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Rational Combination of a Small Inhibitor and Immune Checkpoint Blockade in Hepatocellular Carcinoma Preclinical Models

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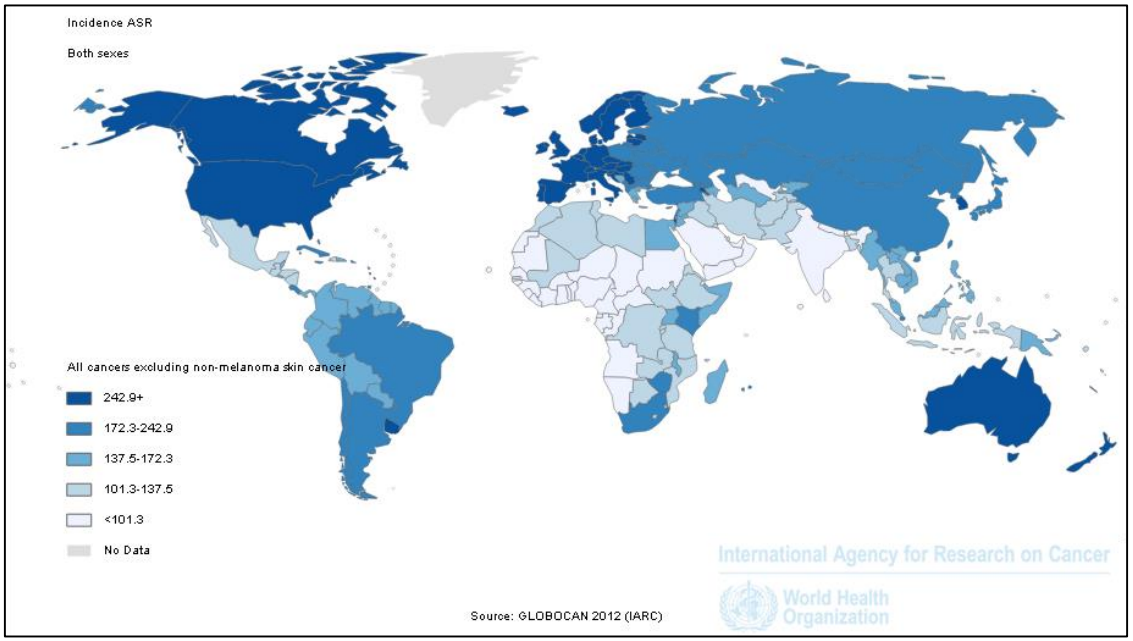
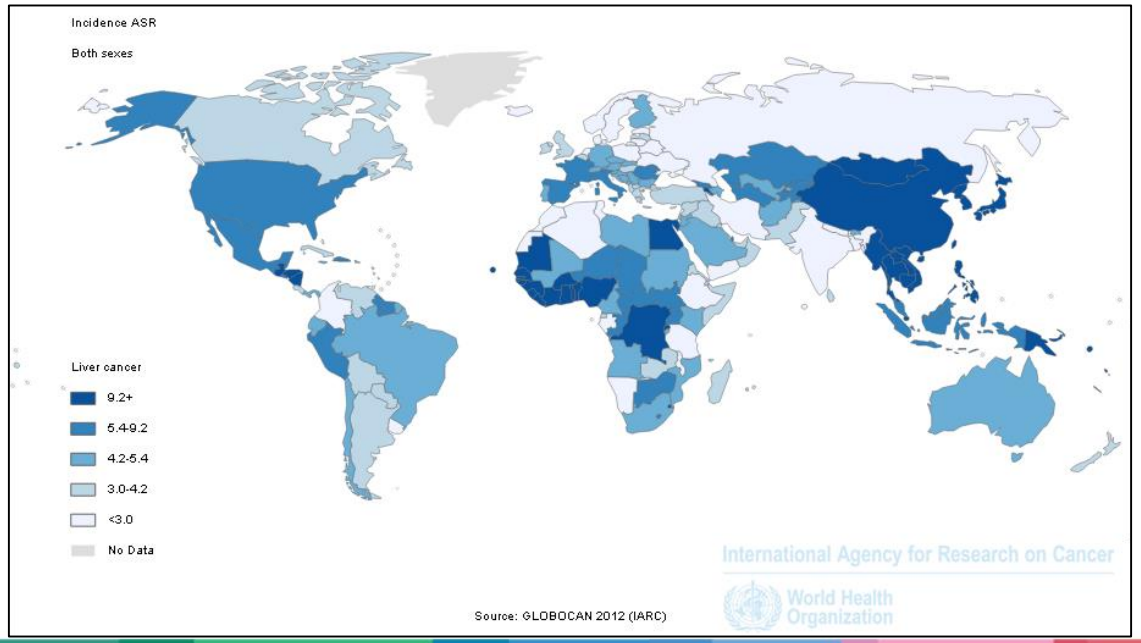
- Employees of ASLAN Pharmaceuticals are not involved in any part of the research work
- No other conflict of interest

All Cancers



Liver Cancer



Risk factors of HCC

- Chronic viral hepatitis (HepB or HepC)
- Aflatoxins
- Alcohol abuse
- Non-alcoholic fatty liver disease (NAFLD)
- Obesity
- Fibrosis
- Cirrhosis

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Hepatocellular Carcinoma (HCC)

