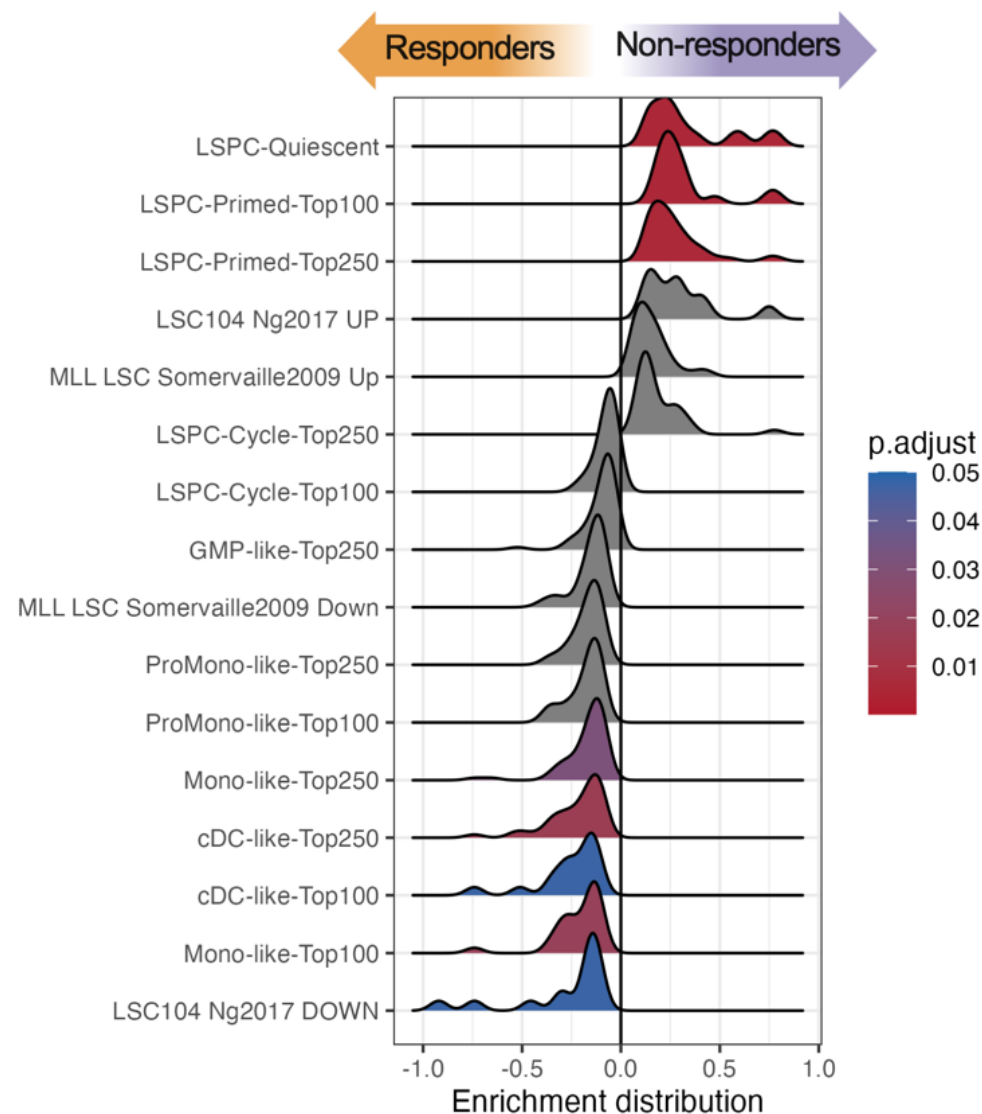
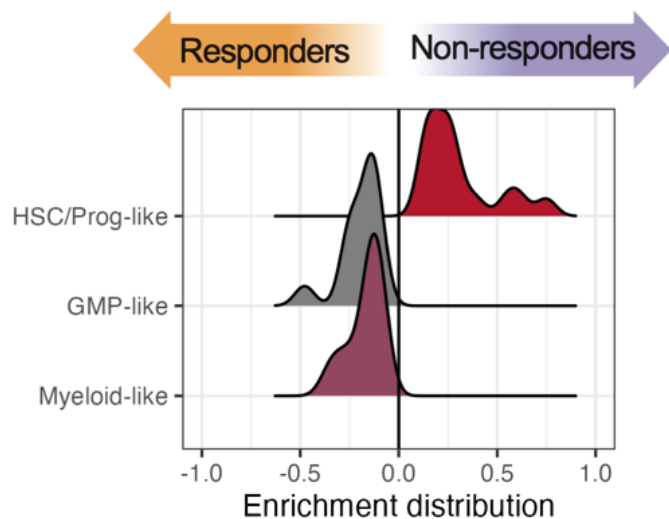
Drug sensitivity and resistance testing 

