

Dasatinib Reverses Myeloid Derived Suppressor Cell (MDSC) Inhibition of T cell Proliferation in a Triple-Negative Breast Cancer Model

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Disclosures



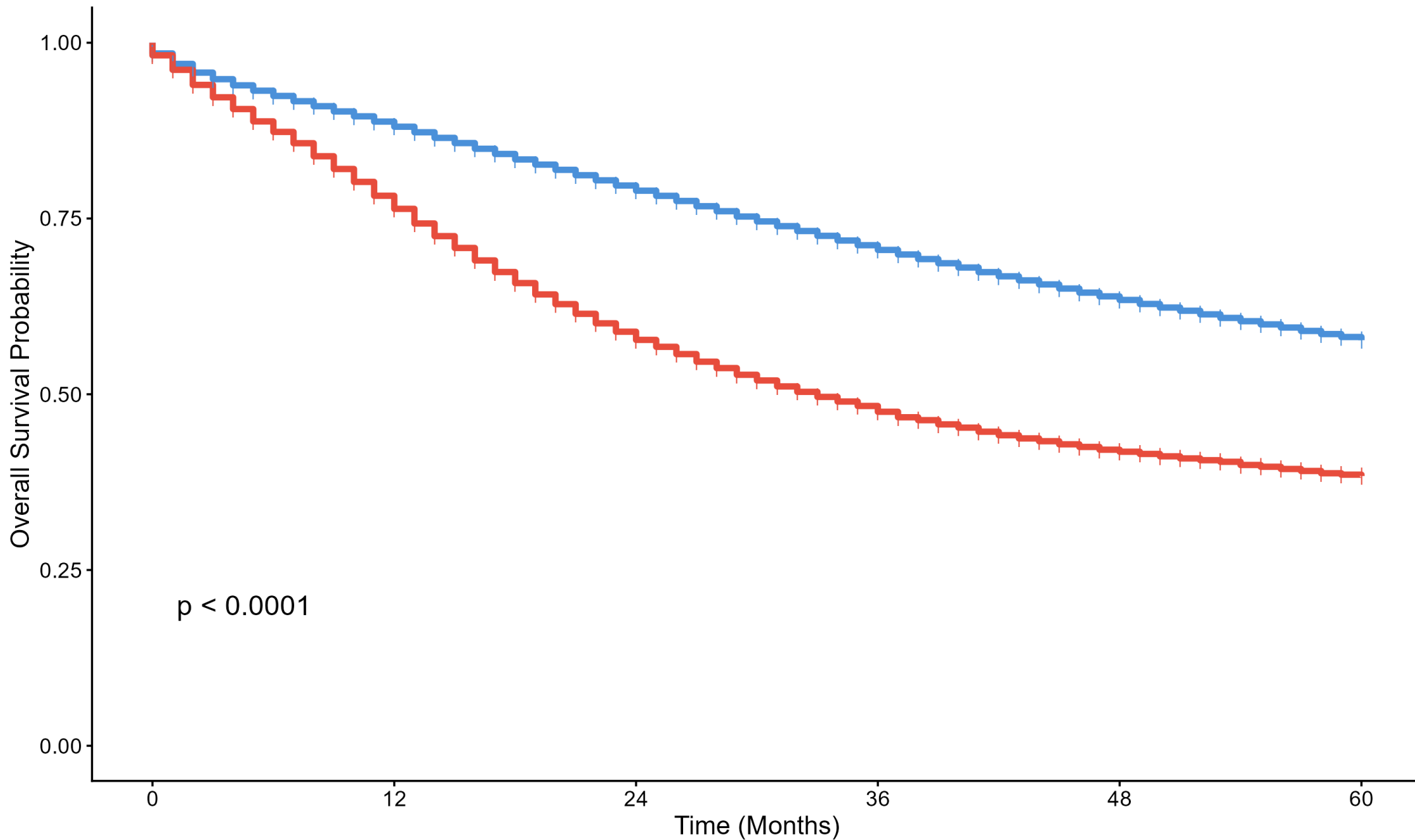
- **No relevant financial relationships with ineligible companies to disclose**

Triple Negative Breast Cancer (TNBC)

Stage III/IV

Non-TNBC vs TNBC

Subtype — Non-TNBC — TNBC

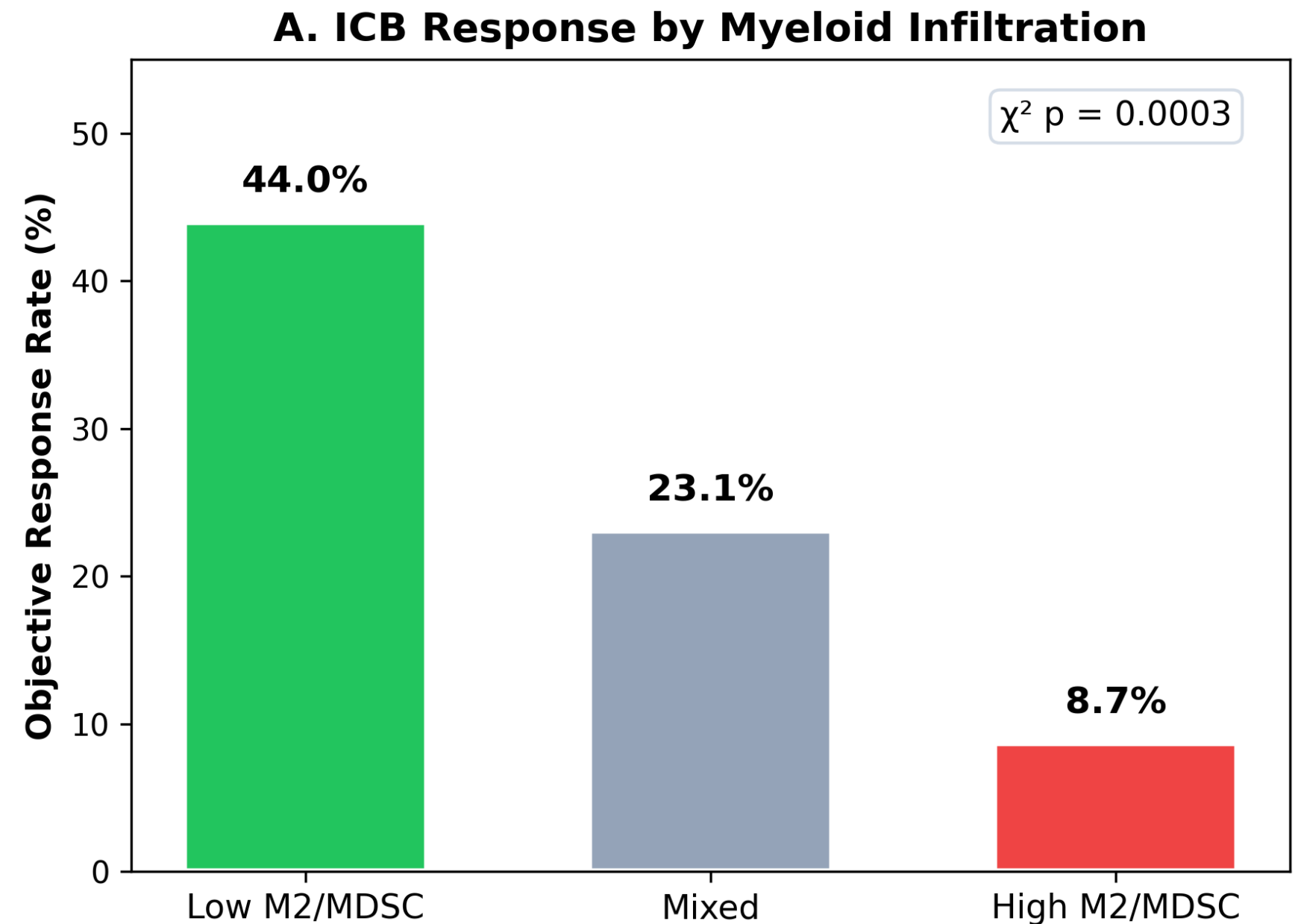


SEER Database 2010-2018

- **TNBC is defined by a lack of ER or PR receptors and HER2 expression**
- **15-20% of breast cancer cases in the US**
- **5-year overall survival <40% for Stage III/IV**