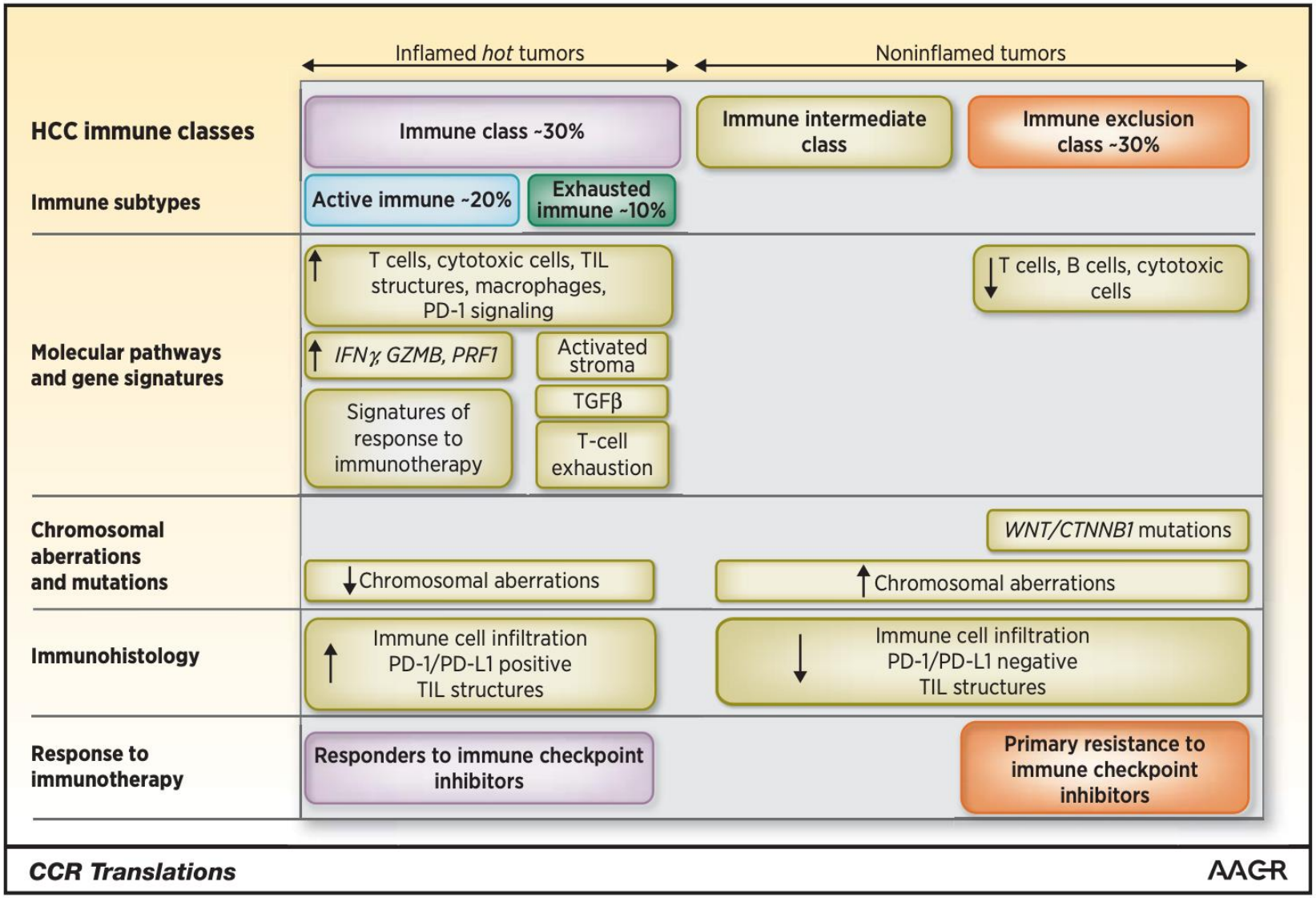
- The 2nd commonest cause of cancer deaths worldwide
- The 3rd most frequent cancer deaths among Singaporean males

- **1st line treatment**
- Sorafenib, a multikinase (RAF/VEGFR/PDGFR) inhibitor – approved in Dec 2007

- **Alternative 1st line treatments**
  - Lenvatinib – a multikinase (FGFR/VEGFR) inhibitor approved in Aug 2018
    - Non-inferior to sorafenib, but not statistically superior to sorafenib for overall survival (OS)
  - Atezolizumab + Bevacizumab – approved as "Breakthrough Therapy Designation" in Sept 2018
    - Positive phase 3 clinical outcome (better OS than sorafenib) shown in Oct 2019

However, there is no treatment and predictive biomarker available

Figure 1:



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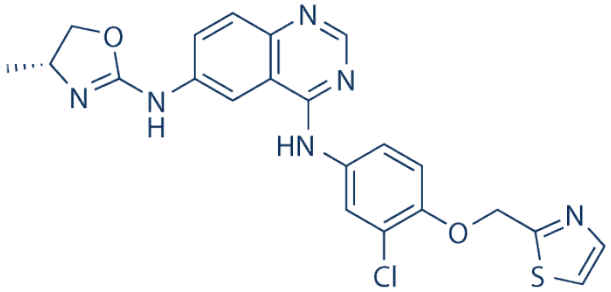
Pan-ErbB targeting small molecule

- Best-in-class EGFR, ErbB2, and ErbB4 inhibitor
- Selective for the ErbB family members
  - No inhibition of > 150 other kinases
- Potent in cell-based assays
  - Activity on clinically important mutants
- Reversible inhibitor, providing a good clinical safety profile



