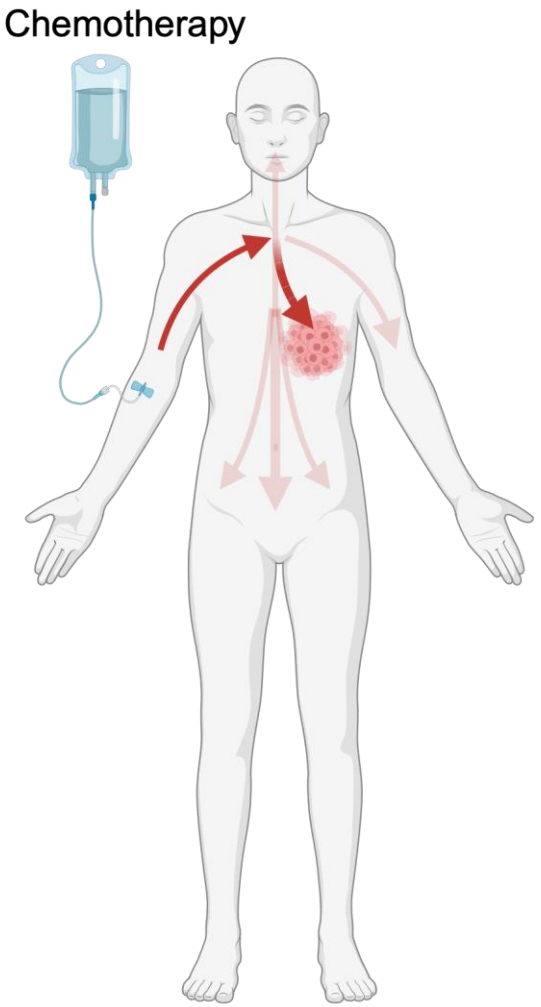
# Tumor Microenvironment is a Key Driver for Drug Delivery and Efficacy in HER2+ Breast Cancer

Rahaf Mihyar

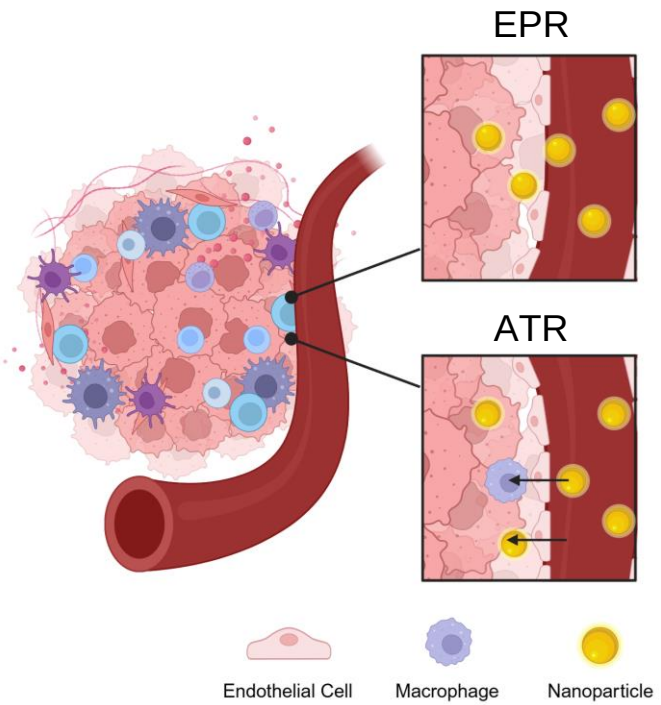
CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

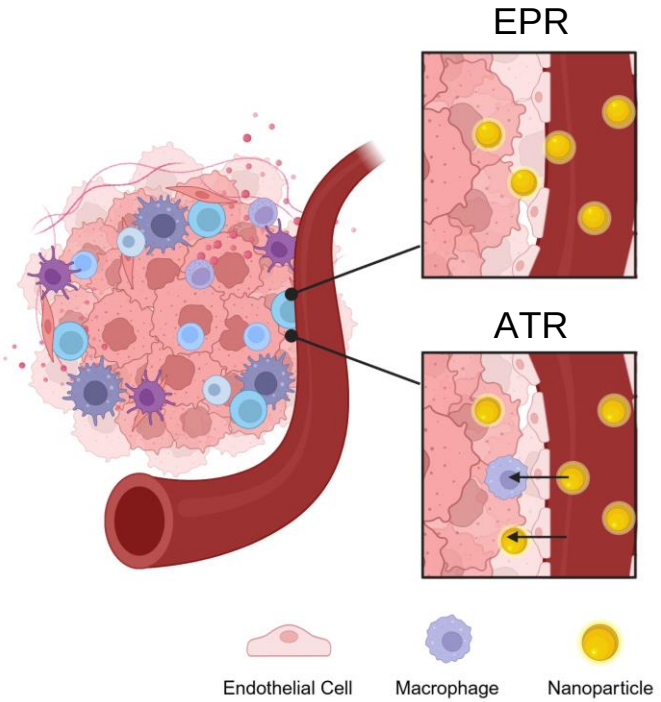
# Challenges of nanomedicine clinical translation

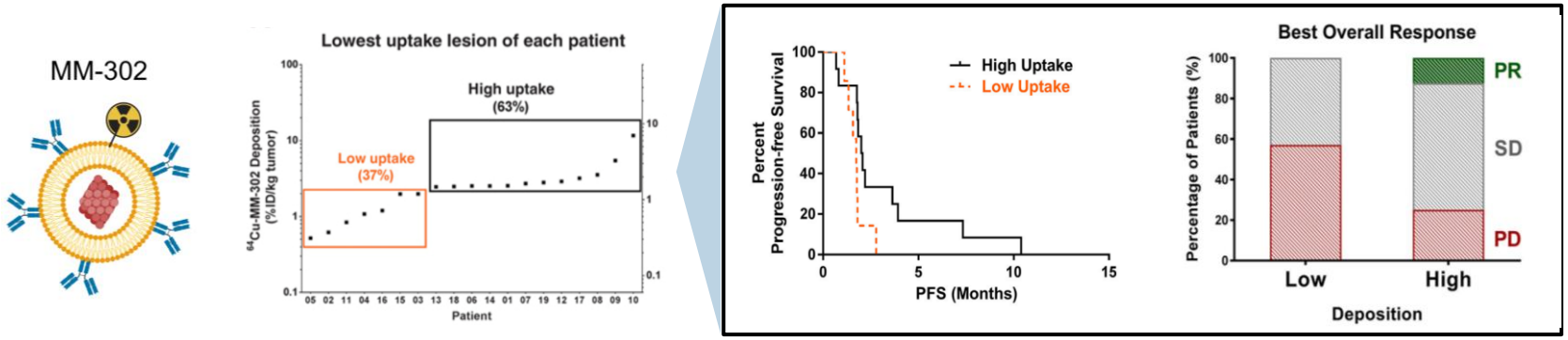


# **Interpatient variability** in accumulation and retention is a key challenge



# **Interpatient variability** in accumulation and retention is a key challenge

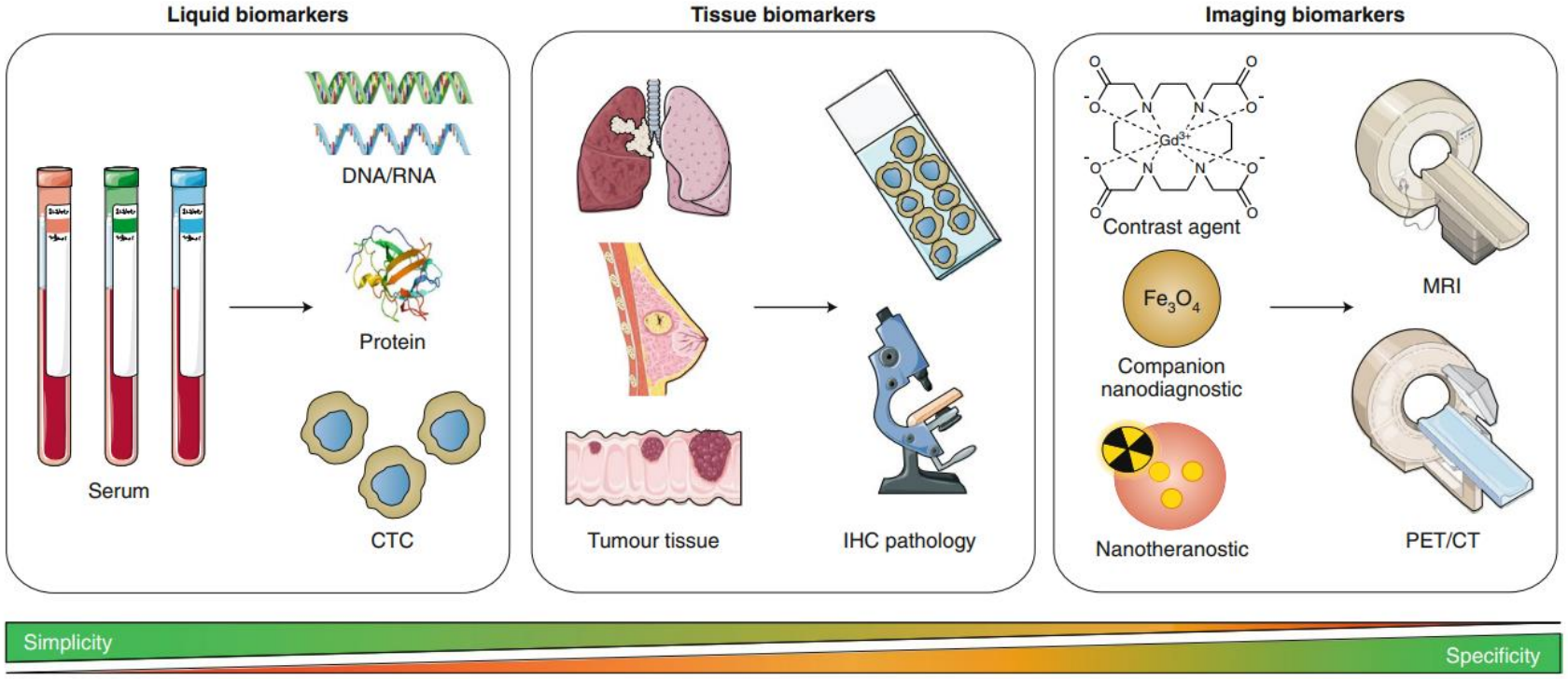



Lee, H. et al. , *Clin. Cancer Research,* 2017, 23 (15), 4190-4202.