TNBC tumors have low rates of response to immune checkpoint blockade (ICB)

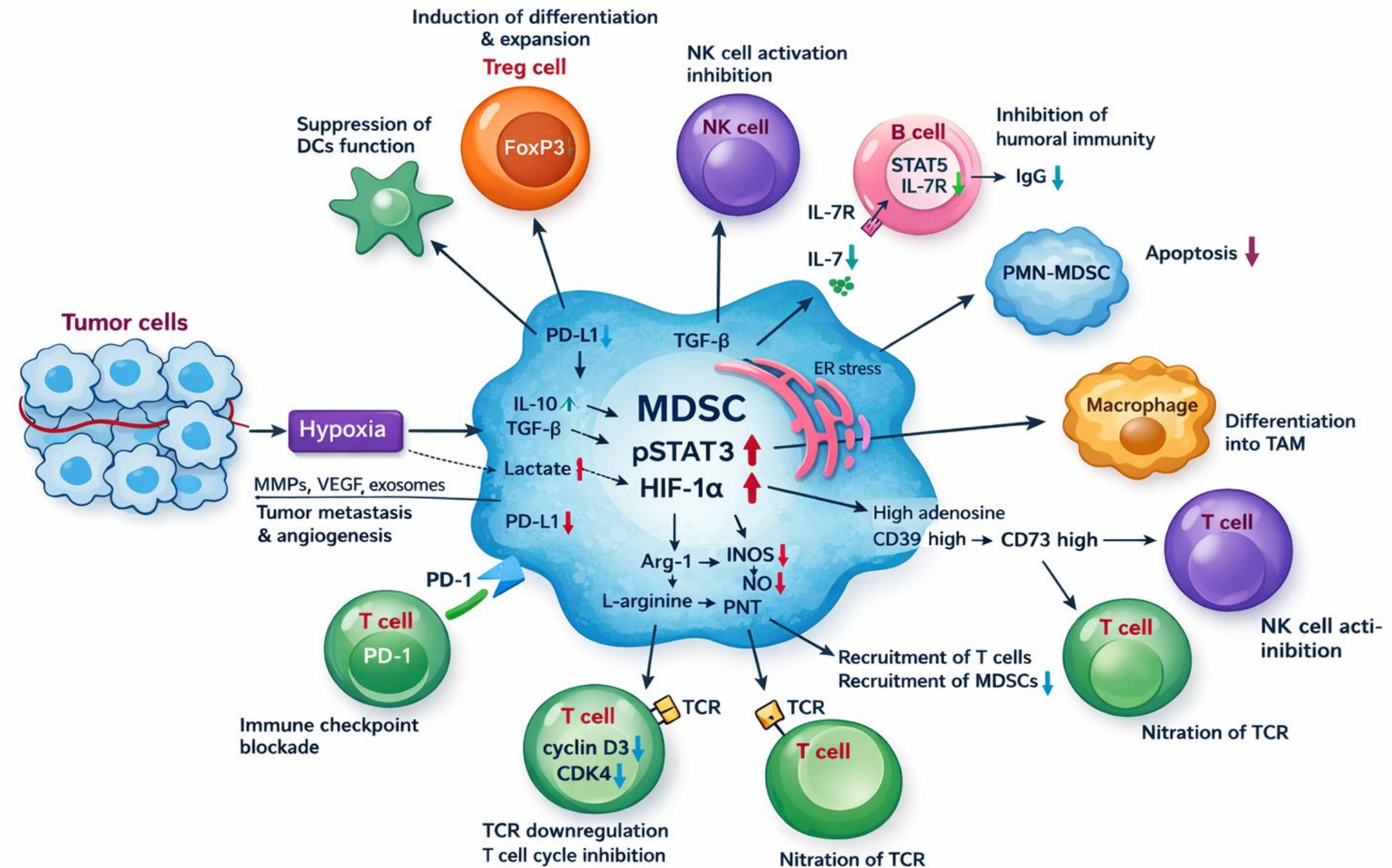
- TNBC characterized by high levels of immune infiltration
- Paradoxical poor response to immune checkpoint blockade (ICB)
- Due to immunosuppressive cell infiltrate
 - Myeloid derived suppressor cells (MDSC)
 - Tumor Associated Macrophages (TAM)