ERBB3 is frequently upregulated in HCC

ERBB2 and *ERBB3* are potential prognostic markers for HCC

SG Dataset
n=48

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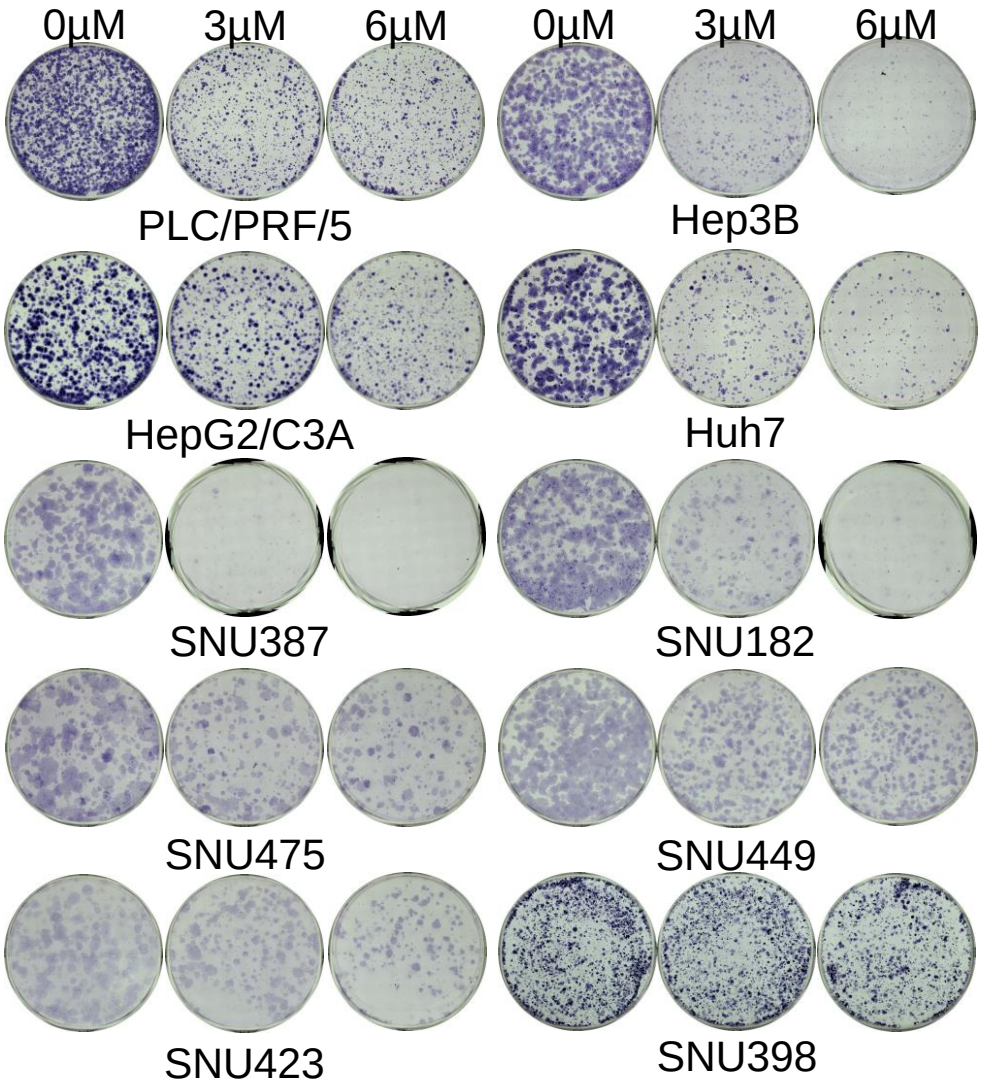
Pan-ErbB inhibitor suppresses *in vitro* cell growth

Colony Formation Assay



Cytotoxicity Assay

Cell lines	IC50 at 96-hour
PLC/PRF/5	5.33uM
Hep3B	4.08uM
HepG2/C3A	5.35uM
Huh7	4.07uM
SNU449	>10uM
SNU475	>10uM

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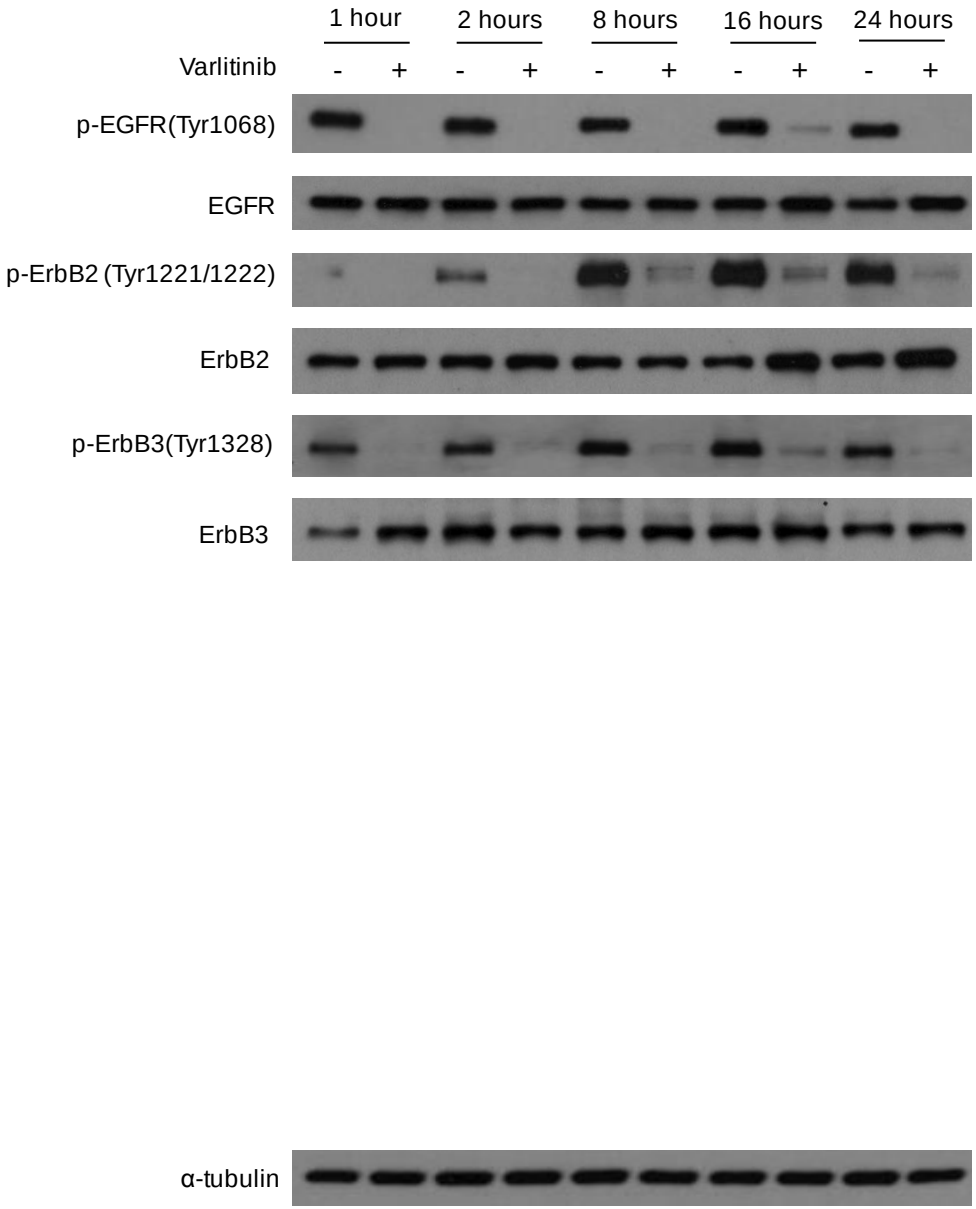
Western blot