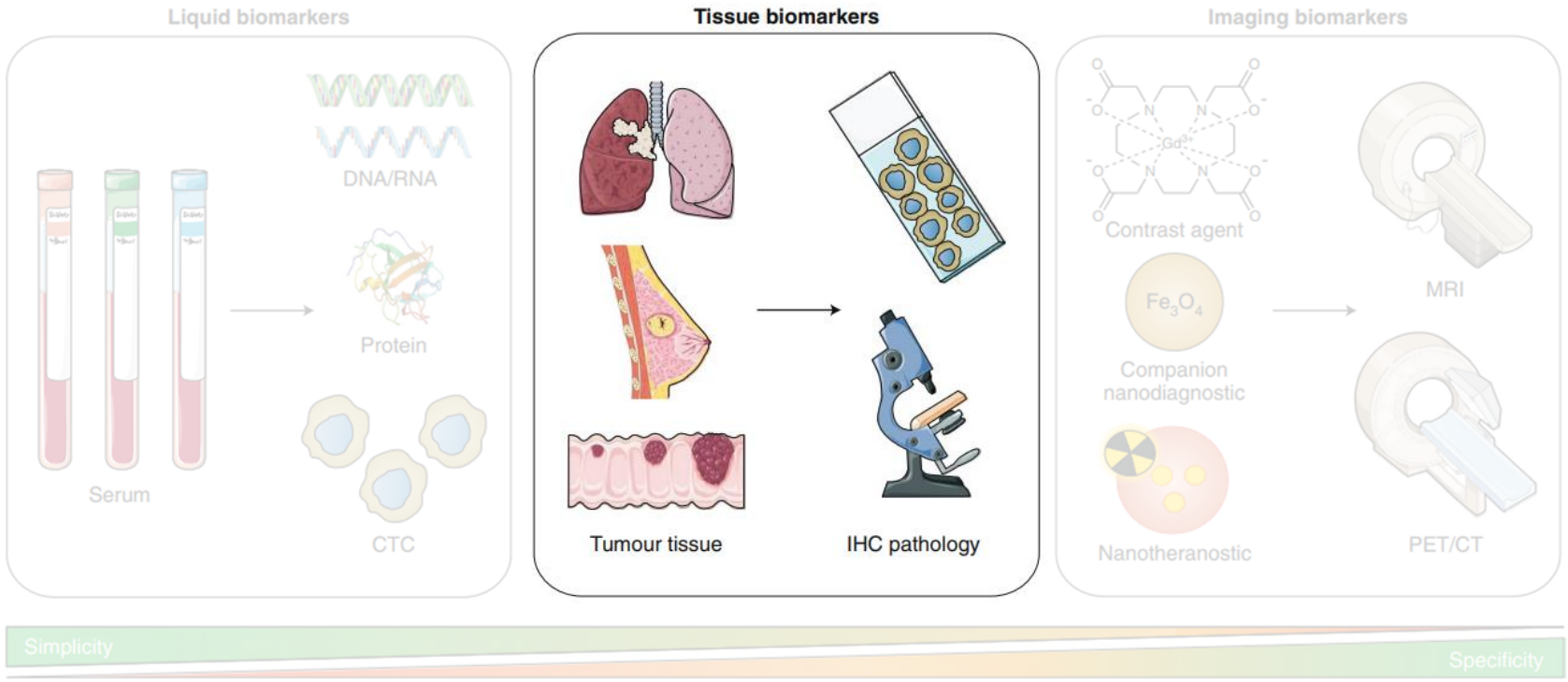
→ Need for patient stratification!

# Cancer nanomedicine patient stratification



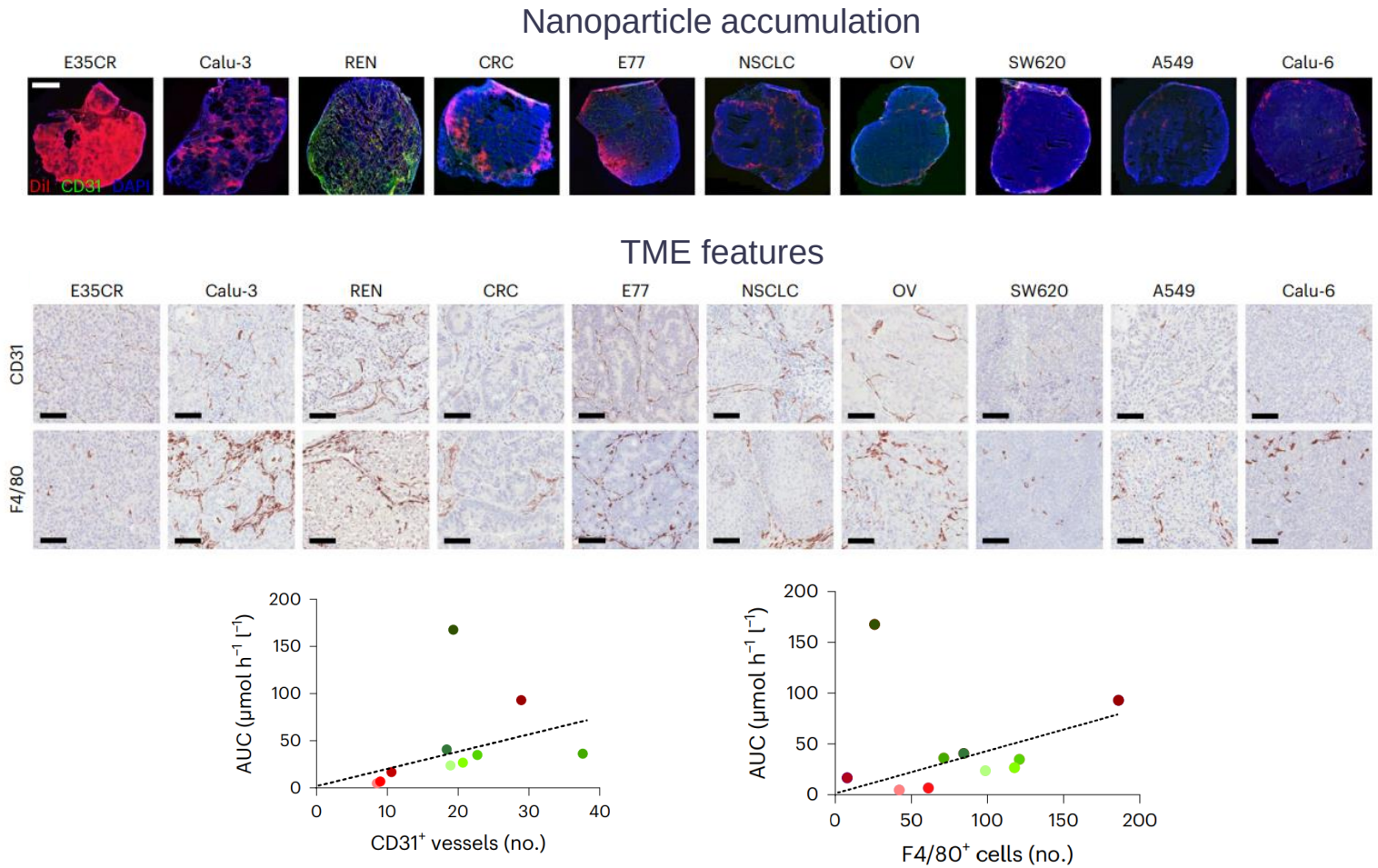

van der Meel, R., Sulheim, E., Shi, Y. et al. *Nat. Nanotechnol.,* 2019, 14, 1007-1017.

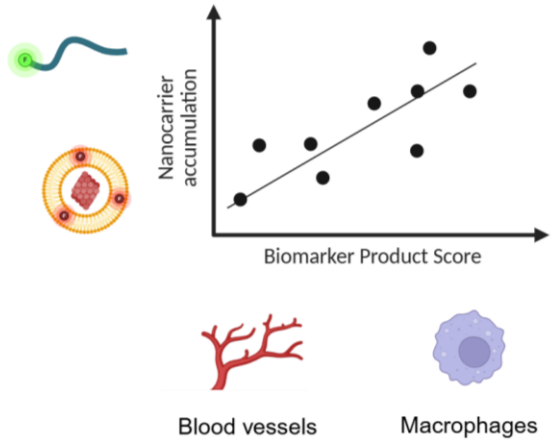
# Tissue biomarkers for cancer nanomedicine patient stratification

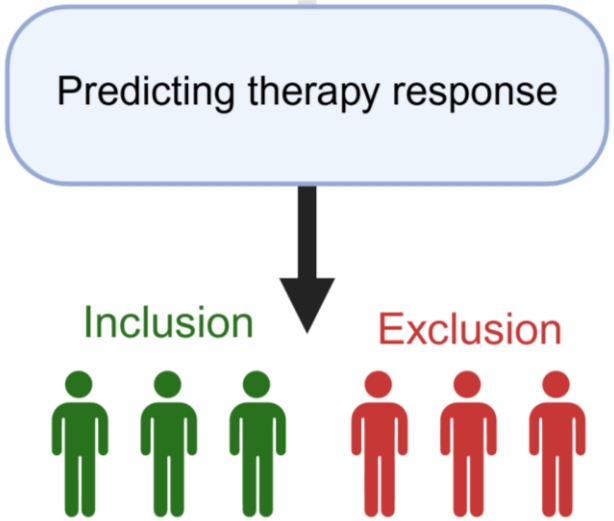



van der Meel, R., Sulheim, E., Shi, Y. et al. *Nat. Nanotechnol.,* 2019, 14, 1007-1017.