Reanalysis of gene expression data from Y Zhang (2021) Cancer Cell

Immunosuppressive functions of MDSC

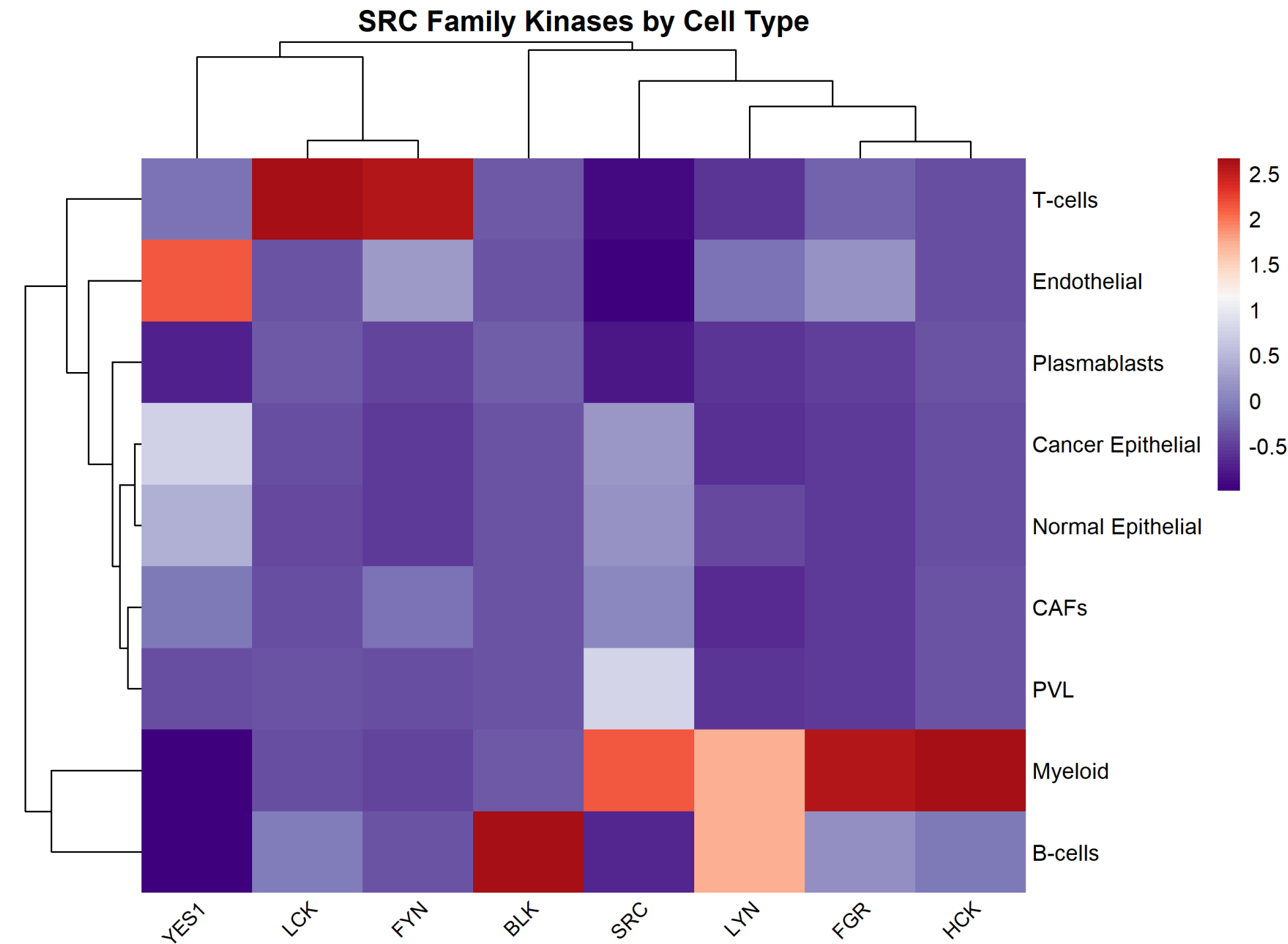
- MDSC are immature progenitor myeloid cells
- Released in response to chronic inflammation
- Exert immunosuppressive function through a variety of synergistic mechanisms



Adapted from Z. Yang 2020 *Journal of Hematology and Oncology*

Src family kinases regulate MDSC function

- **Dasatinib is a multi-kinase inhibitor targeting Src family kinases**
- **FDA-approved and in use to treat hematologic malignancies**
- **Src family kinase modulated many immunosuppressive functions of MDSC**