PLC/PRF/5

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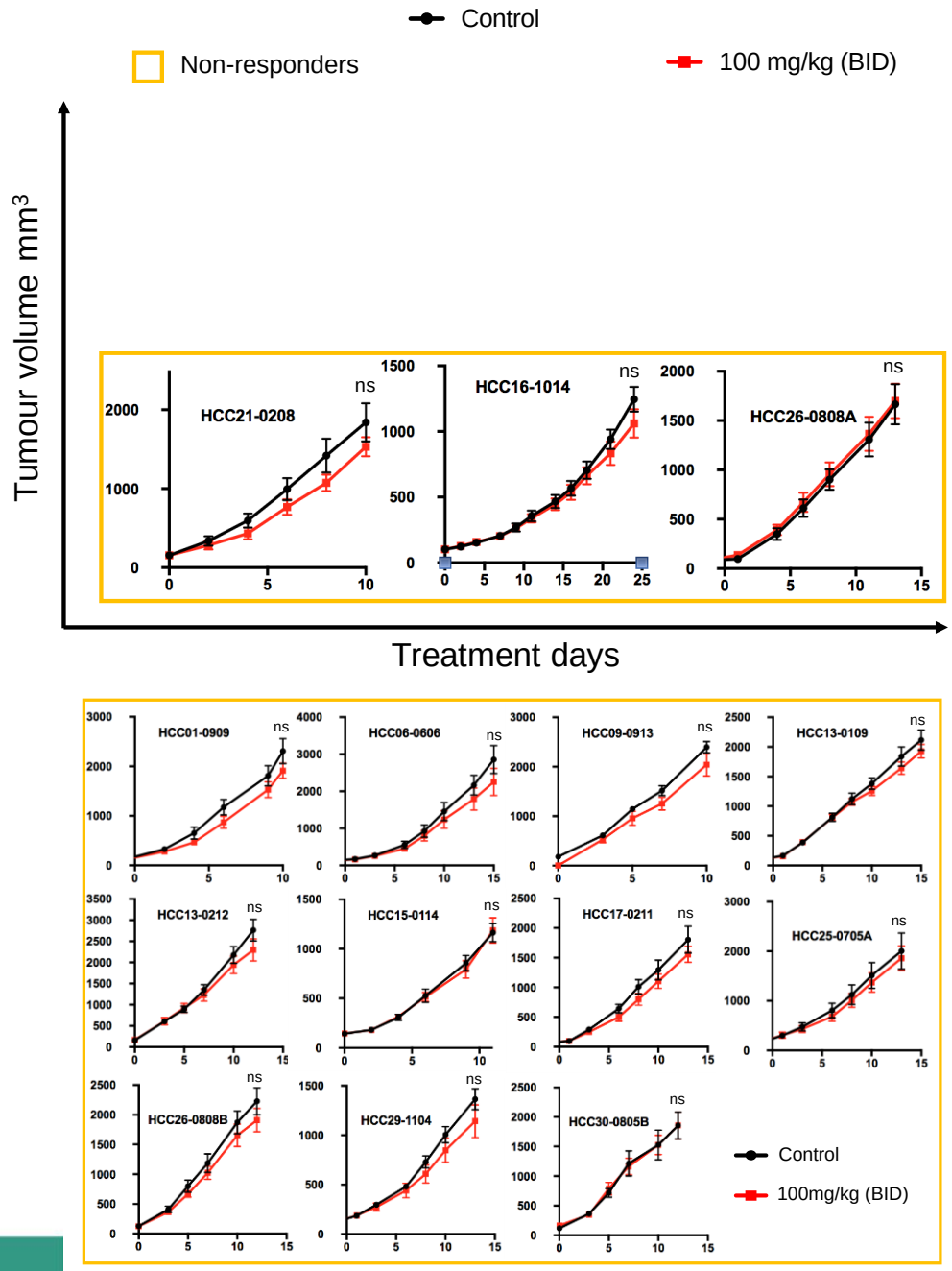
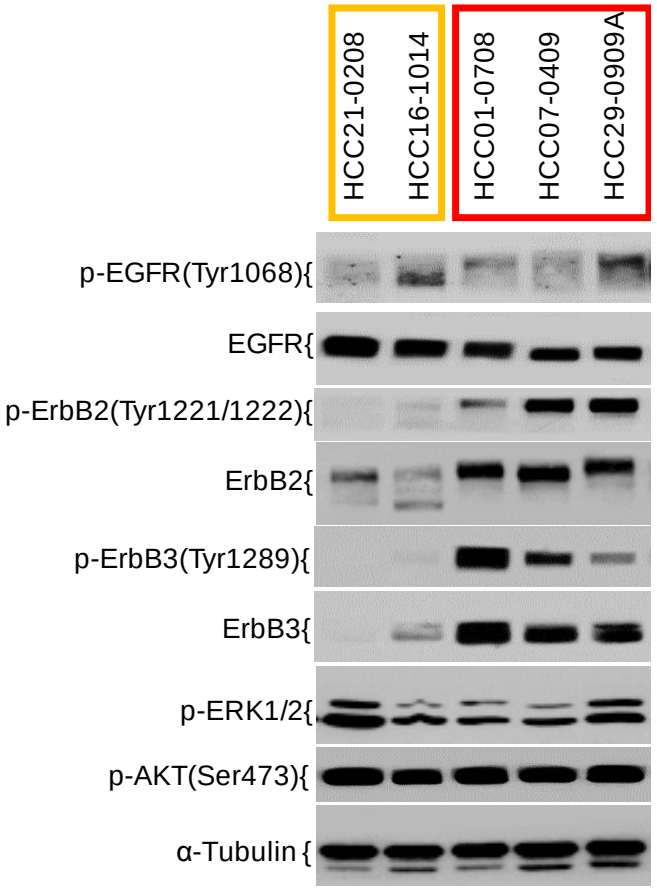
ErbB family expression in HCC PDXs