# Tumor features as tumor targeting biomarkers

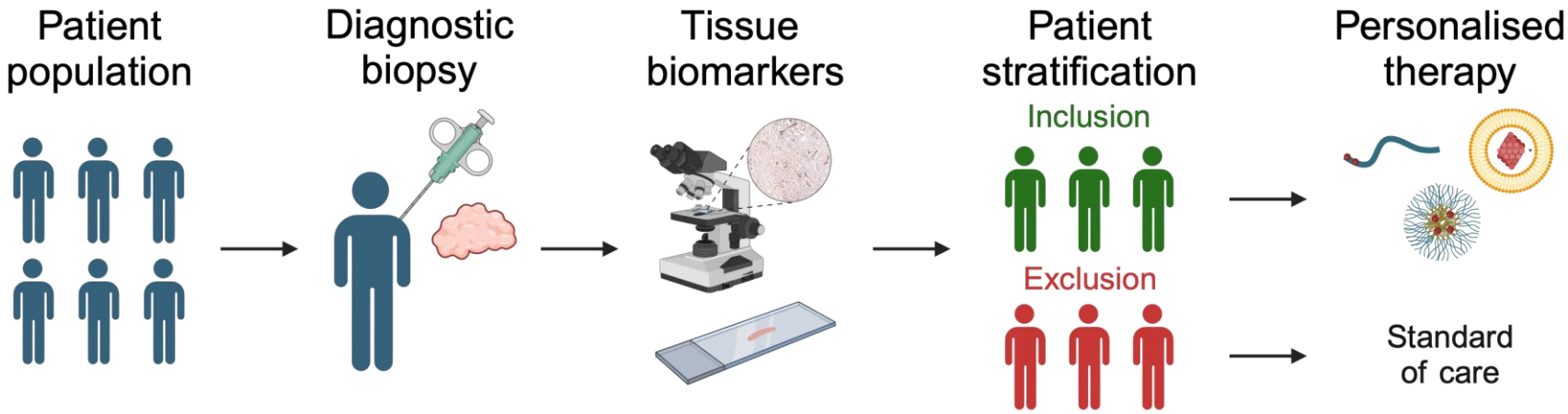



May, J.N., Moss, J.I., …, Lammers, T., *Nat. Biomed. Eng.*, 2024.

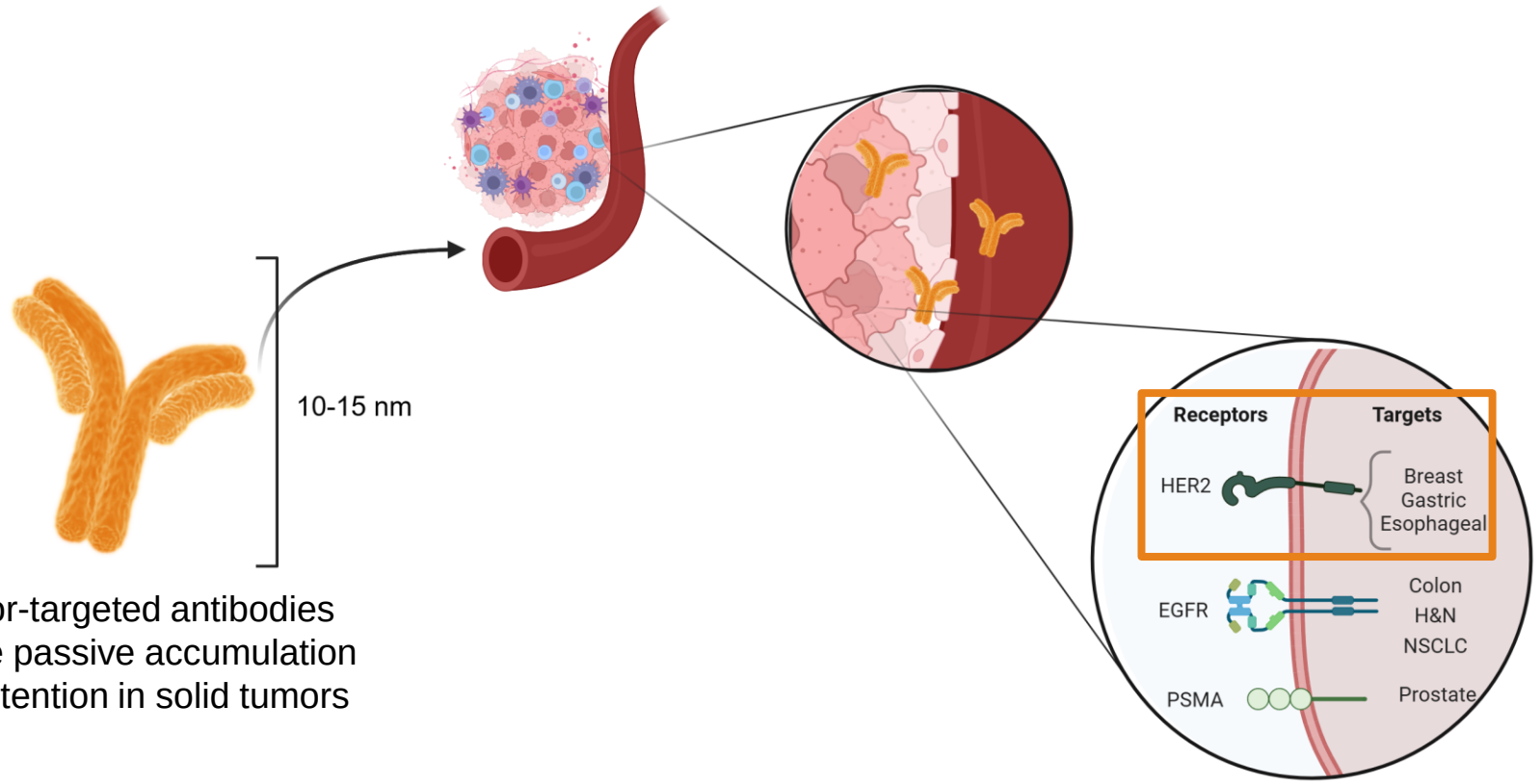
# Towards personalised cancer nanotherapy in clinical practice




**Limitations:**

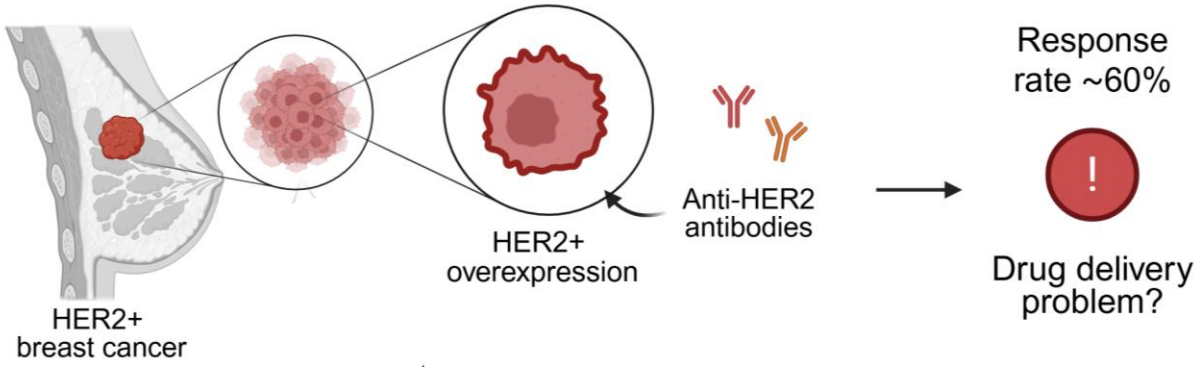
- Nanomedicine are mostly used in advanced/metastatic cancers
- Not as a first-line

# Towards personalised cancer HER2-targeted therapy in clinical practice




Tumor-targeted antibodies require passive accumulation and retention in solid tumors