Clinical data 

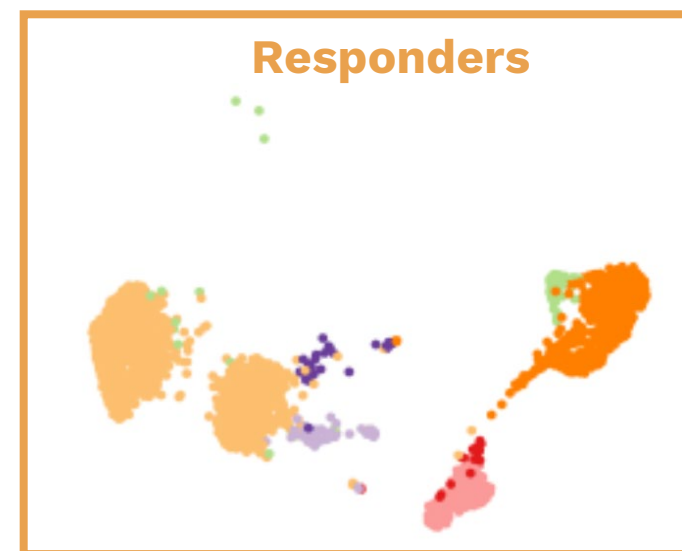
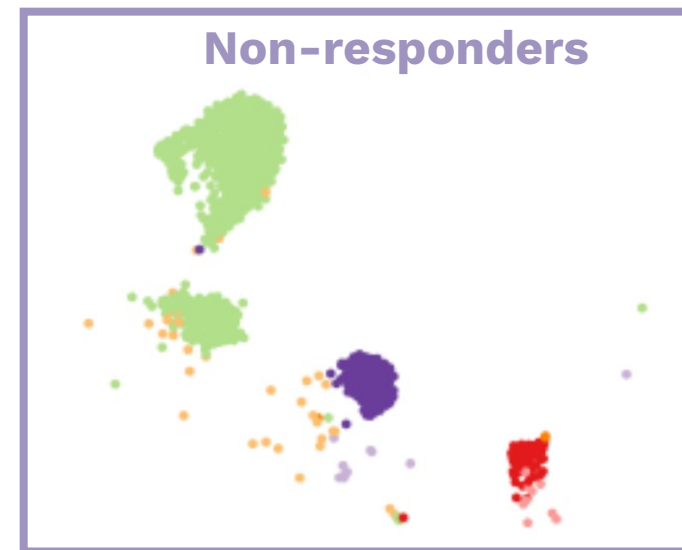
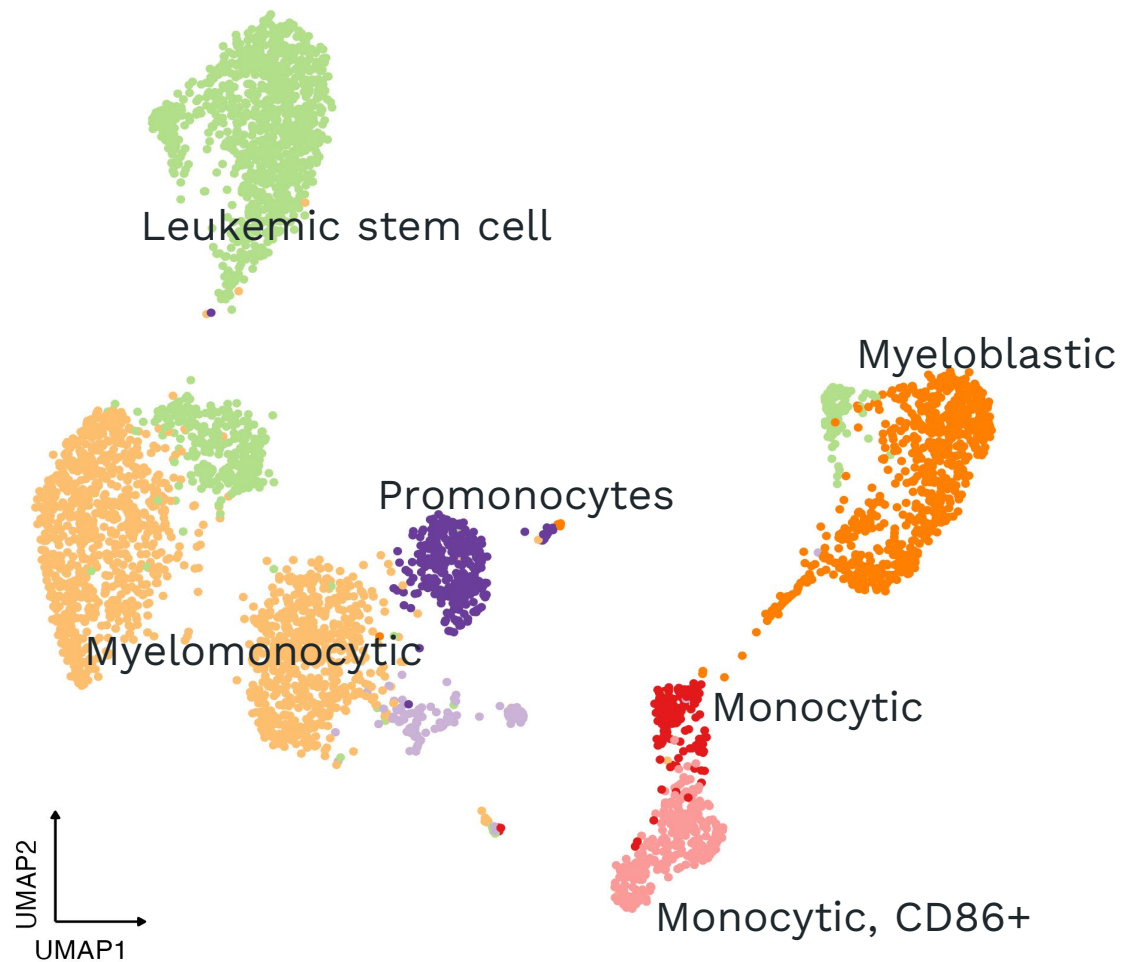


# Midostaurin non-responders are enriched for immature phenotypes

- Non-responders enriched for HSC and LSPC phenotypes
- Responders myeloid/monocytic