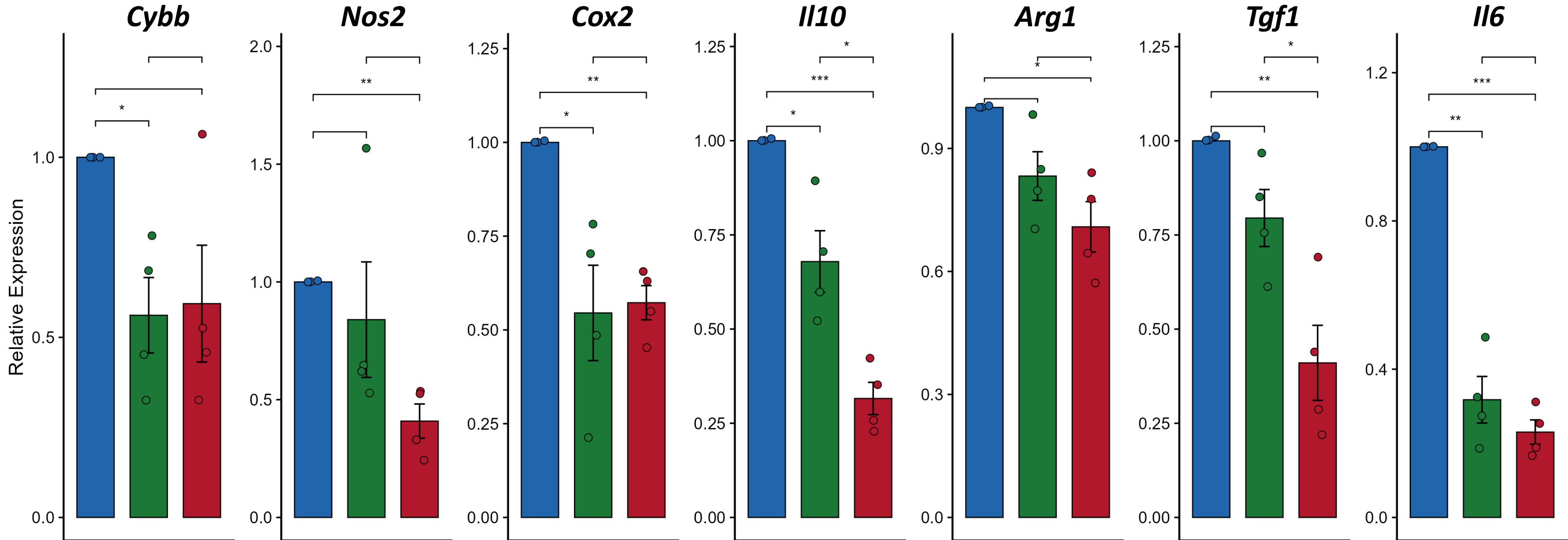


Reanalysis of gene expression data from SZ Wu (2021)
Nature Genetics

Dasatinib reduces MDSC gene signature

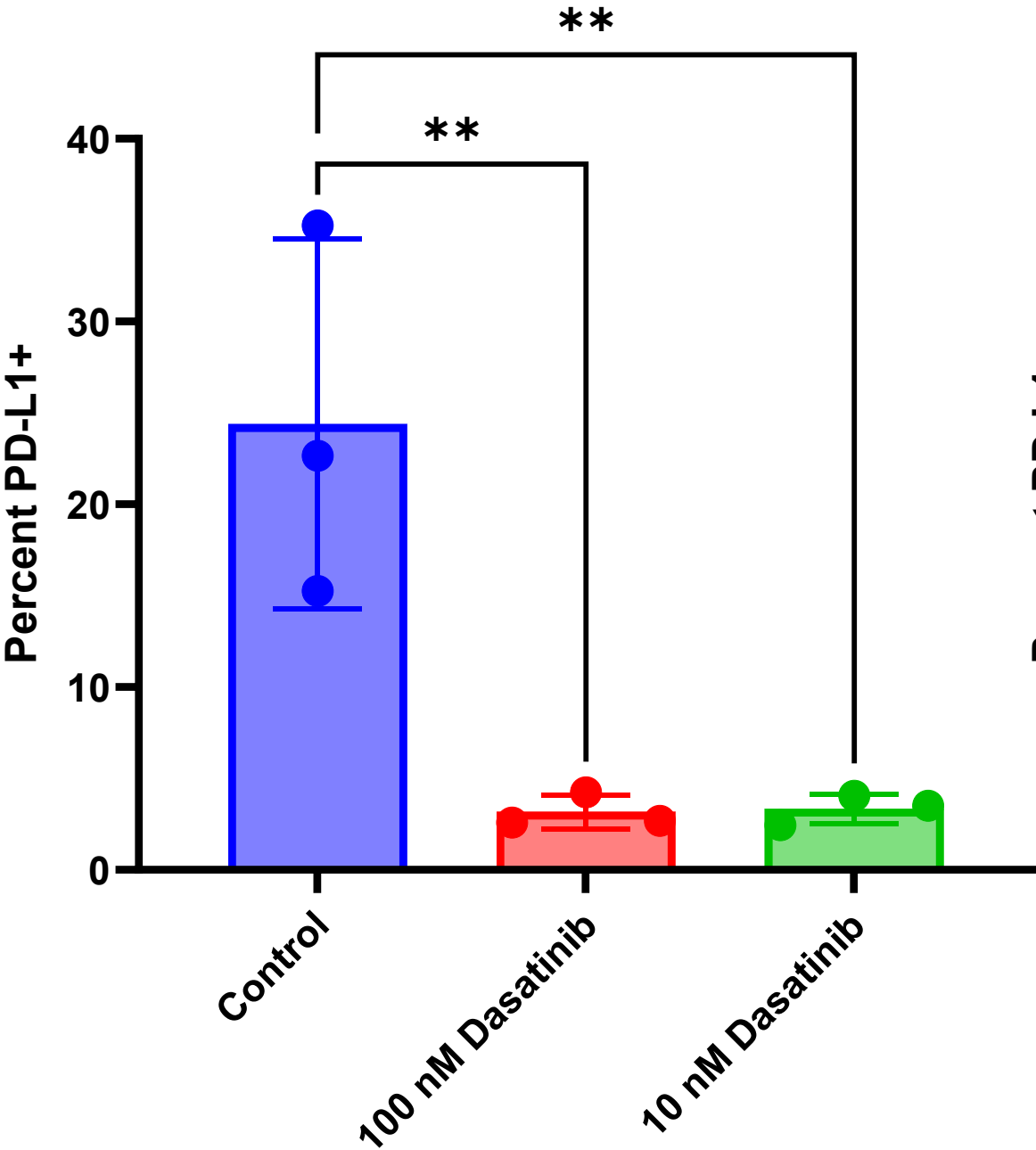
Murine MDSCs

■ DMSO ■ 10 nM Dasatinib ■ 100 nM Dasatinib