# Towards personalised cancer HER2-targeted therapy in clinical practice



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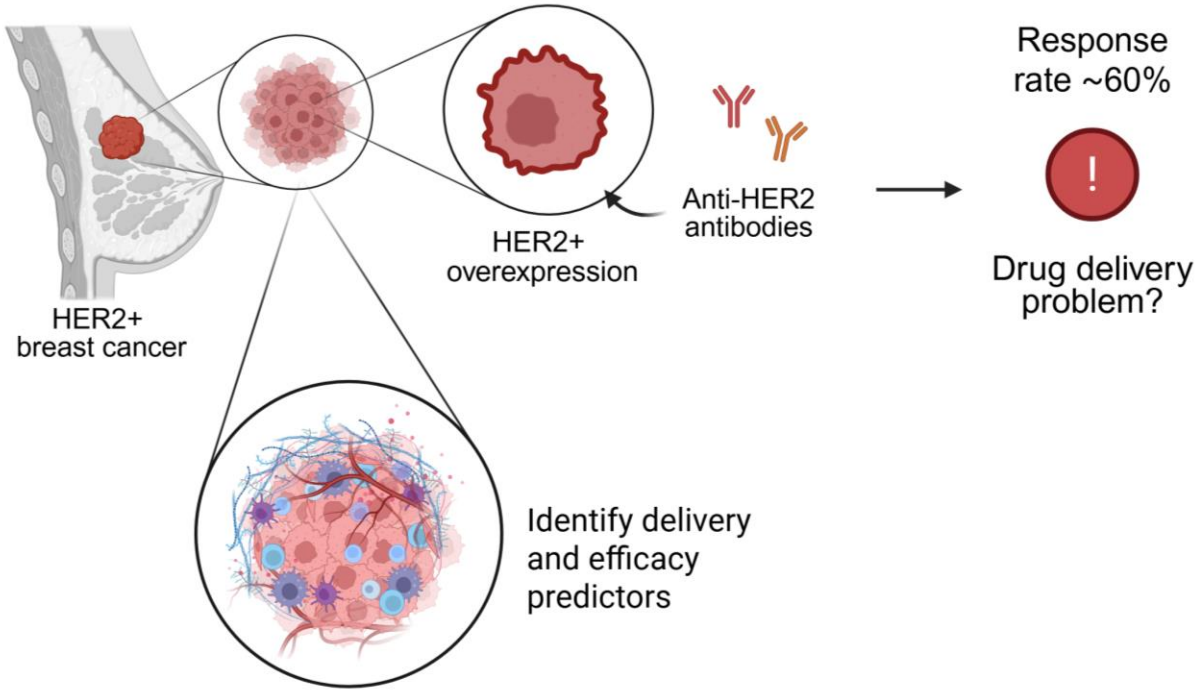
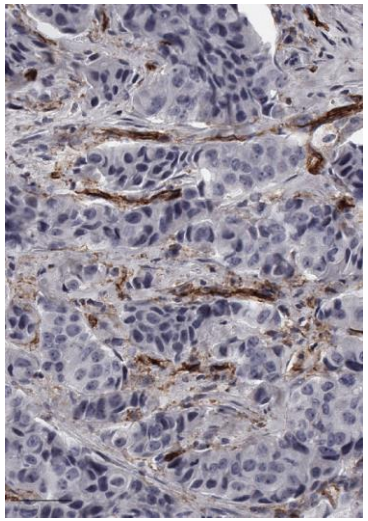
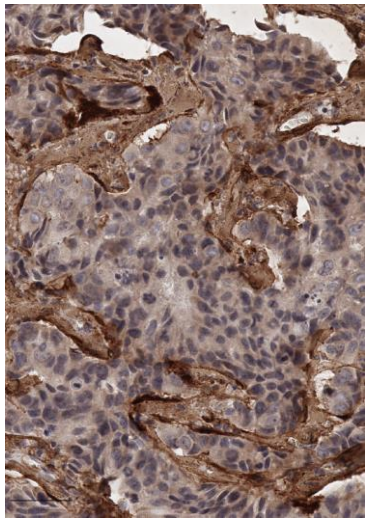



## Predictive Tissue Biomarkers

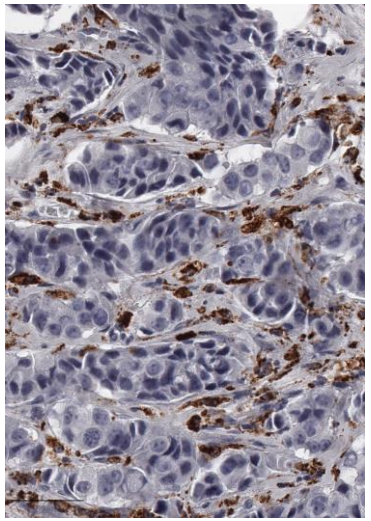
Vasculature



Collagen

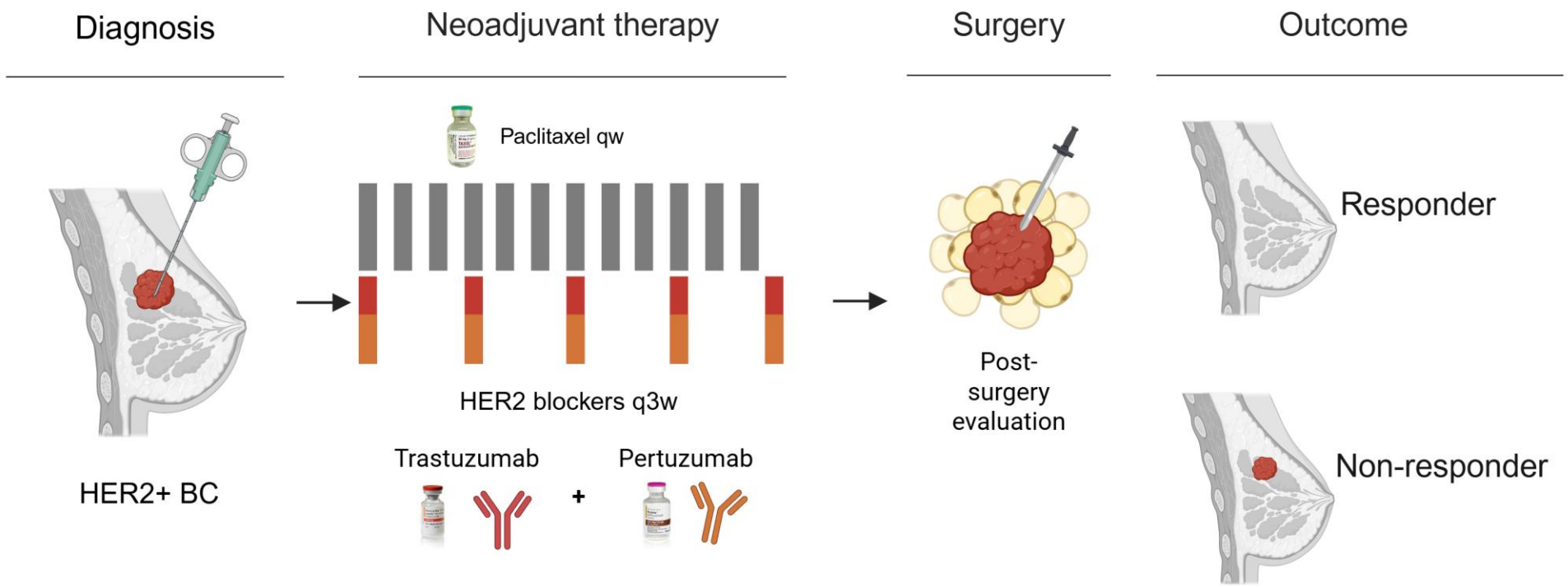


TIL



TIL: tumor infiltrating lymphocytes

# HER2Nano clinical study setup




Responders: patients who achieved pathological complete response (pCR)

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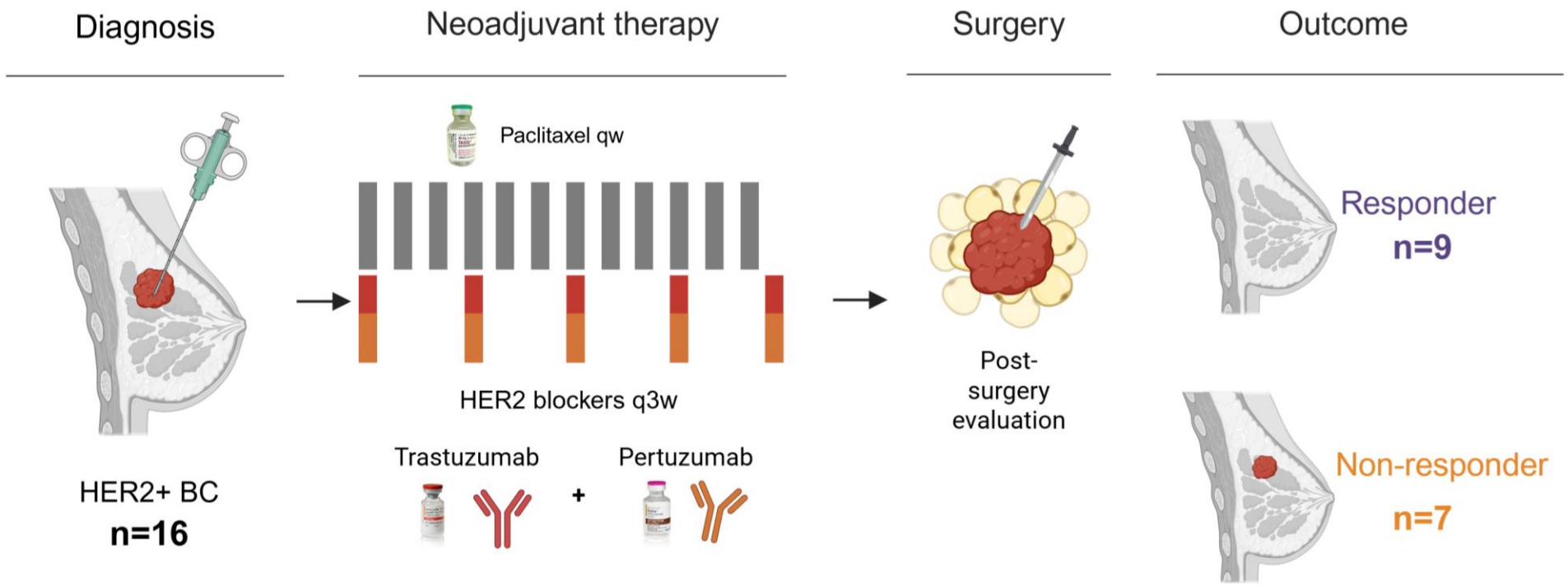