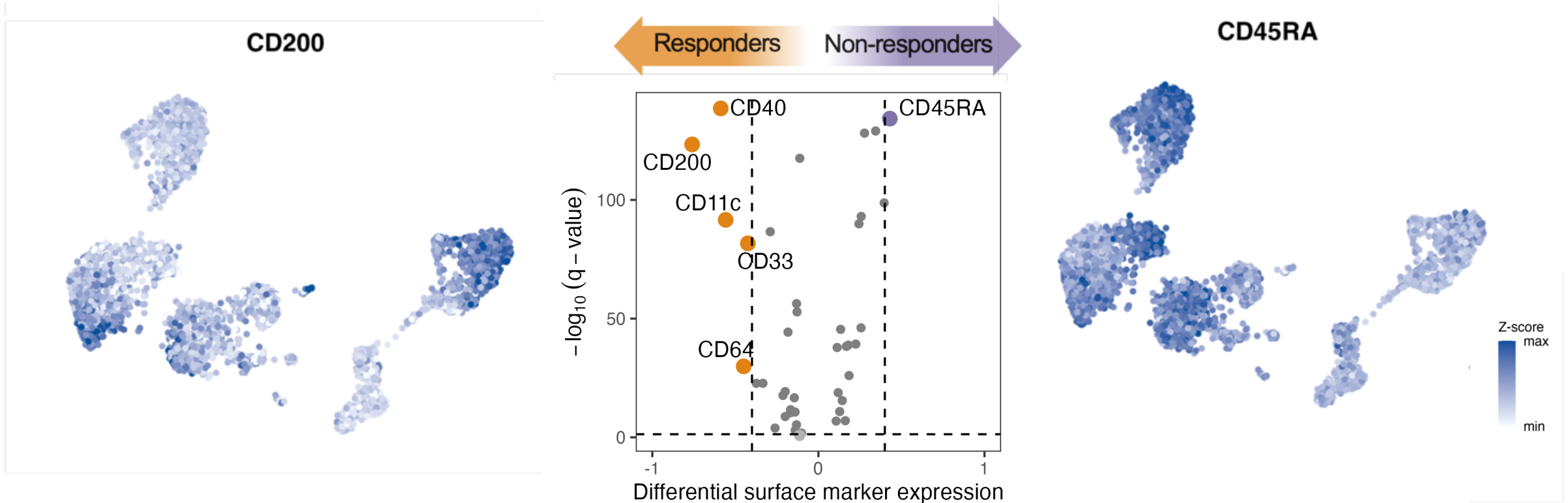


# Midostaurin non-responders are enriched for immature phenotypes

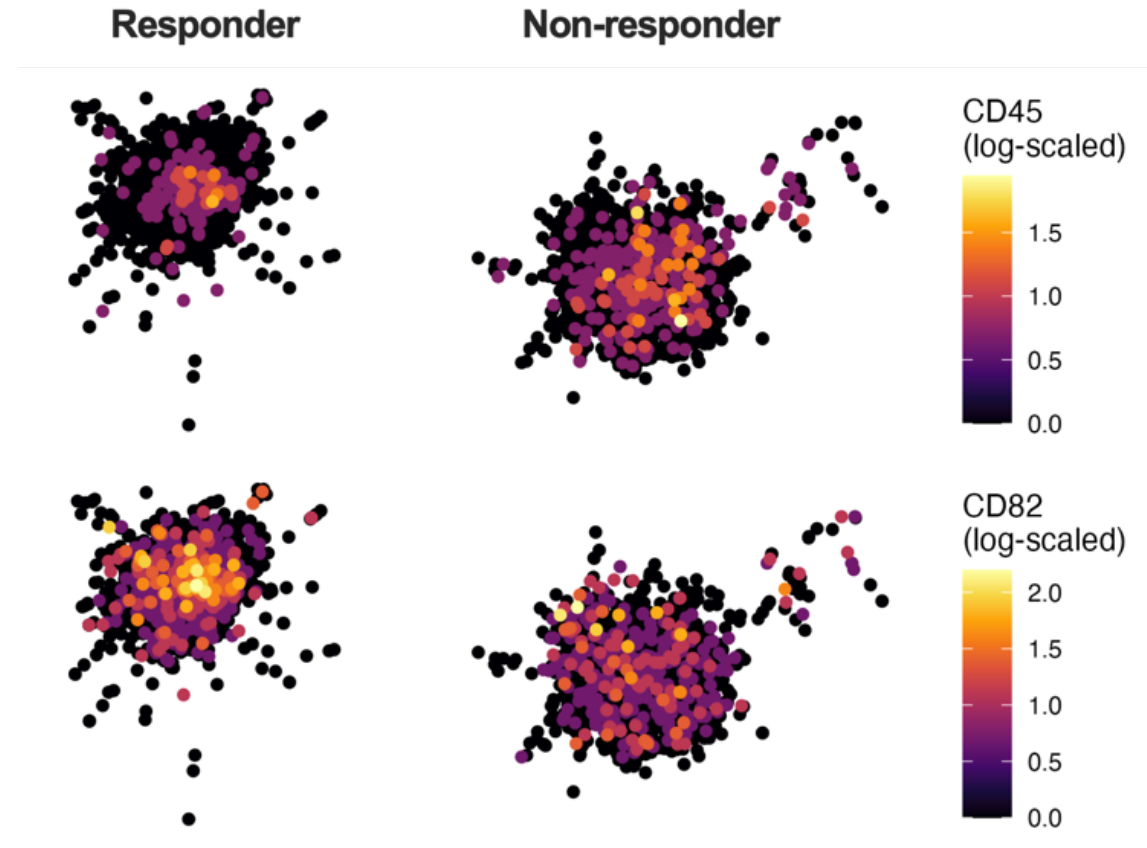
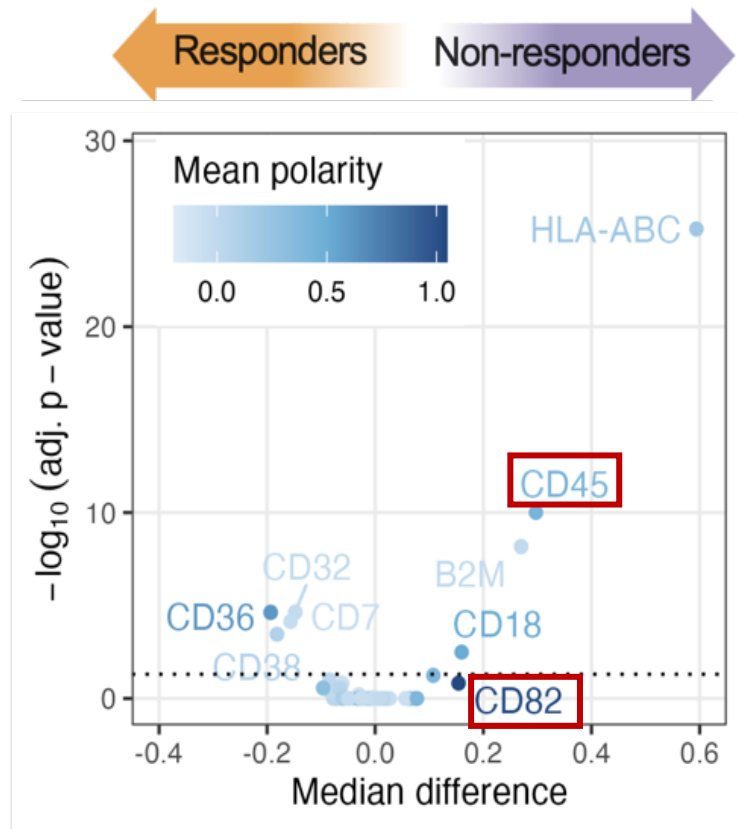