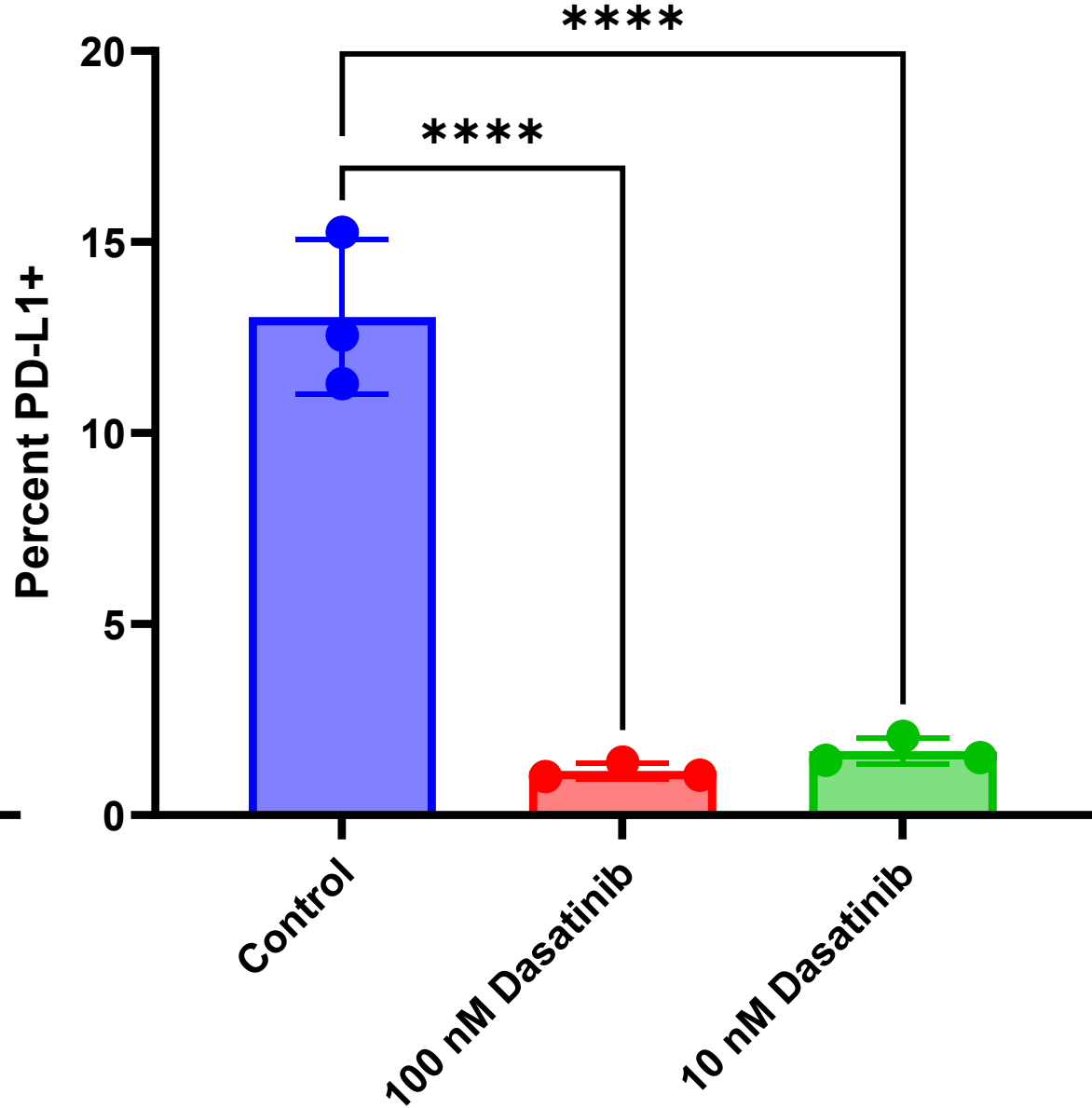


Dasatinib reduces immunosuppressive proteins

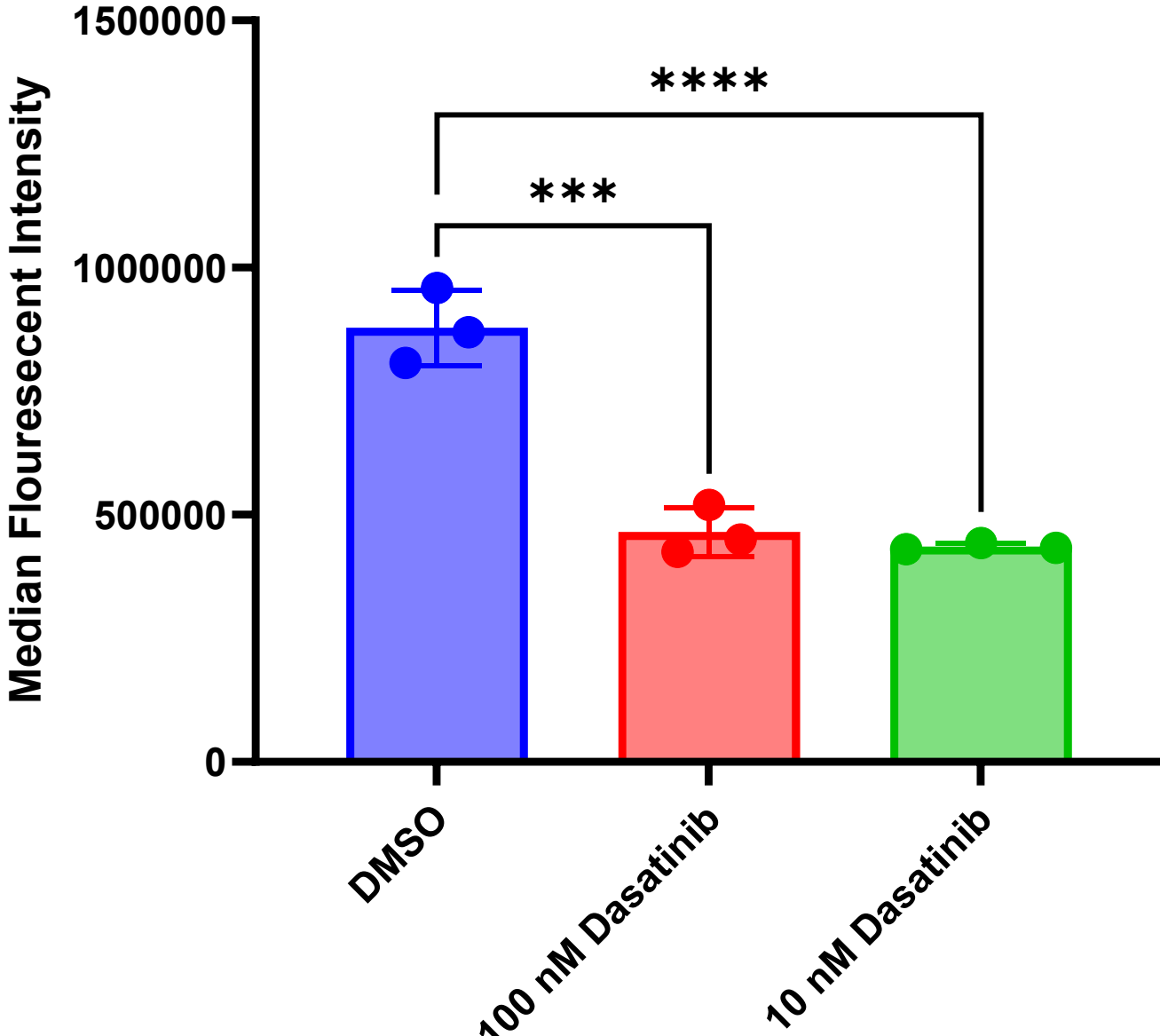
Human MDSC
% PD-L1 Positive



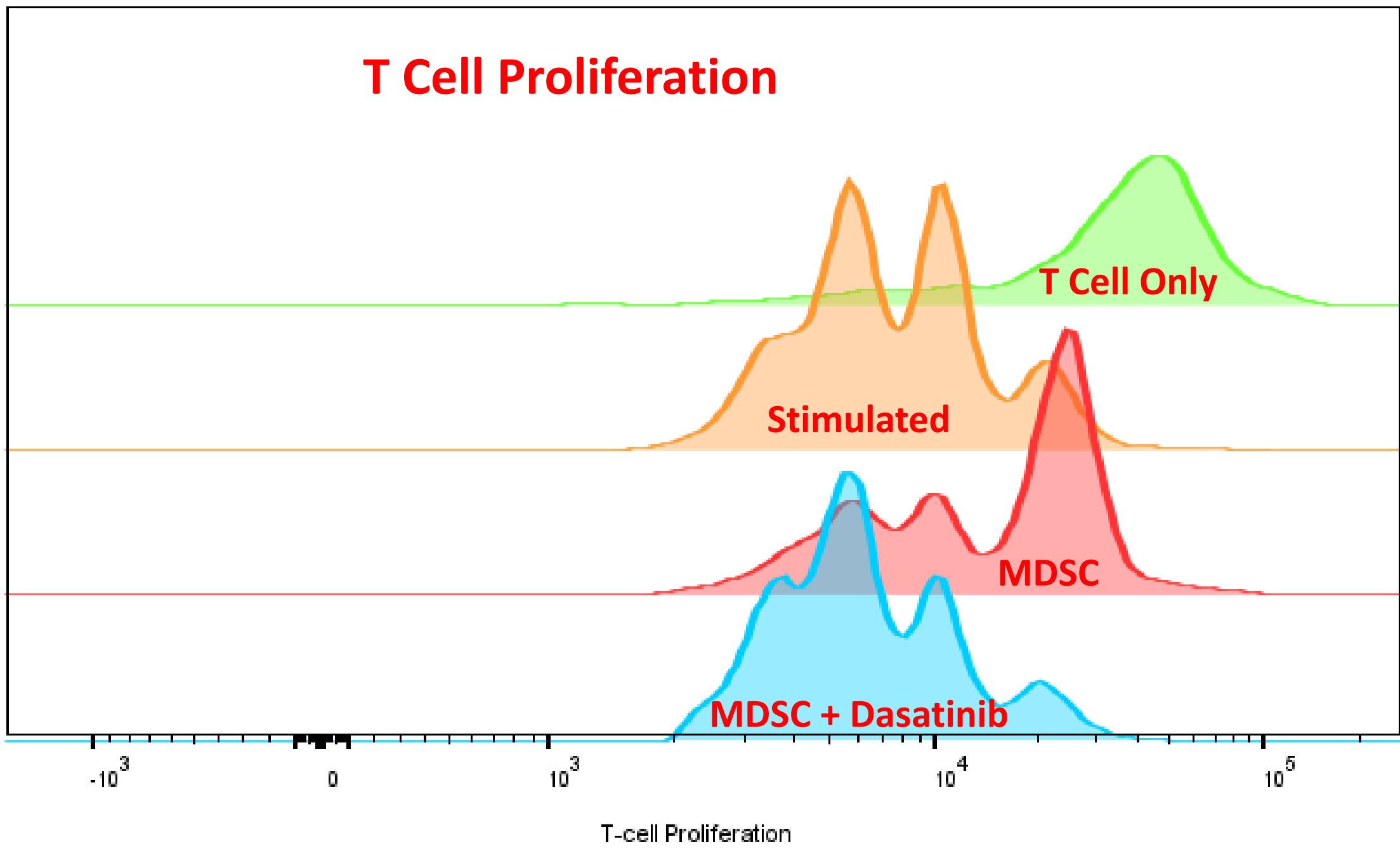
Human MDSC
% Galectin 3 Positive



Human MDSC
Nitric Oxide (NO)