Pan-ErbB inhibitor selectively suppresses a subset of HCC PDXs





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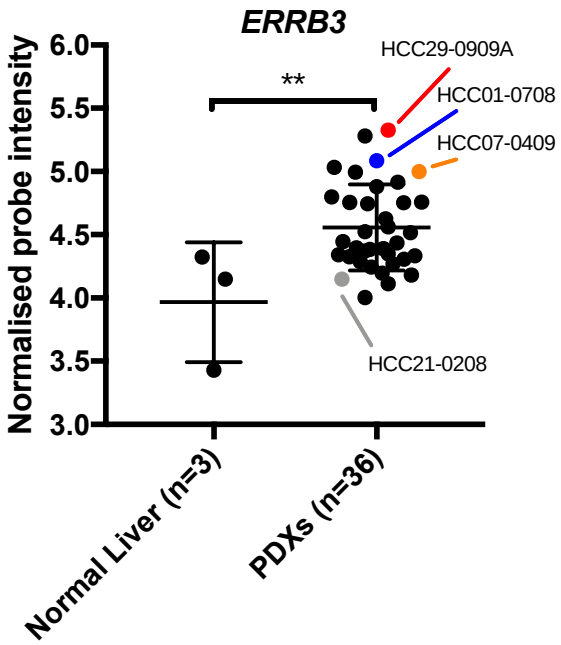
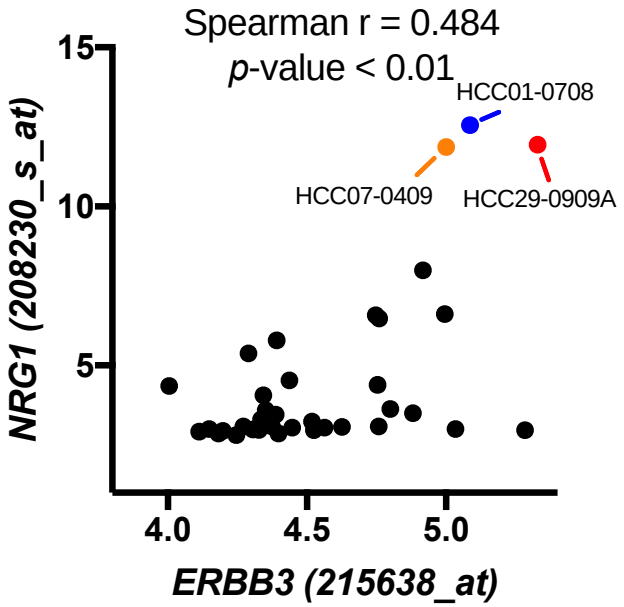
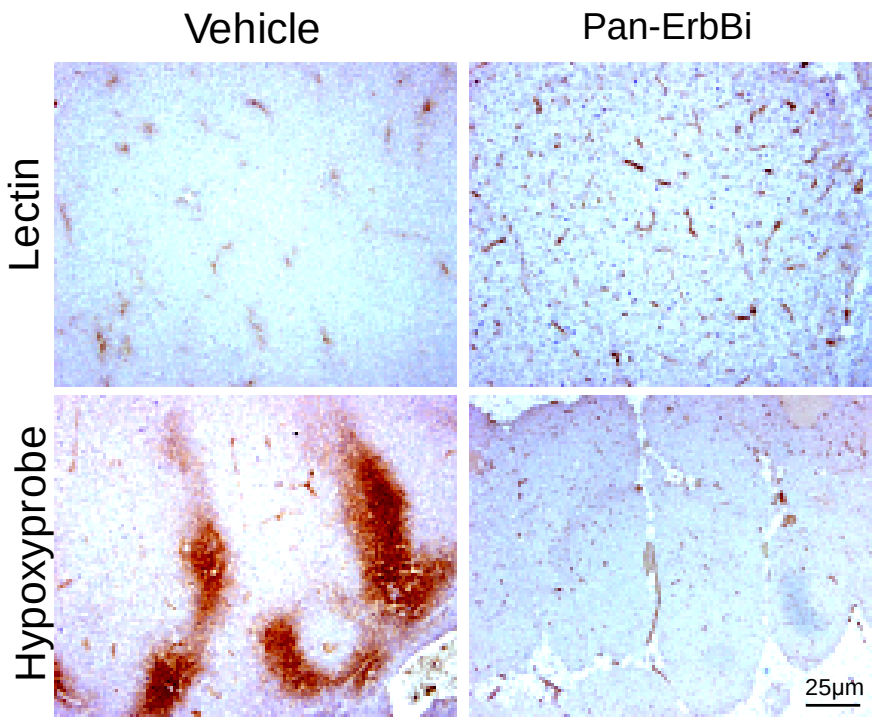
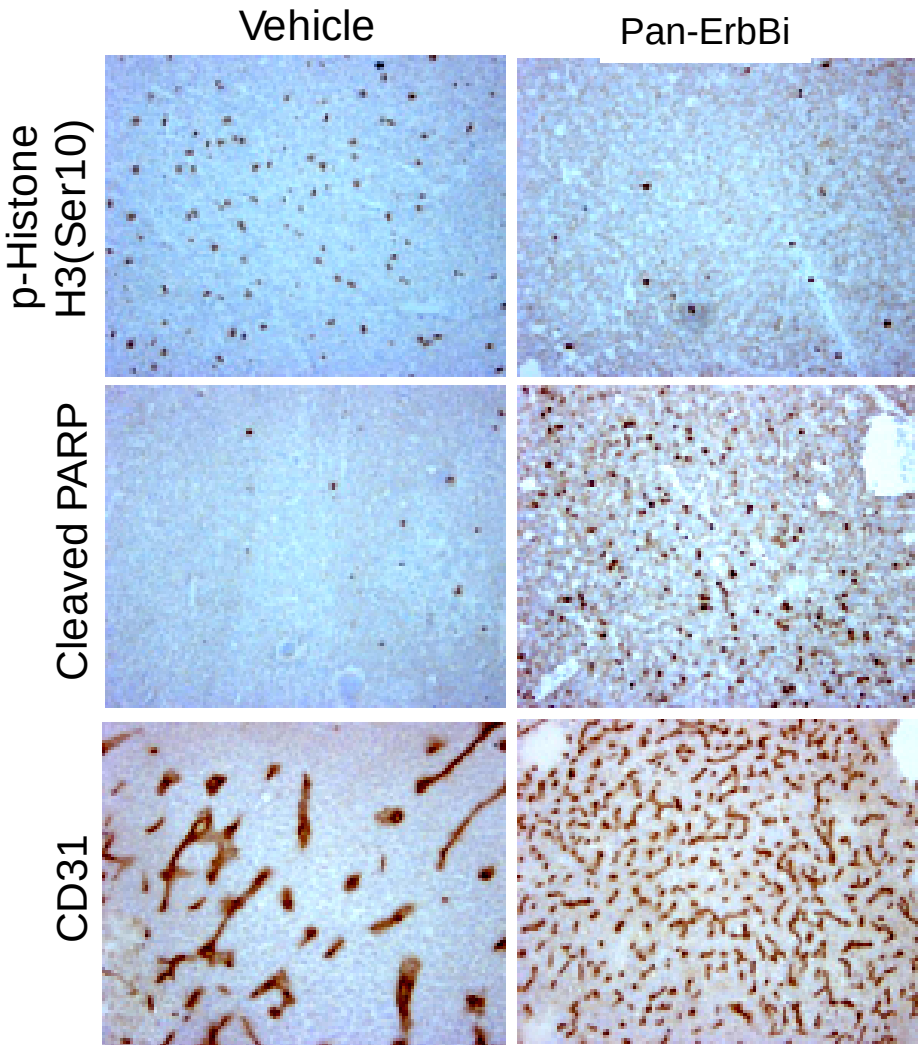