# CD200 expression higher in responders CD45RA expression higher in non-responders

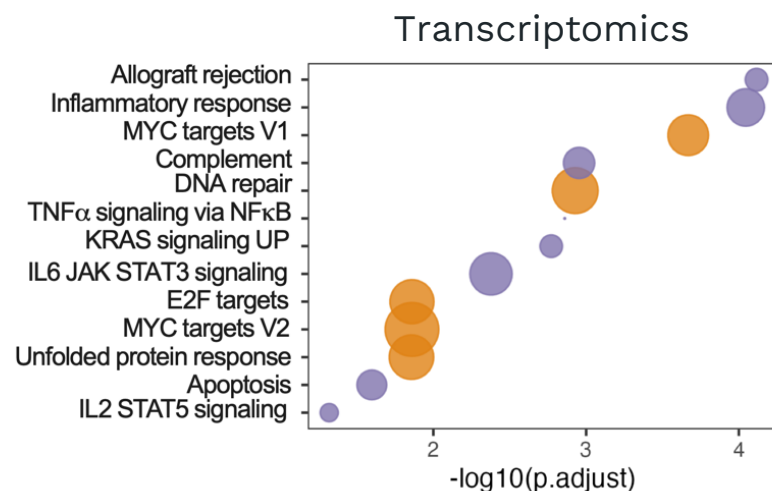
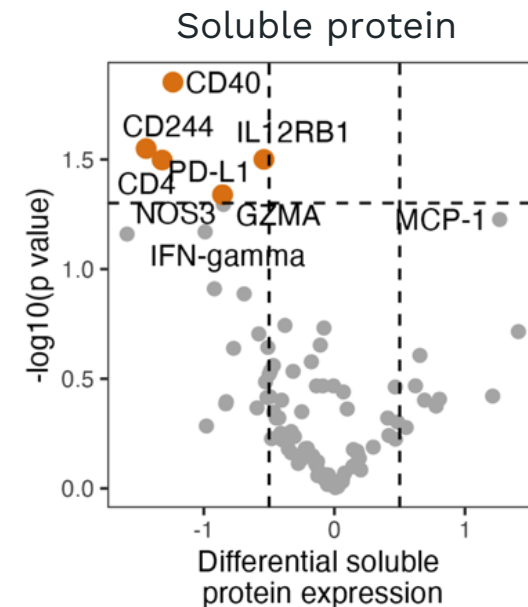
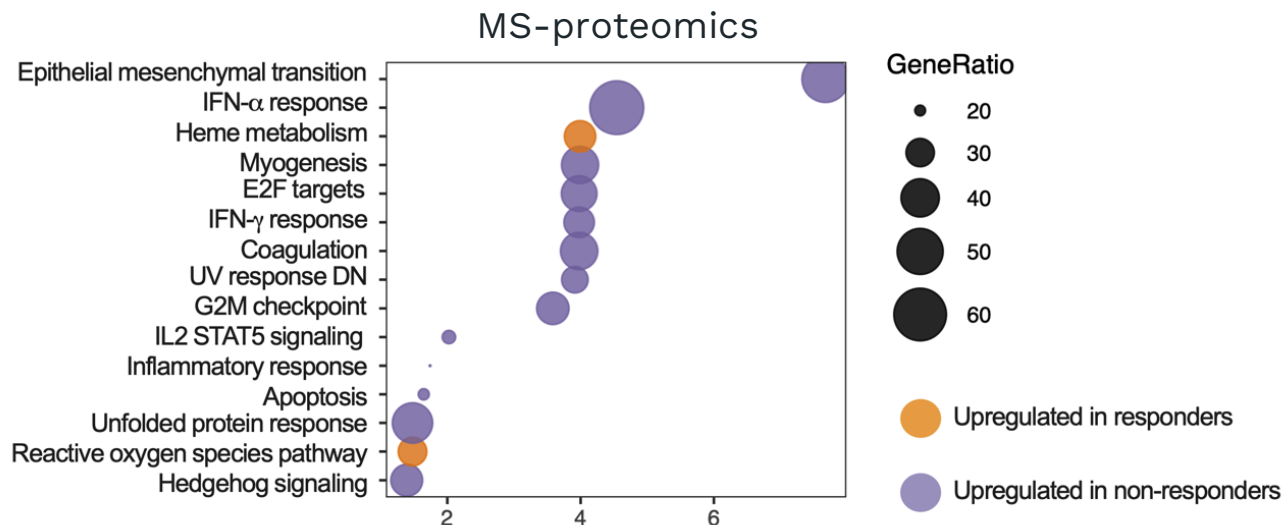
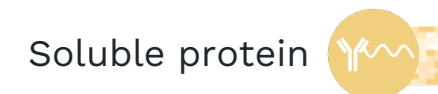