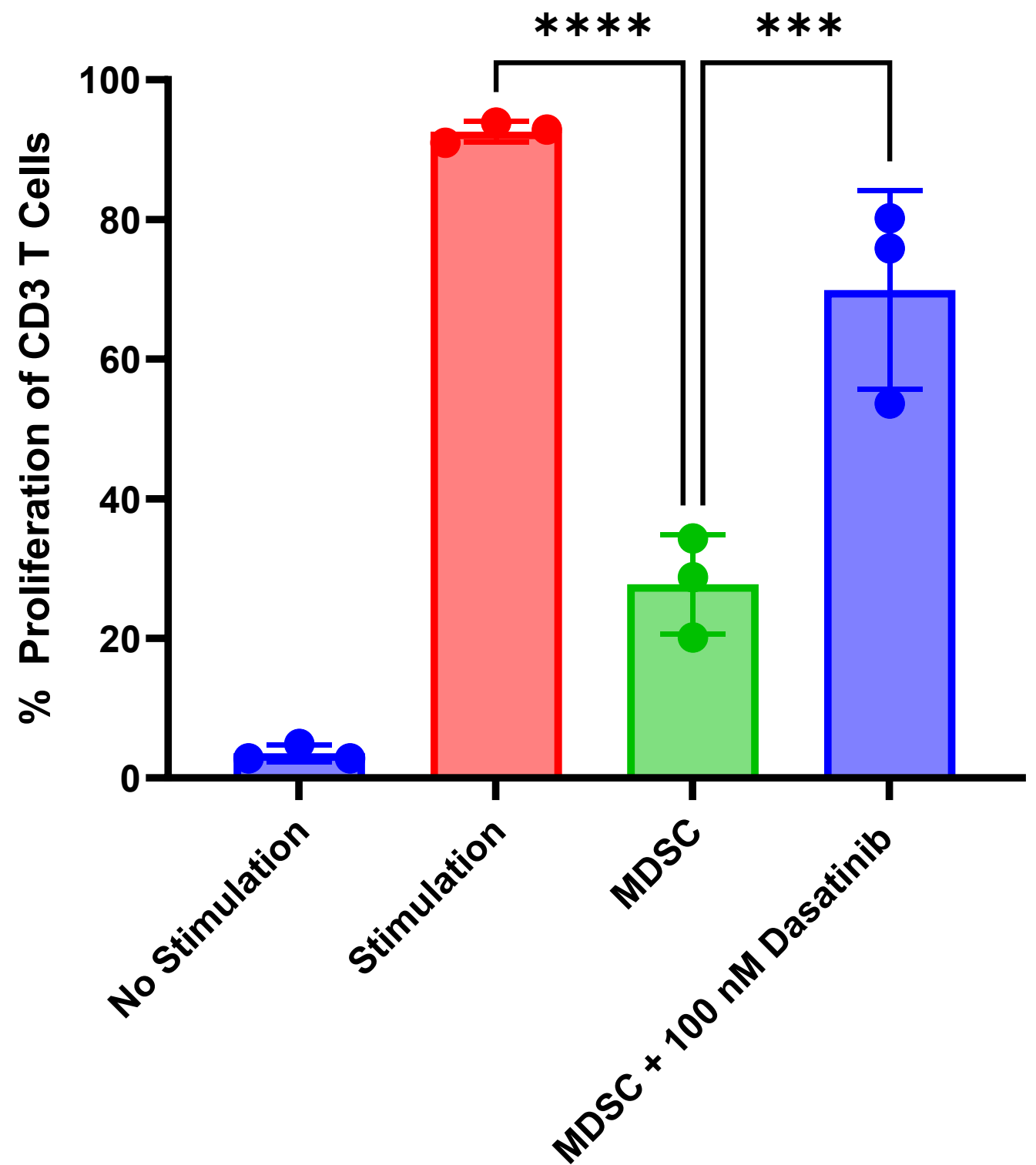


Dasatinib rescues T cell proliferation



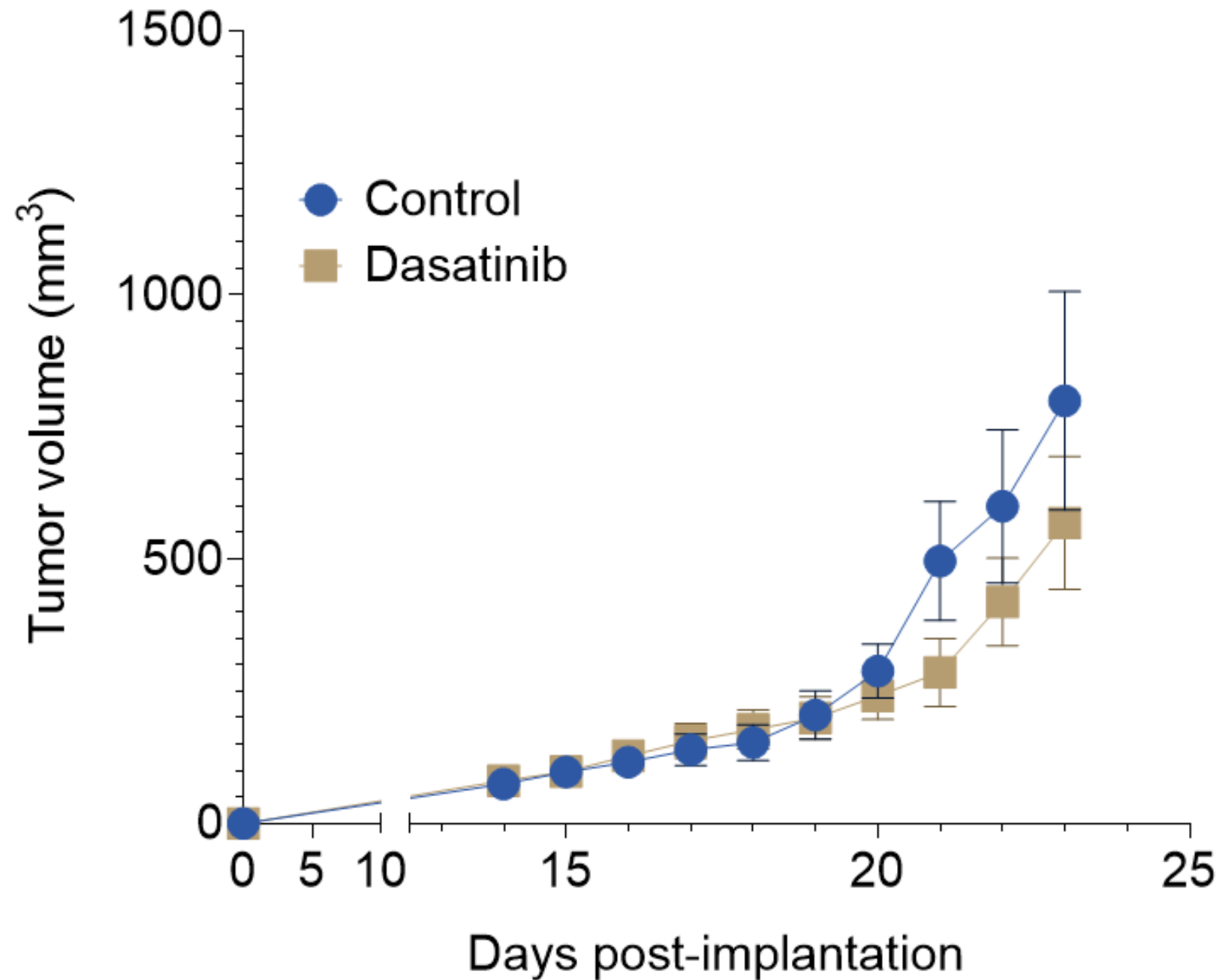
Stimulated = addition of antiCD3/CD28 Dynabeads