Effects of Pan-ErbB Targeting in PDXs





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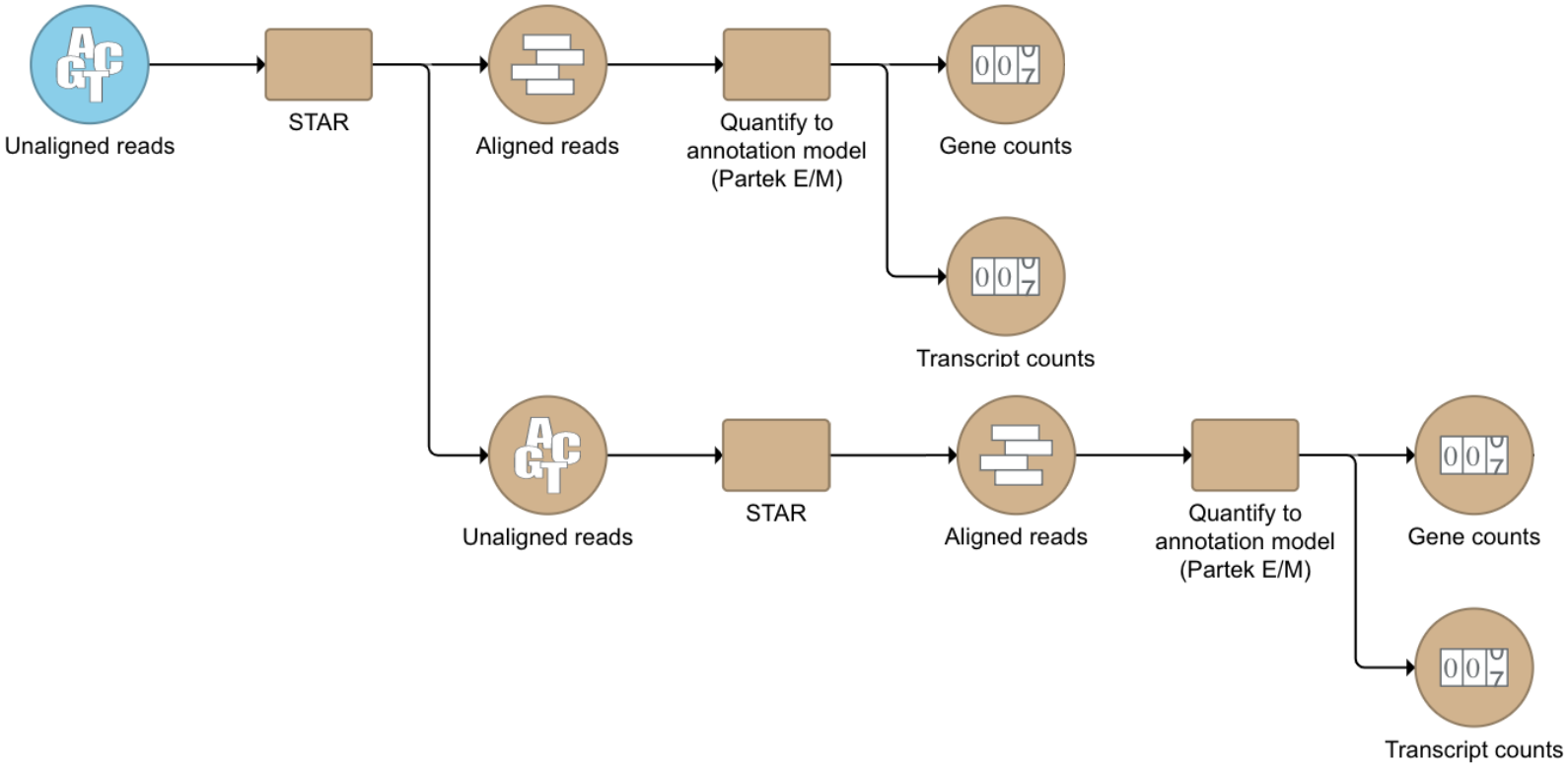
Mechanisms of Pan-ErbB Targeting by RNA-Seq Analysis