# Spatial localization of CD82 suggests disruption of CD45 isoform stability



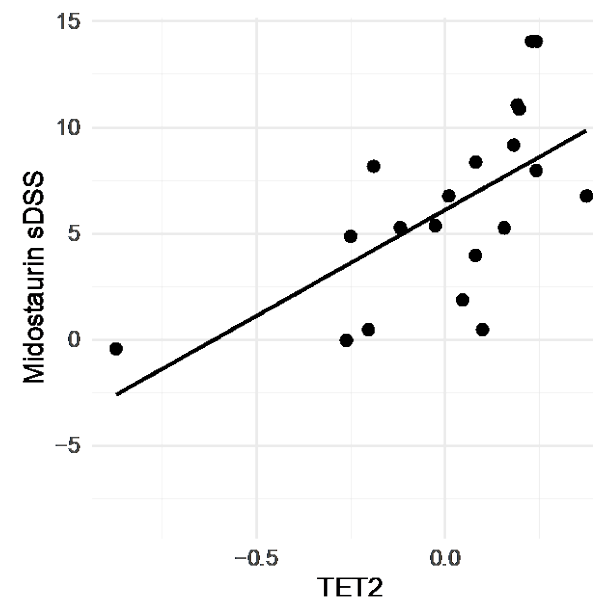
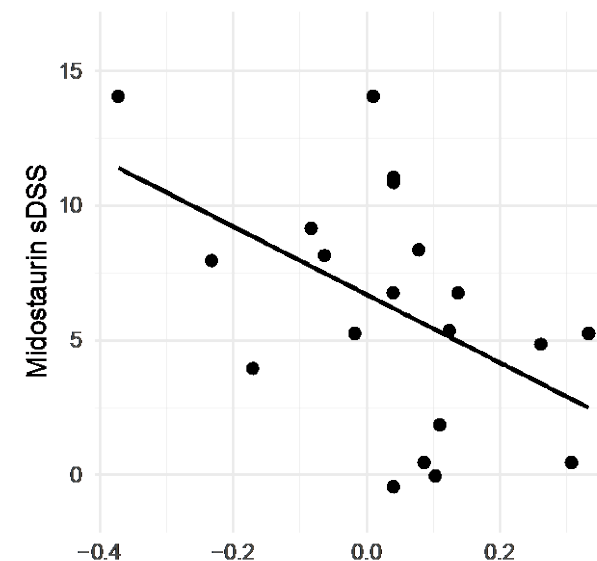
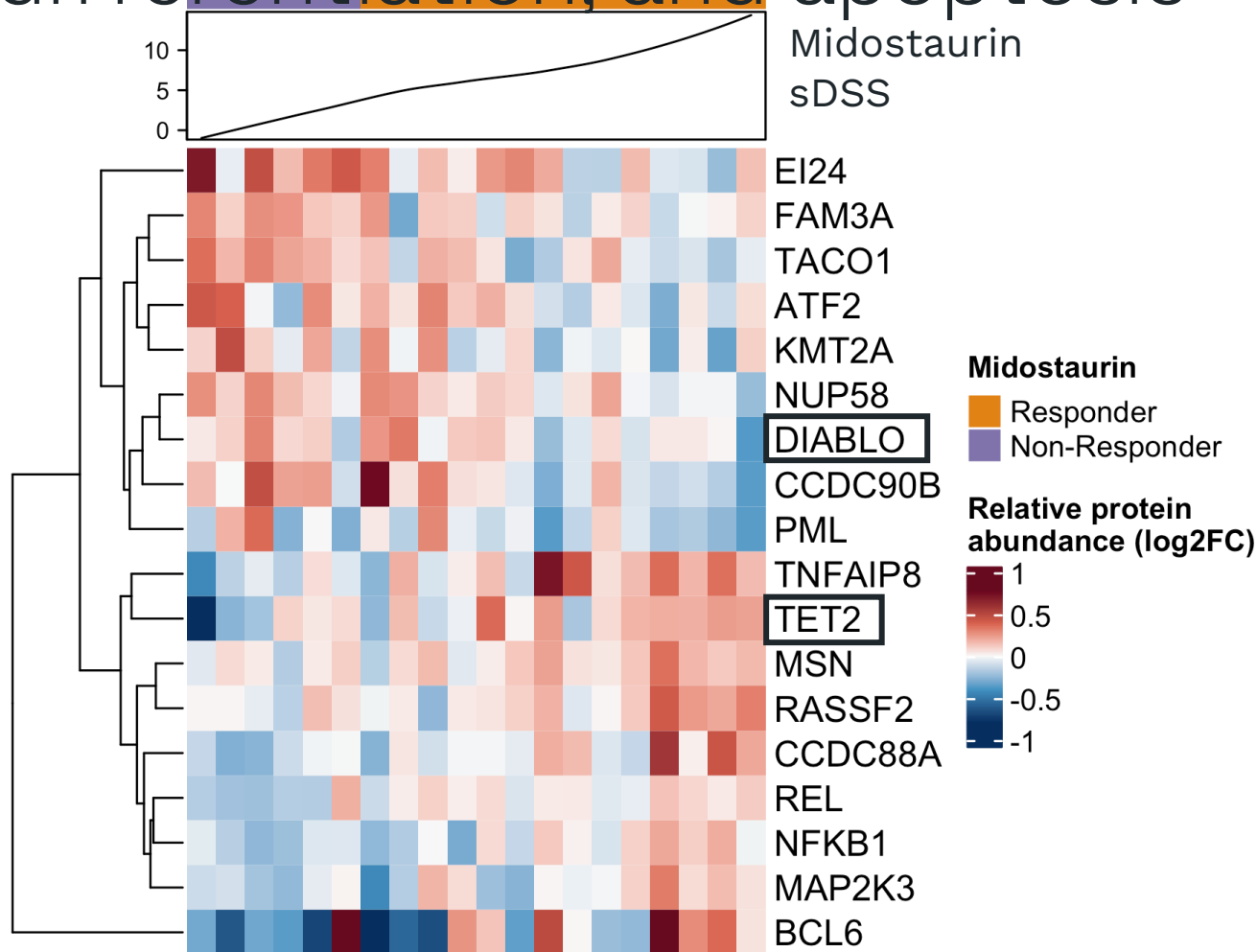
Increased polarity and reduced co-localization of CD82 and CD45