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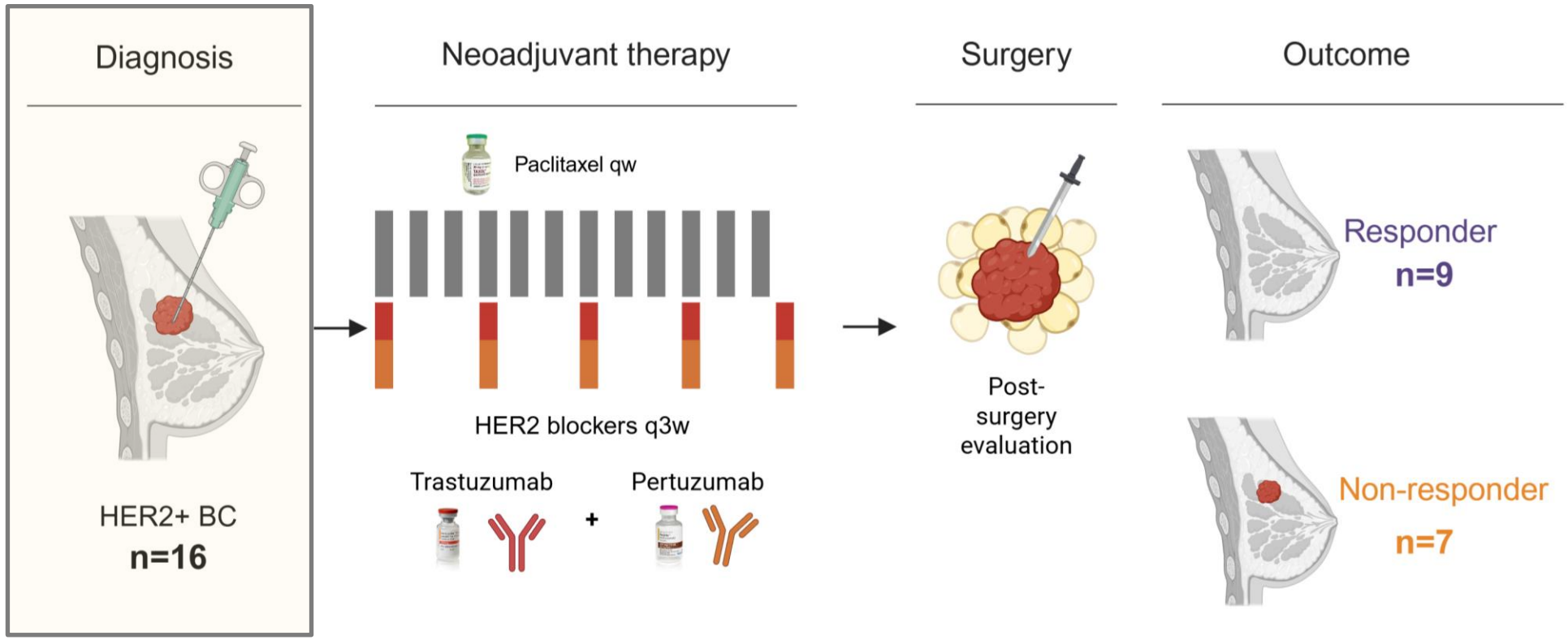


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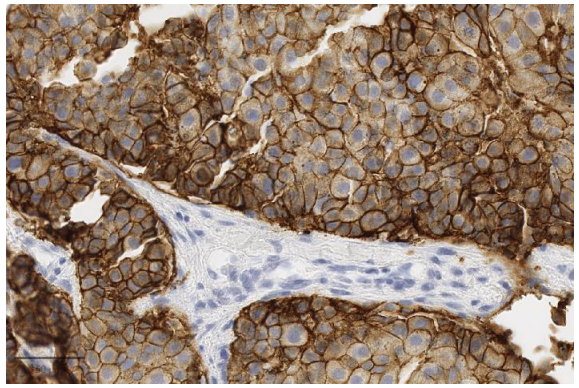
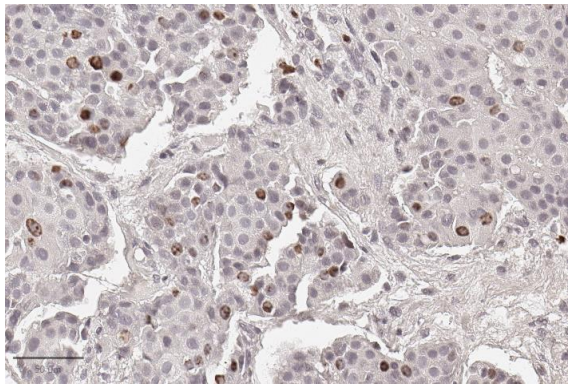
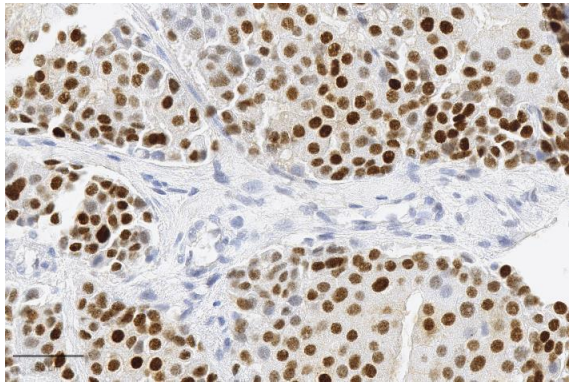
HER2