Human Proliferation Assay

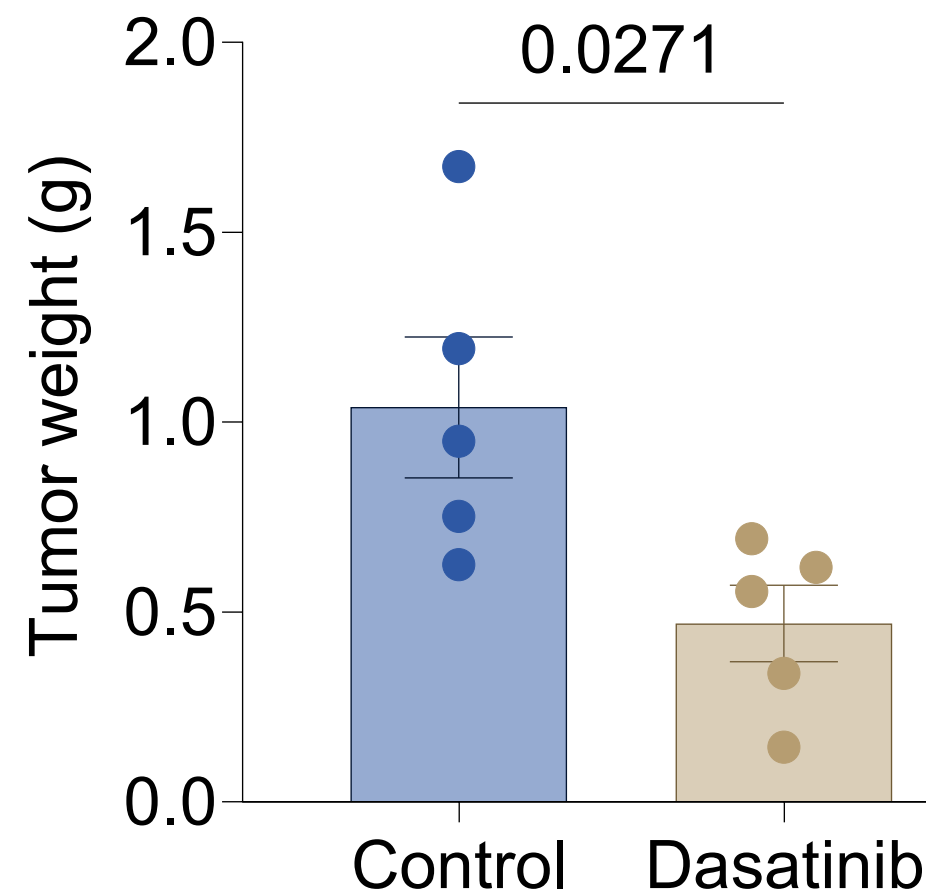


Dasatinib alone modestly reduces tumor growth in 4T1 model

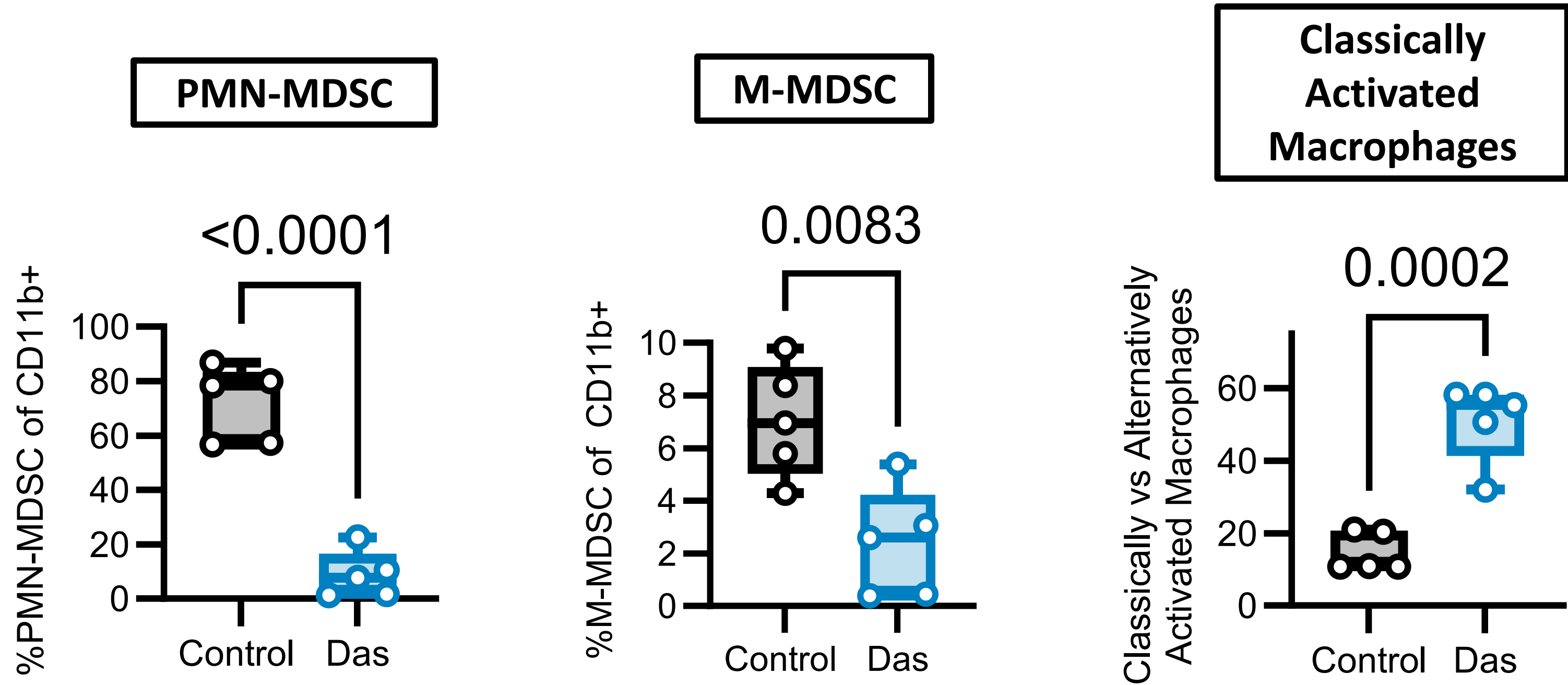
Tumor Growth



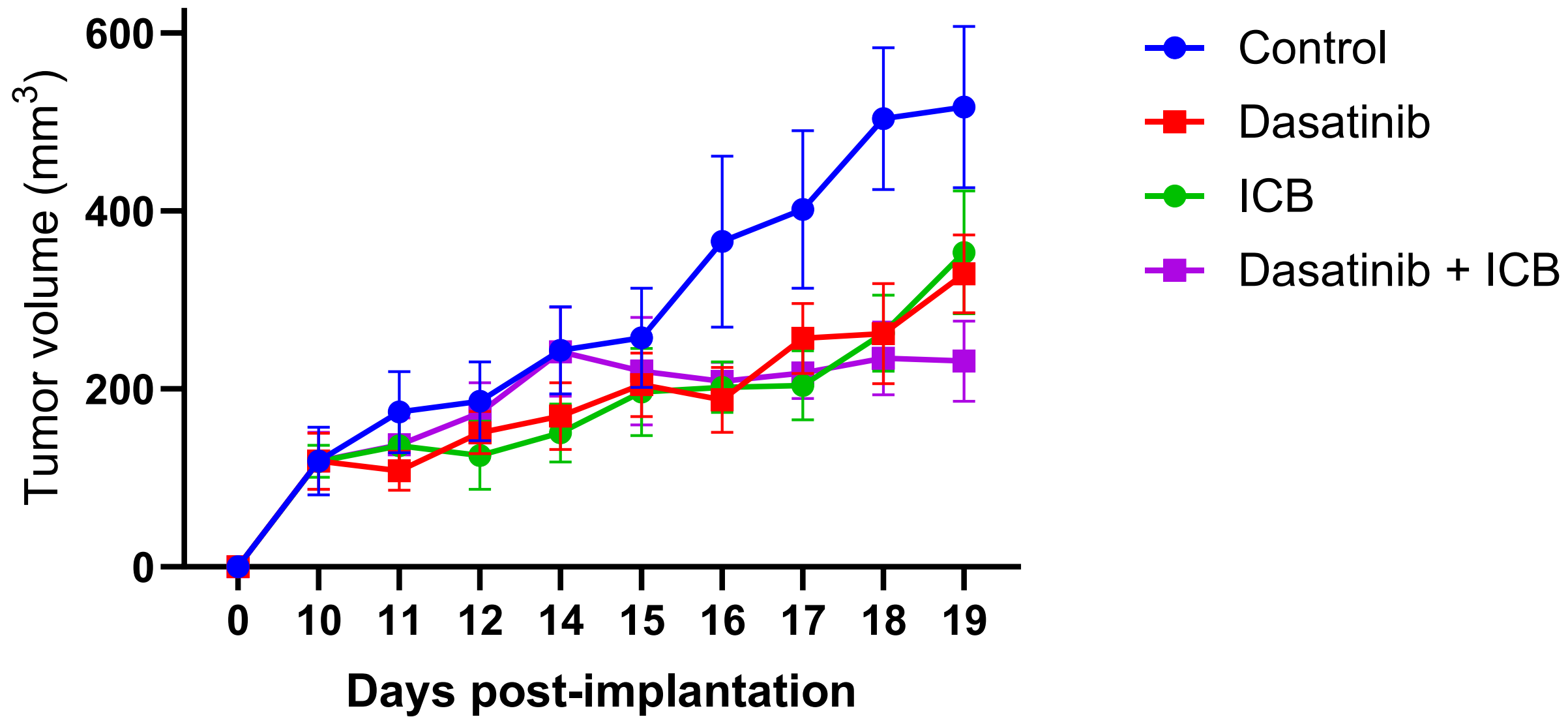
Tumor Weight



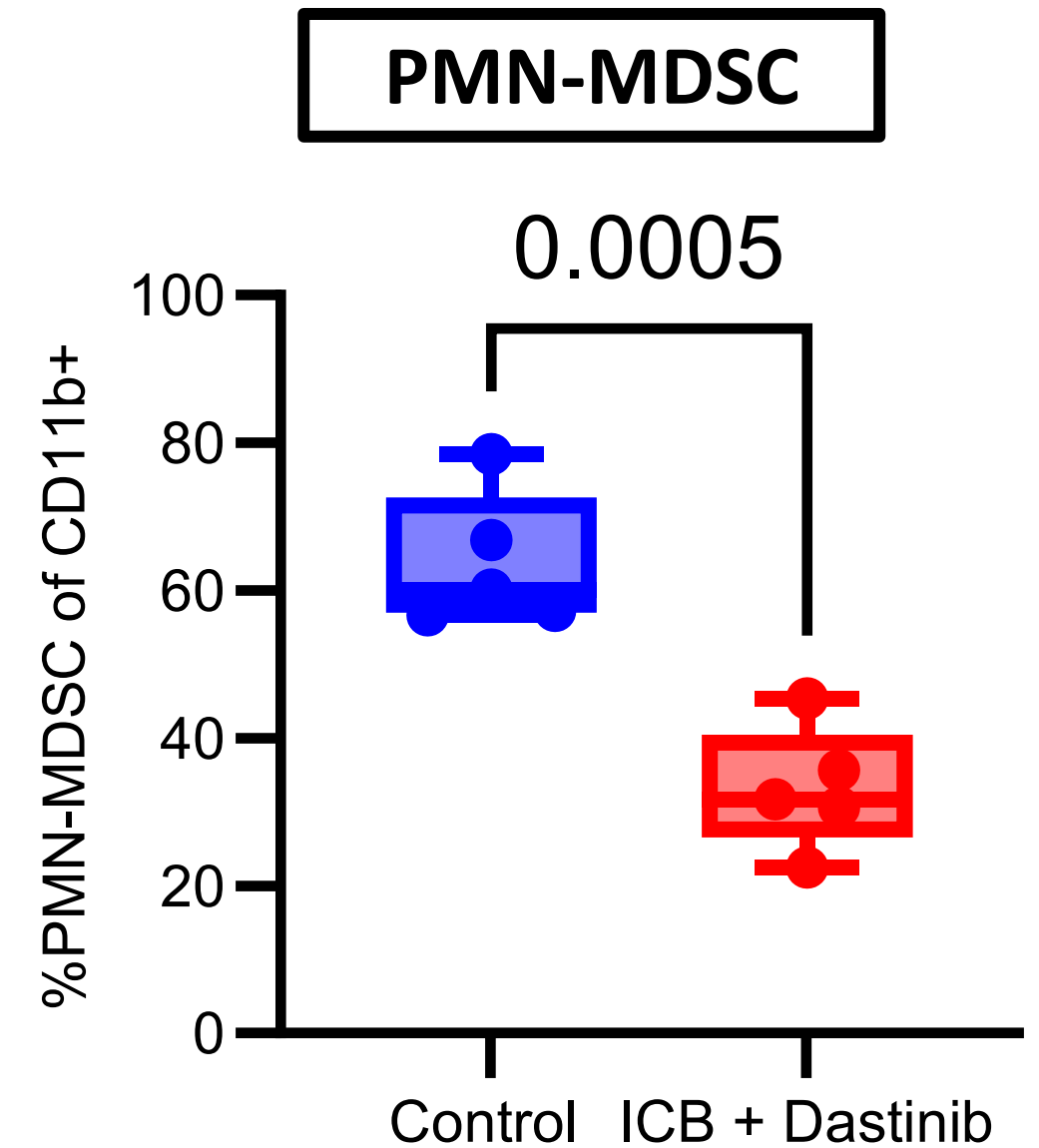
Dasatinib targets myeloid compartment



Dasatinib + Immune Checkpoint Blockade



Dual ICB: anti-Lag3 + anti-PD1



Conclusions

- **TNBC is associated with worse overall prognosis and high levels of immunosuppressive myeloid cells compared to other types of breast cancer**
- **These immunosuppressive cells contribute to reduce efficacy of ICB**
- **Src family kinases regulate MDSC function**
- **Dasatinib is a potent inhibitor of Src kinases and can reduce MDSC function in vitro**
- **Modest efficacy as a single agent**
- **Evidence of synergism with ICB**
- **Additional experiments to dissect interplay between intratumoral cells ongoing as well as different models of TNBC**



Acknowledgments



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**THANK
YOU!**

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