# Midostaurin non-responders show higher immune activation

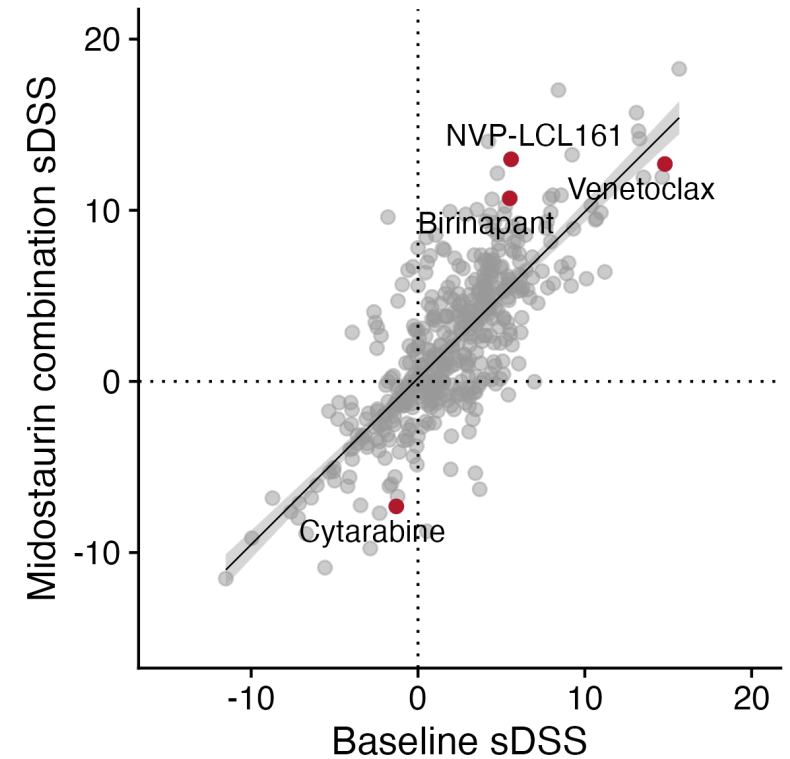
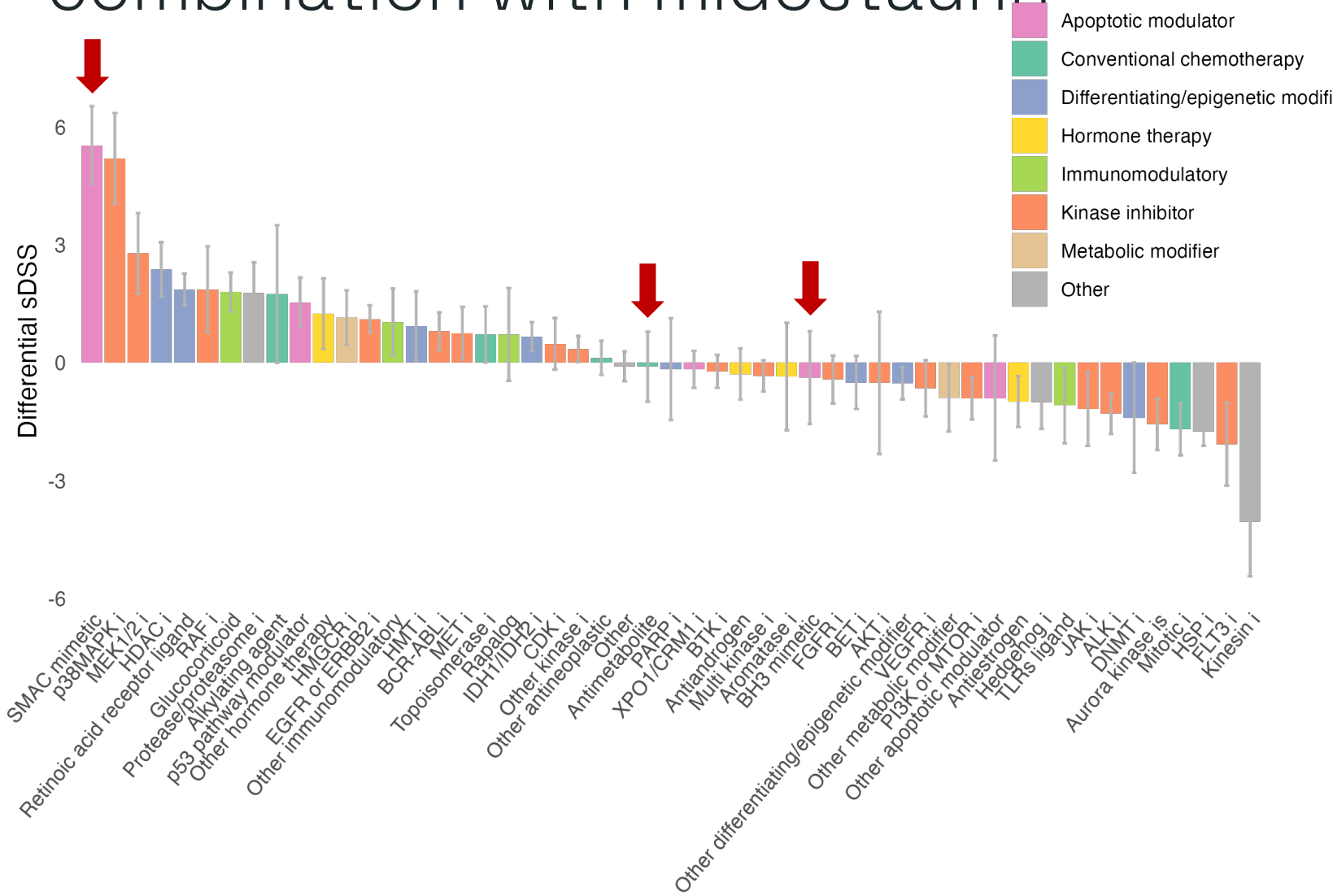


- Immune activation in non-responders
- Upregulated STAT signaling pathways
- Immune suppressive cytokines secreted by responders