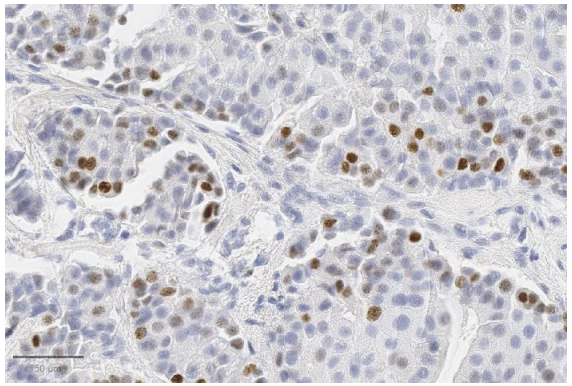
Ki67



ER

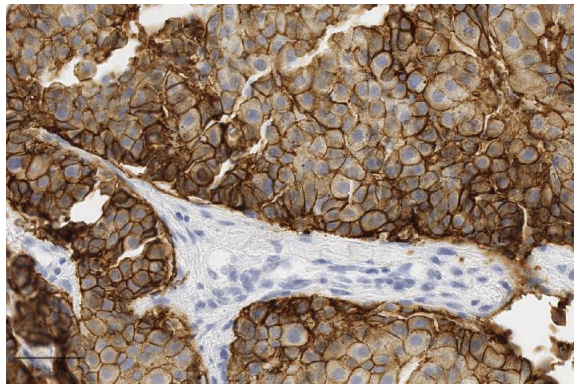


PR

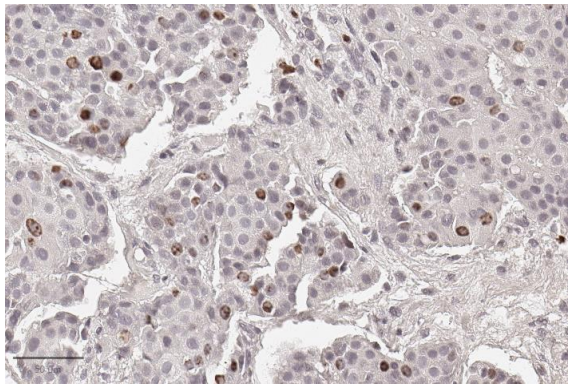


# No significant association between cellular biomarkers (HER2, ER, PR and Ki67) and response

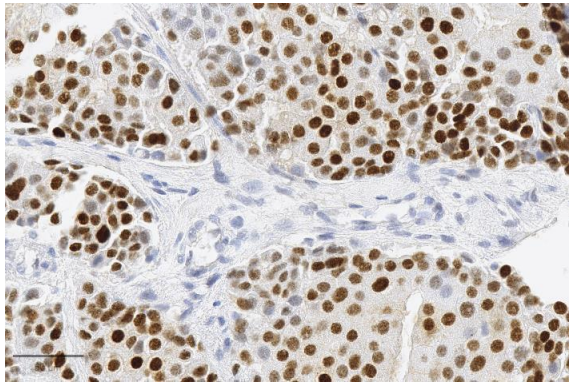
HER2



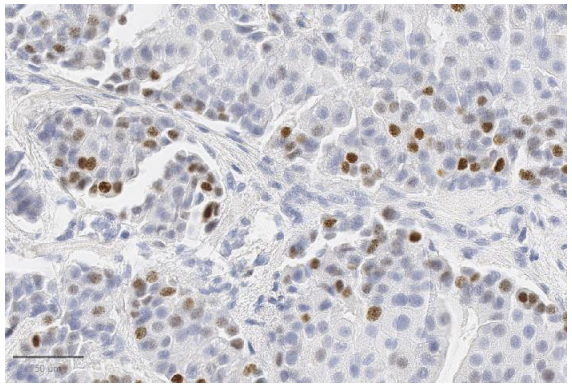
Ki67

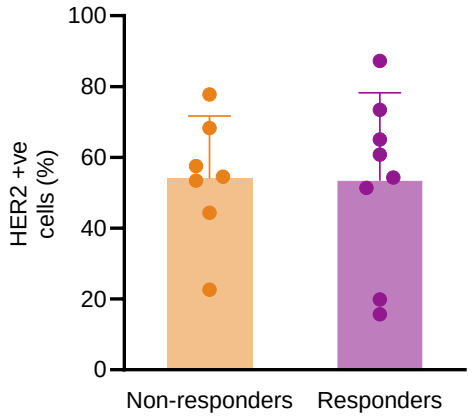


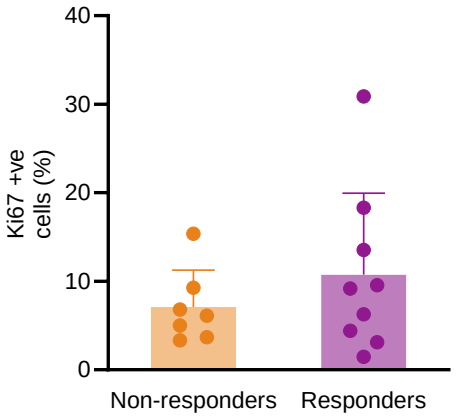
ER

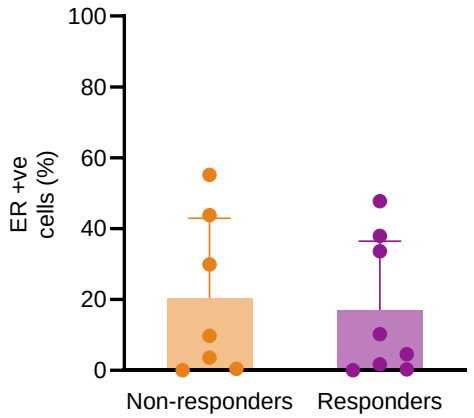


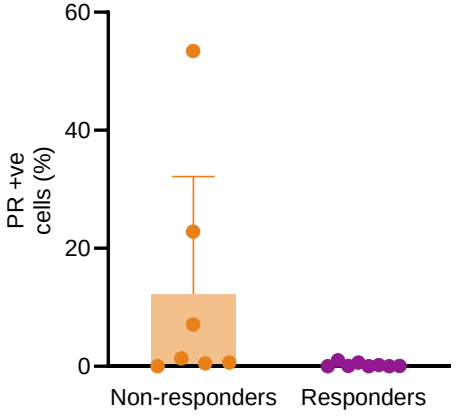
PR



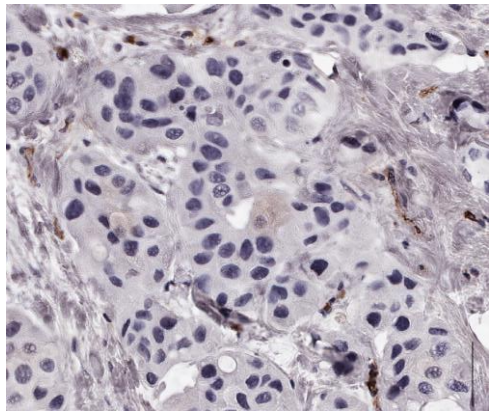


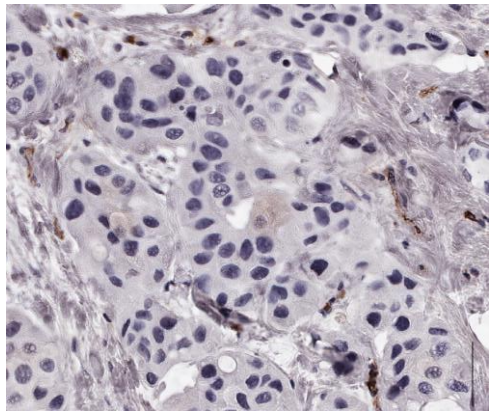



Non-responders

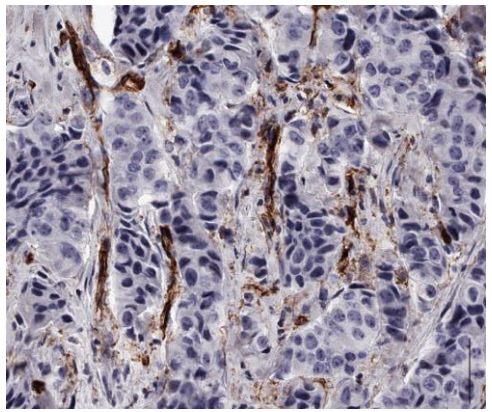


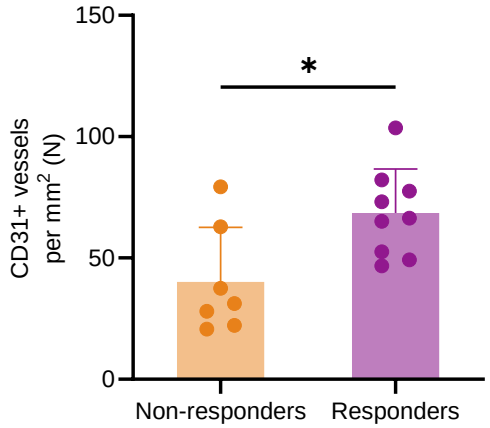
# Number of CD31+ blood vessels was significantly higher in responders

Non-responders



Responders





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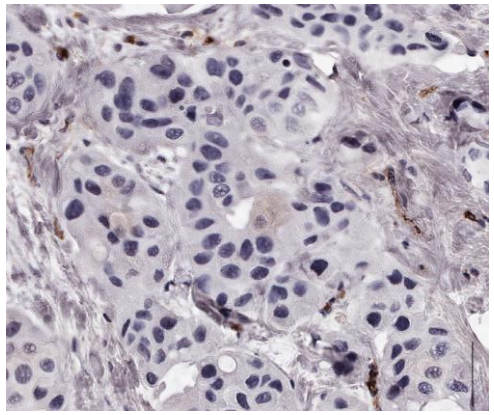
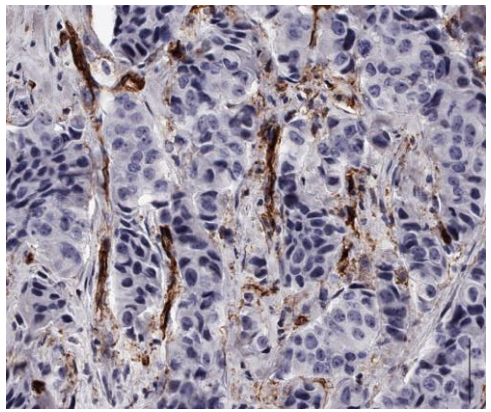
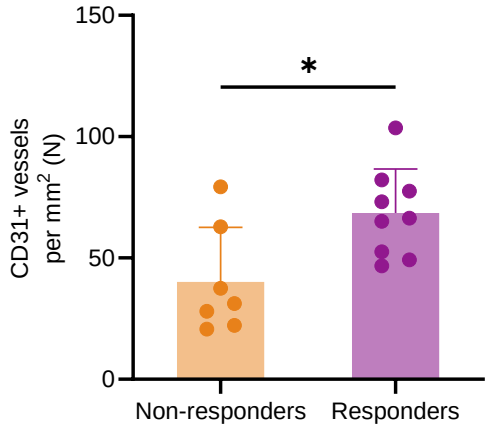
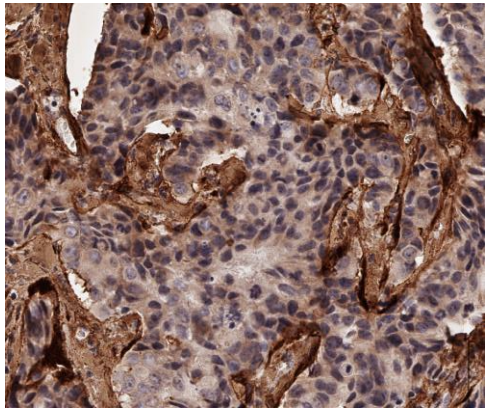
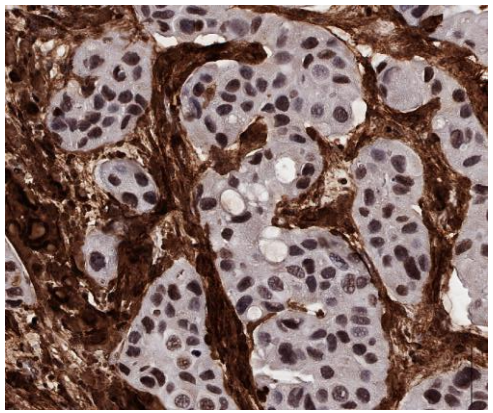


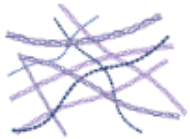
Responders

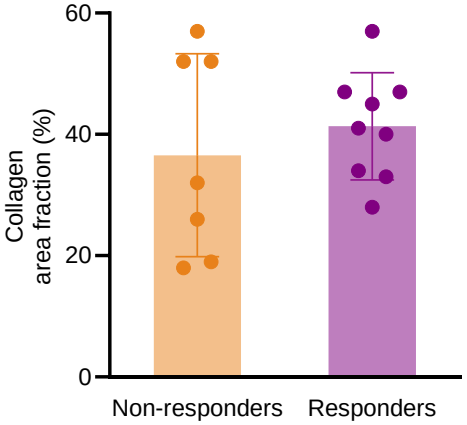




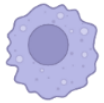




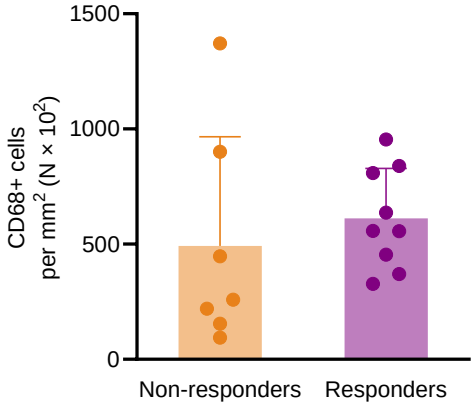


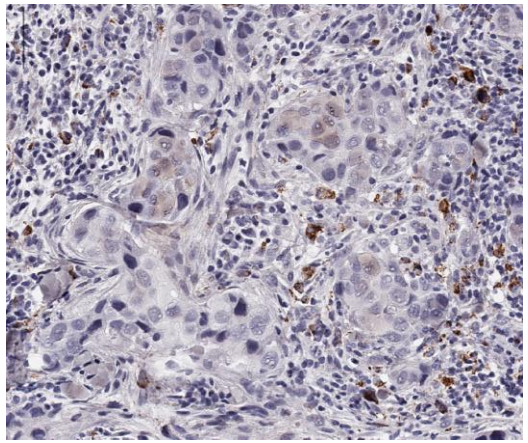

→ **High vascularization is a key driver for efficacy**

# The presence of immune cells prior therapy could potentiate HER2-related immune responses

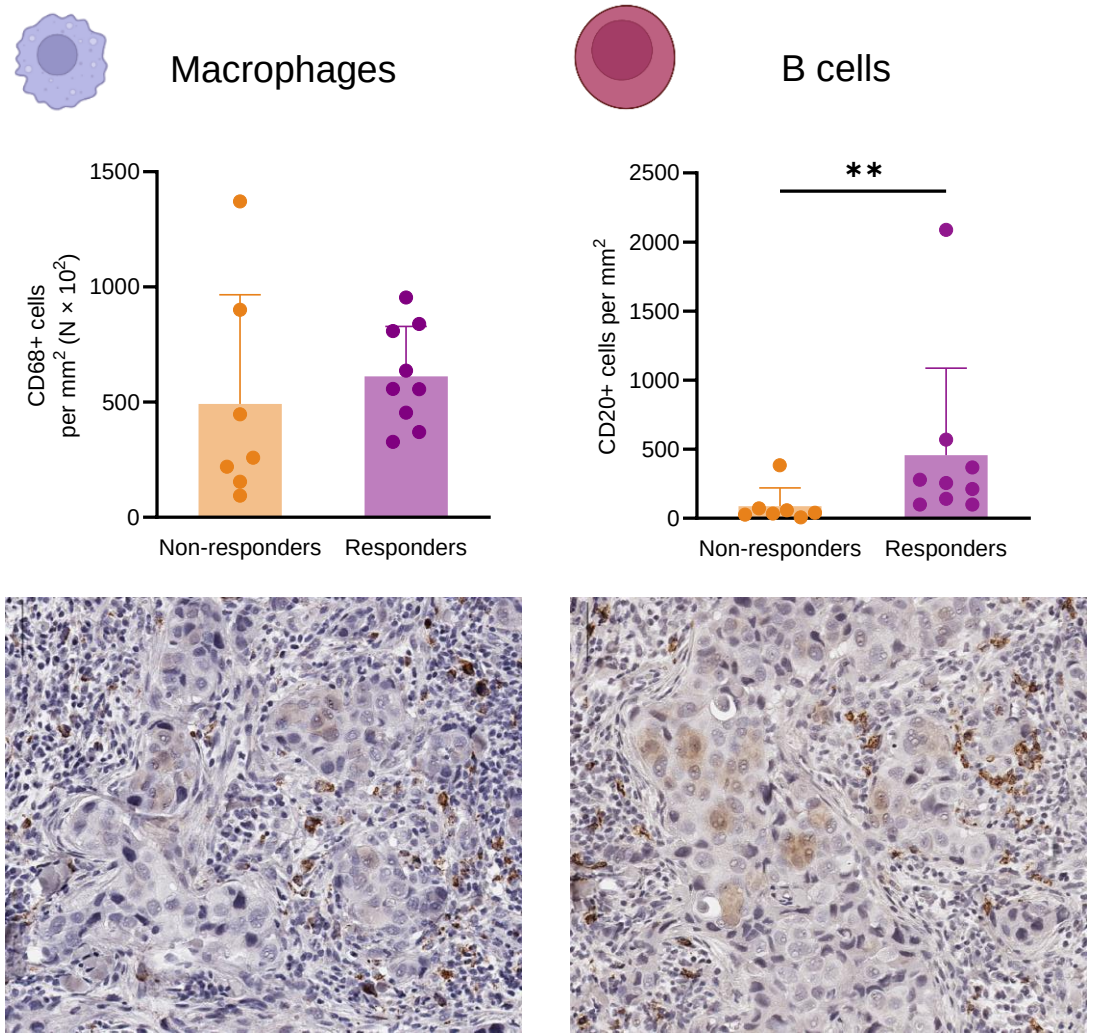


Macrophages



# The presence of immune cells prior therapy could potentiate HER2-related immune responses



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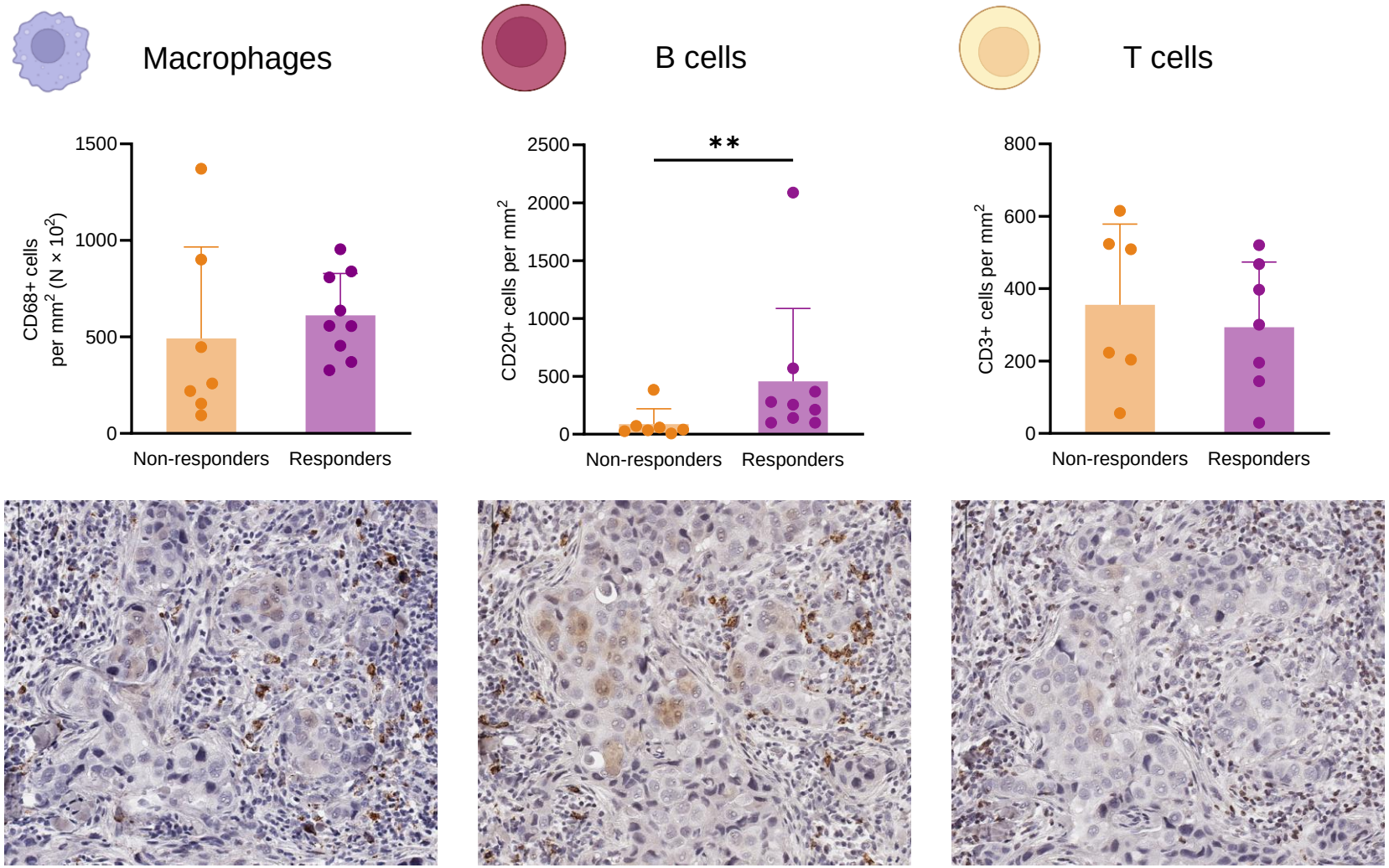
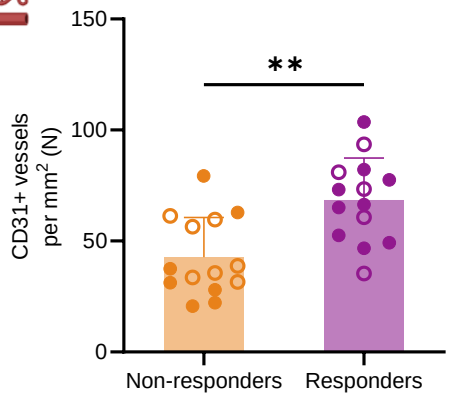
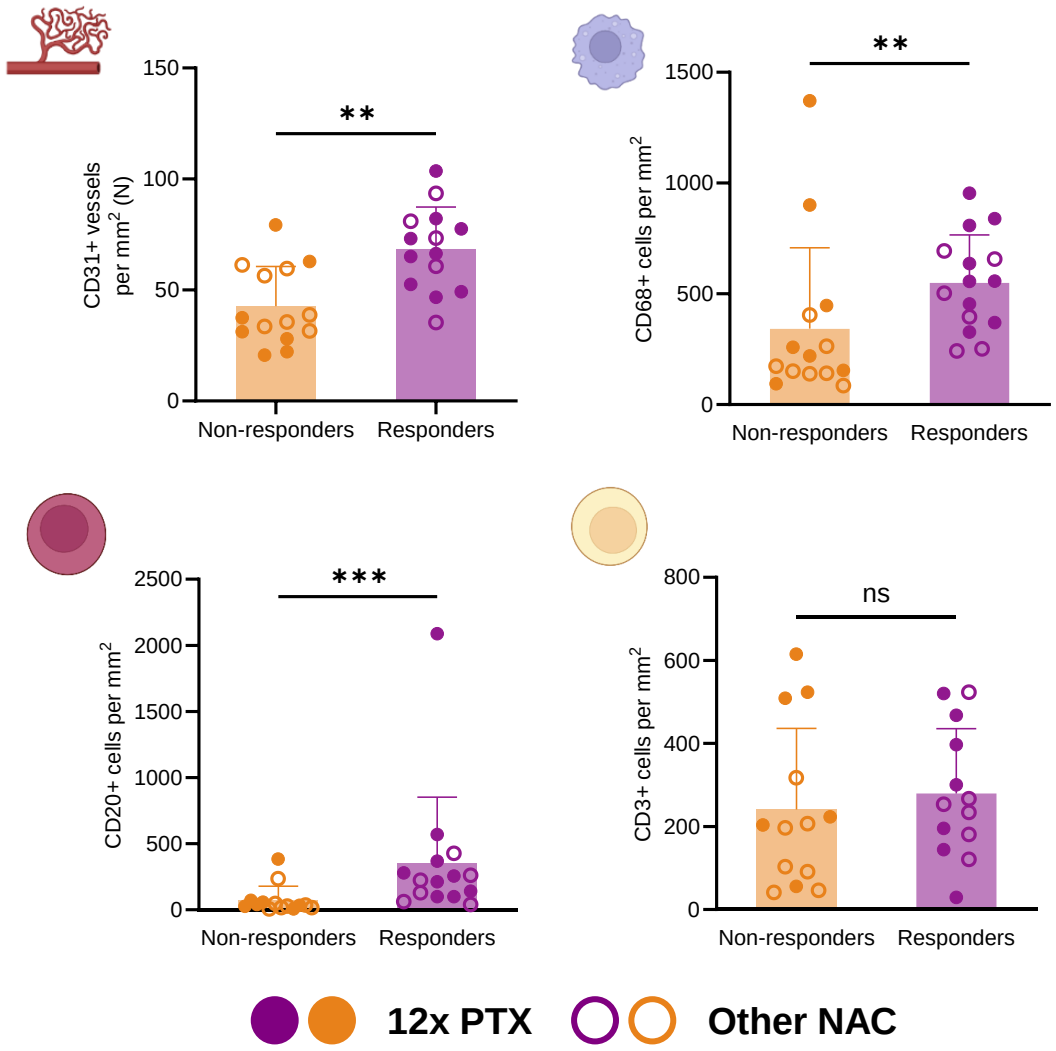