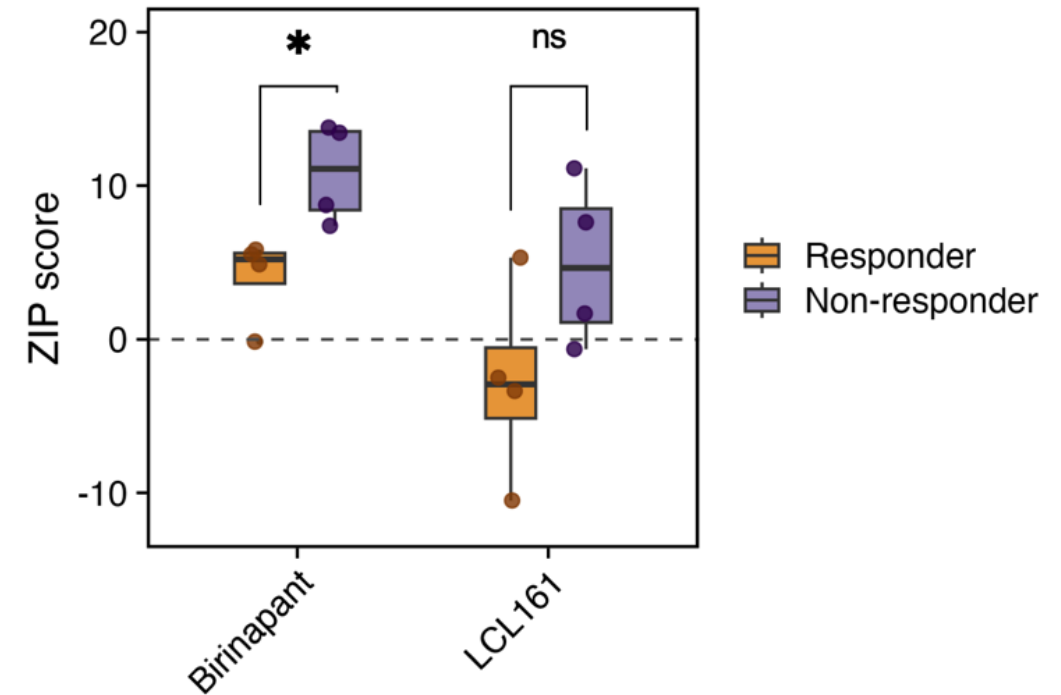
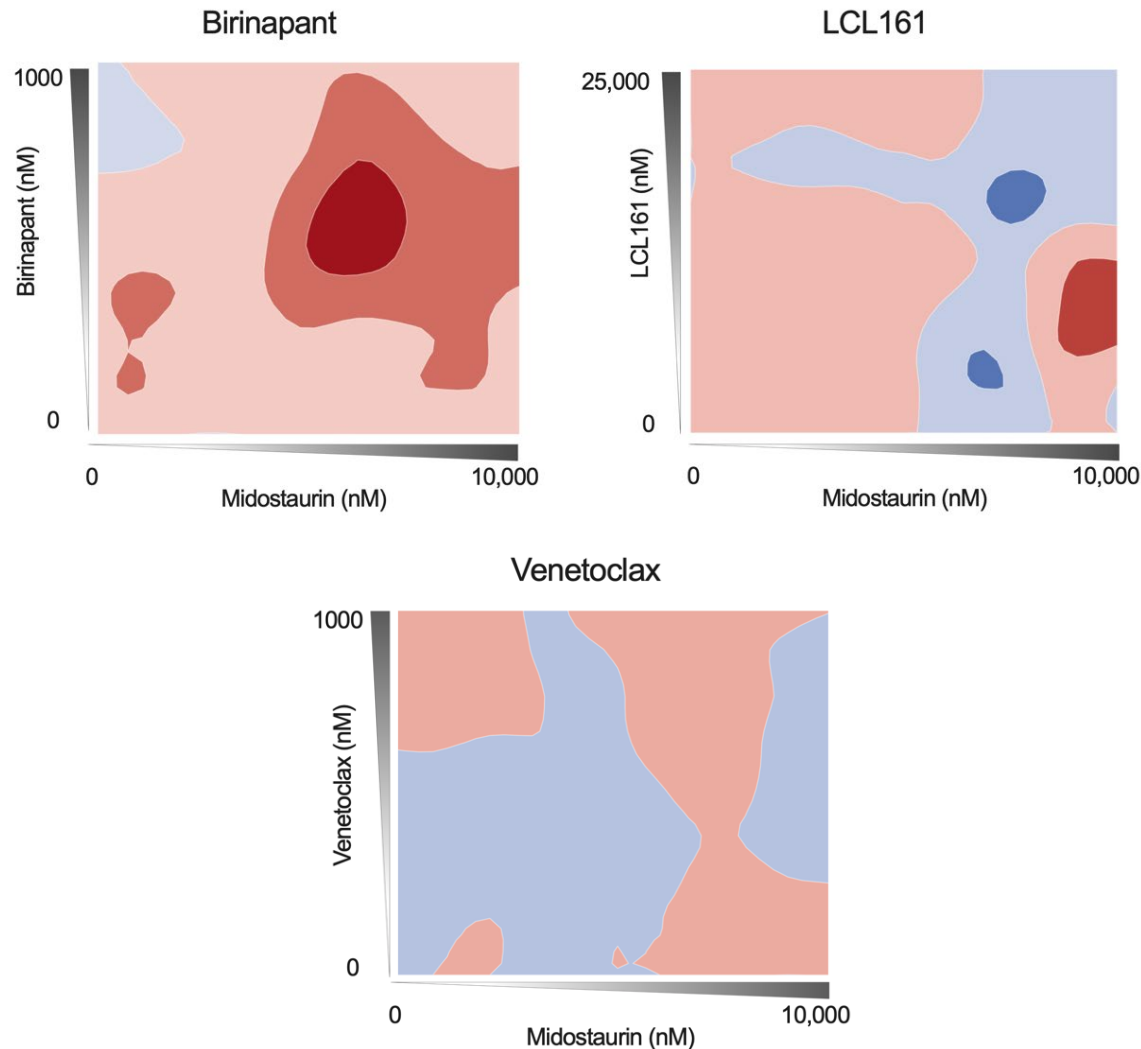
# Midostaurin response is associated to proteins involved in mitochondrial metabolism, differentiation, and apoptosis



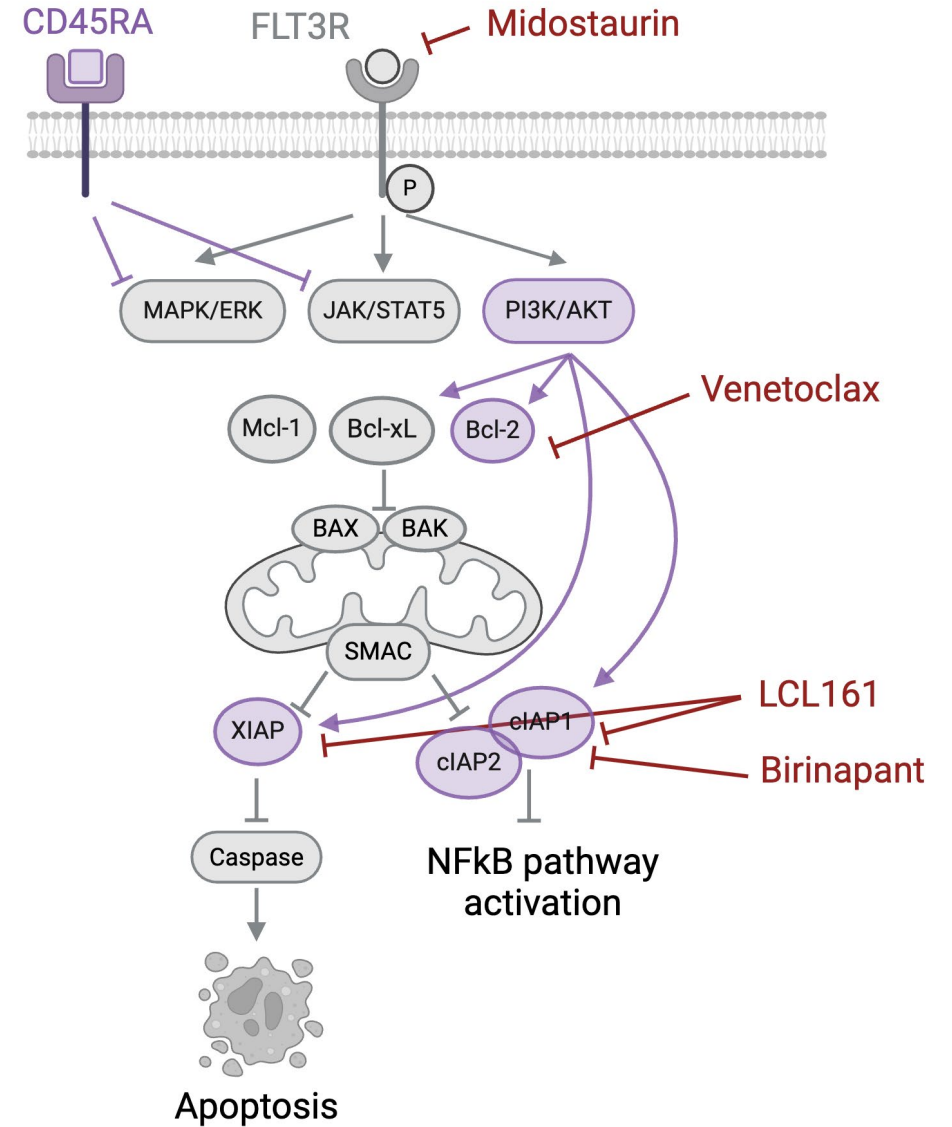
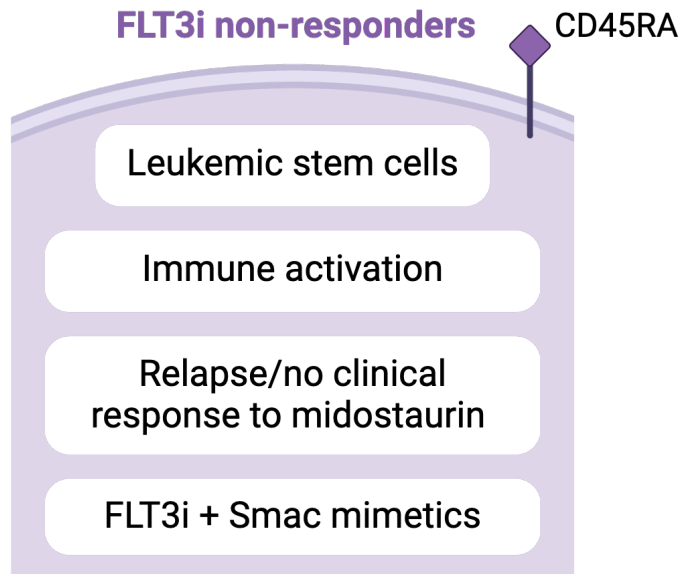
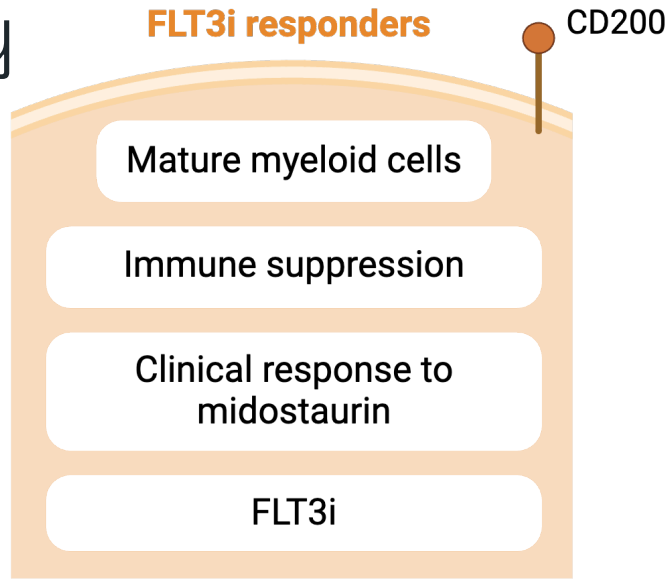
# SMAC mimetics show highest sDSS increase in combination with midostaurin



# Midostaurin synergizes with SMAC-mimetic birinapant in resistant patient cells



# Summary



# Acknowledgements



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