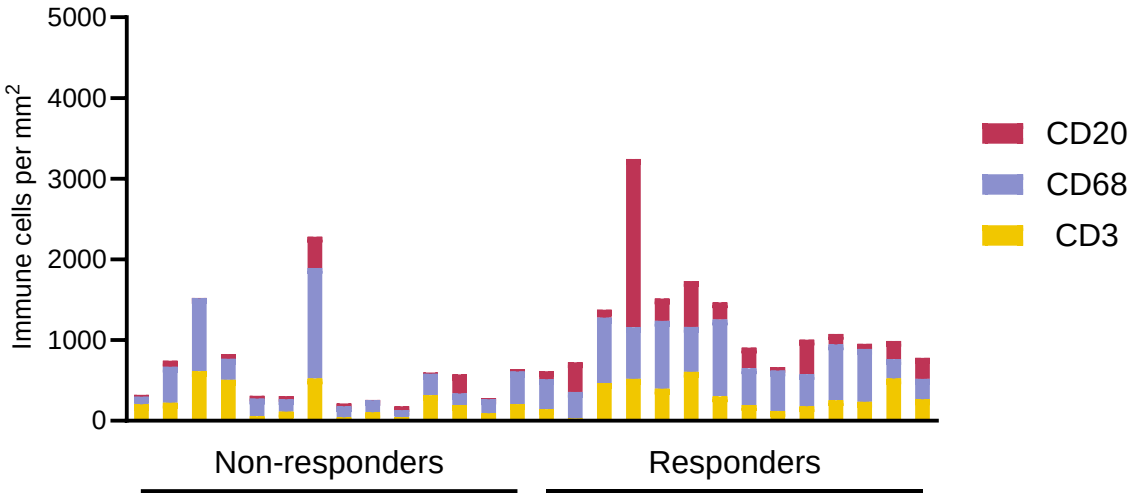
## What about other NAC regimens?




12x PTX  Other NAC

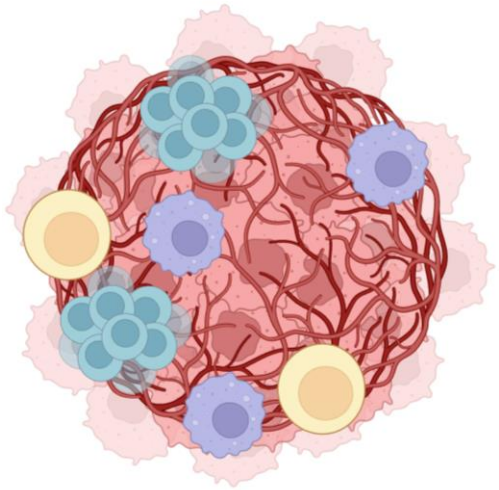
# Pre-existing infiltration of tumors by B cells and macrophages is a key driver for HER2-targeted therapies



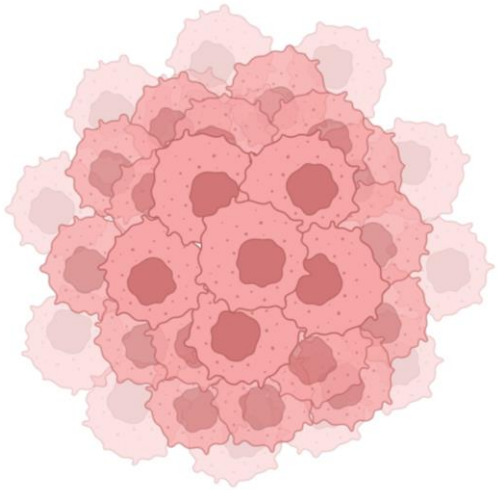



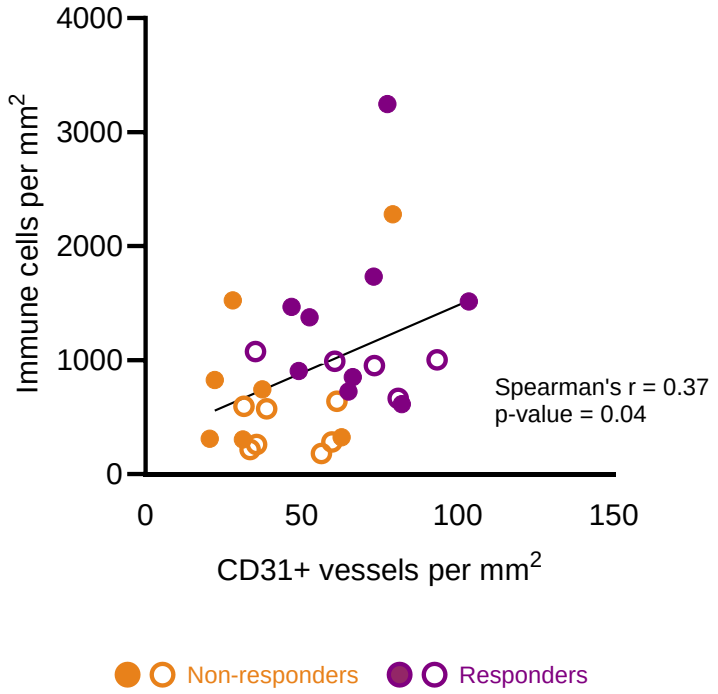
# Responders often have well-vascularized tumors, promoting lymphocyte infiltration and therapy delivery

Responders



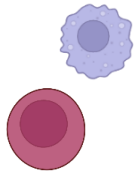
Non-responders



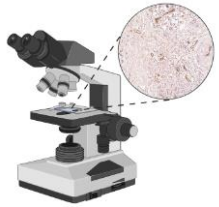


Regardless of HER2 expression level, HER2-blockers such as monoclonal antibodies have variable responses between patients

HER2-targeted therapy efficacy is dependent on TME features such as blood vessels that enable efficient delivery.



Highly vascularized tumors tend to have elevated levels of tumor-infiltrating lymphocytes (TILs), which can enhance anti-tumor immune responses when treated with HER2-targeted therapies



By highlighting this interplay between drug delivery, immune engagement and TME features, we pave the way for patient stratification for tumor-targeted antibodies and nanomedicines.

# Acknowledgments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Jan-Niklas May, MSc

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RTG 2375

Deutsche Forschungsgemeinschaft

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