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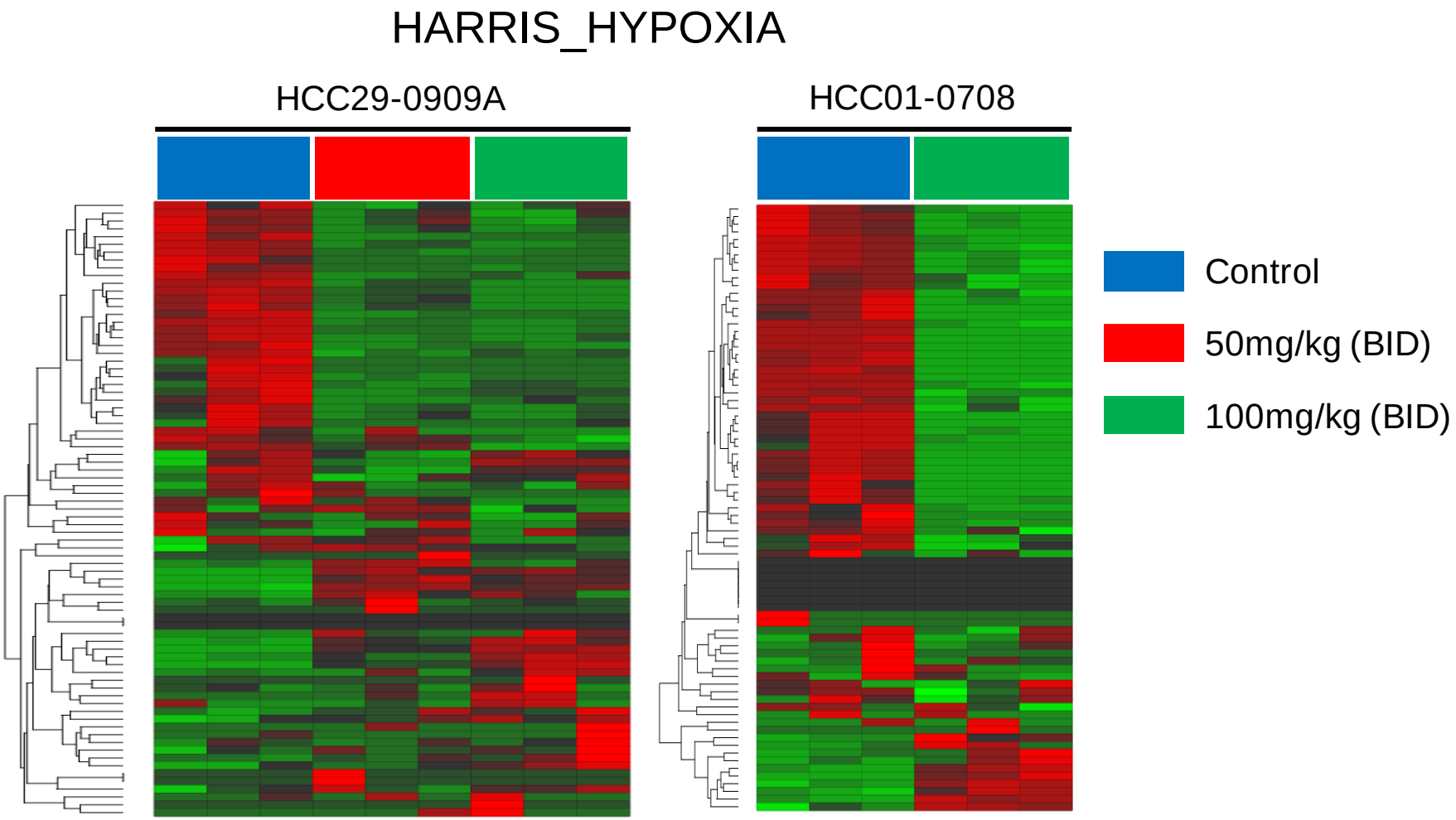
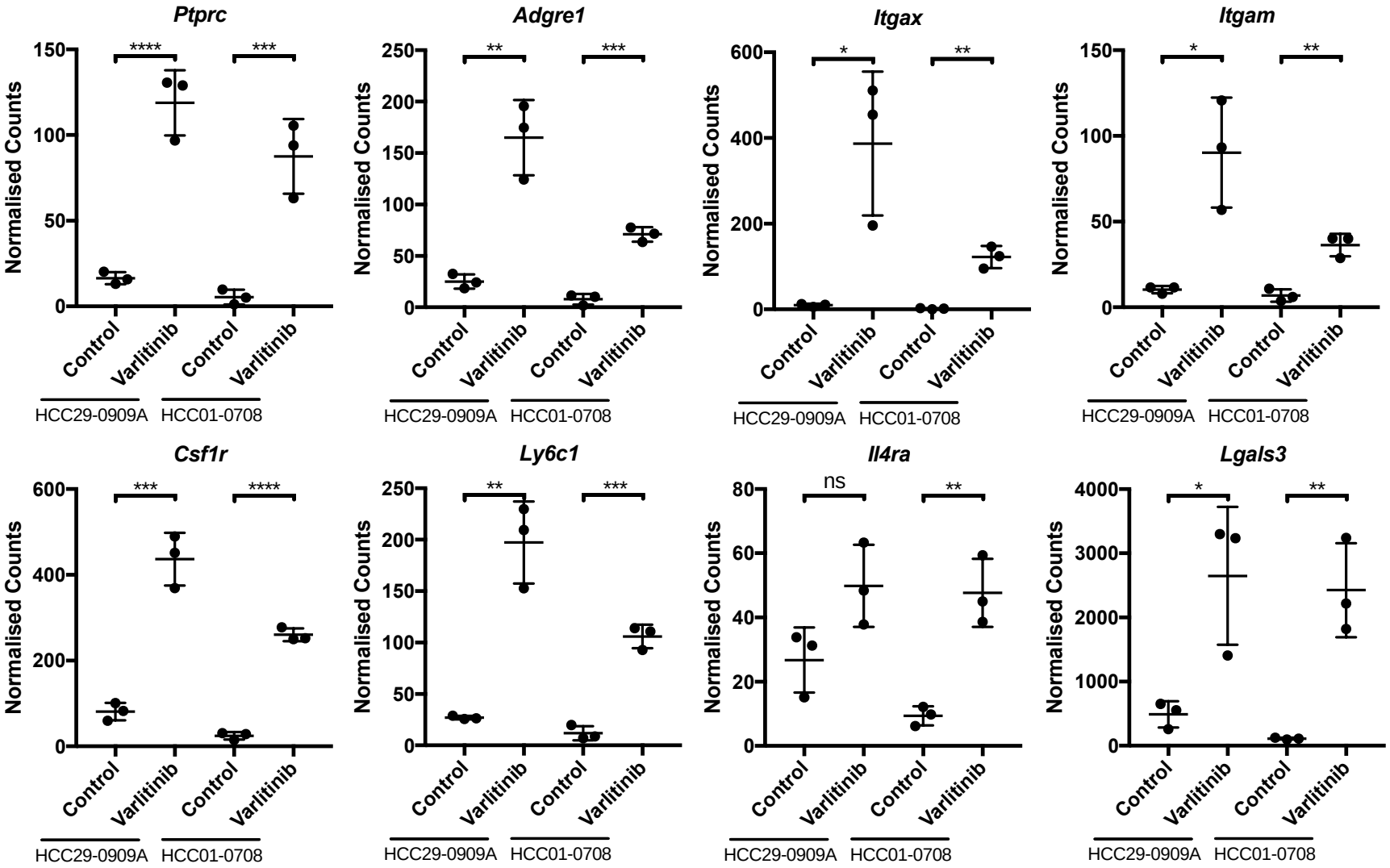
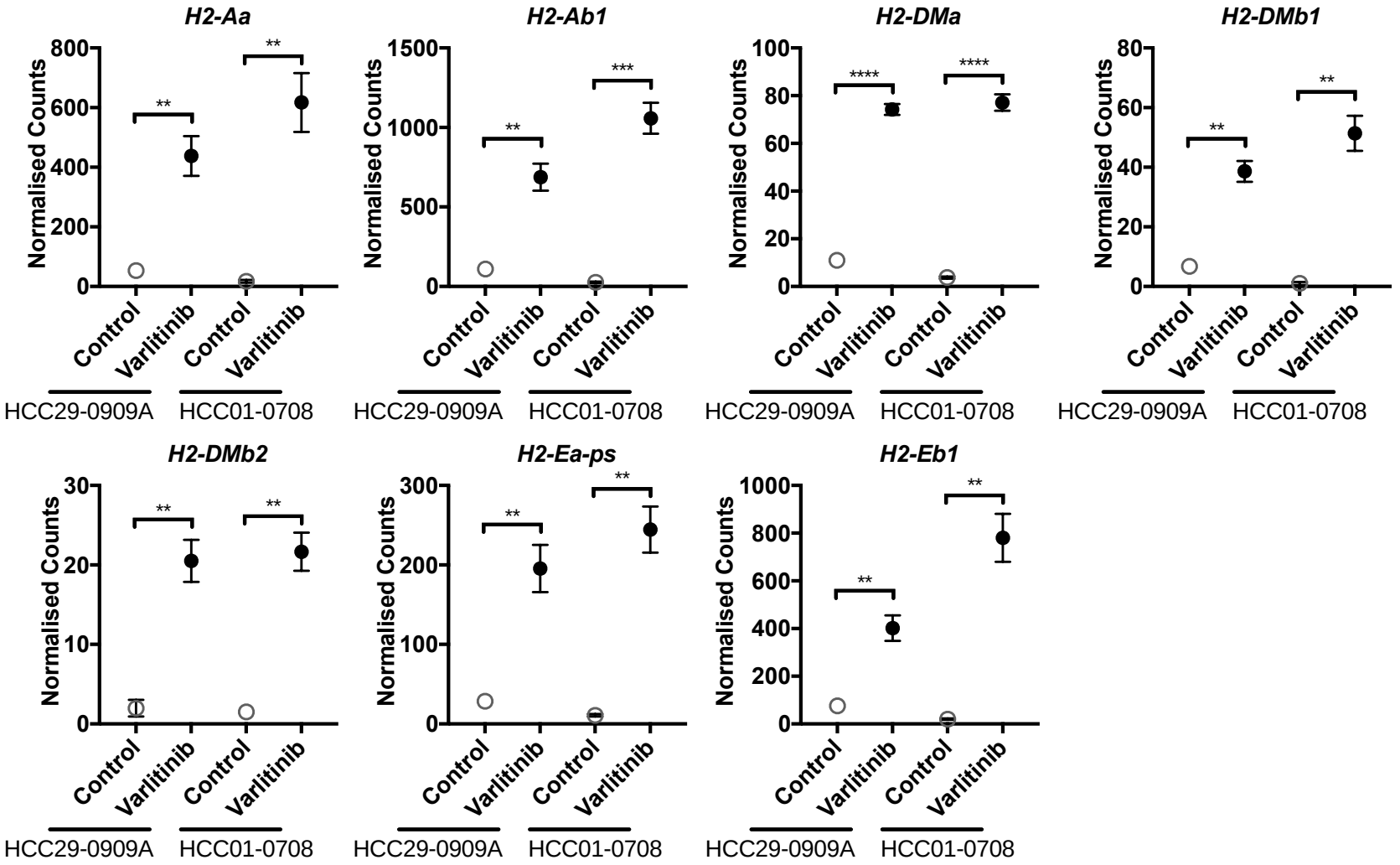


Pan-ErbB targeting facilitated immune infiltration



Higher HLA expression is found in PDXs following pan-ErbB targeting



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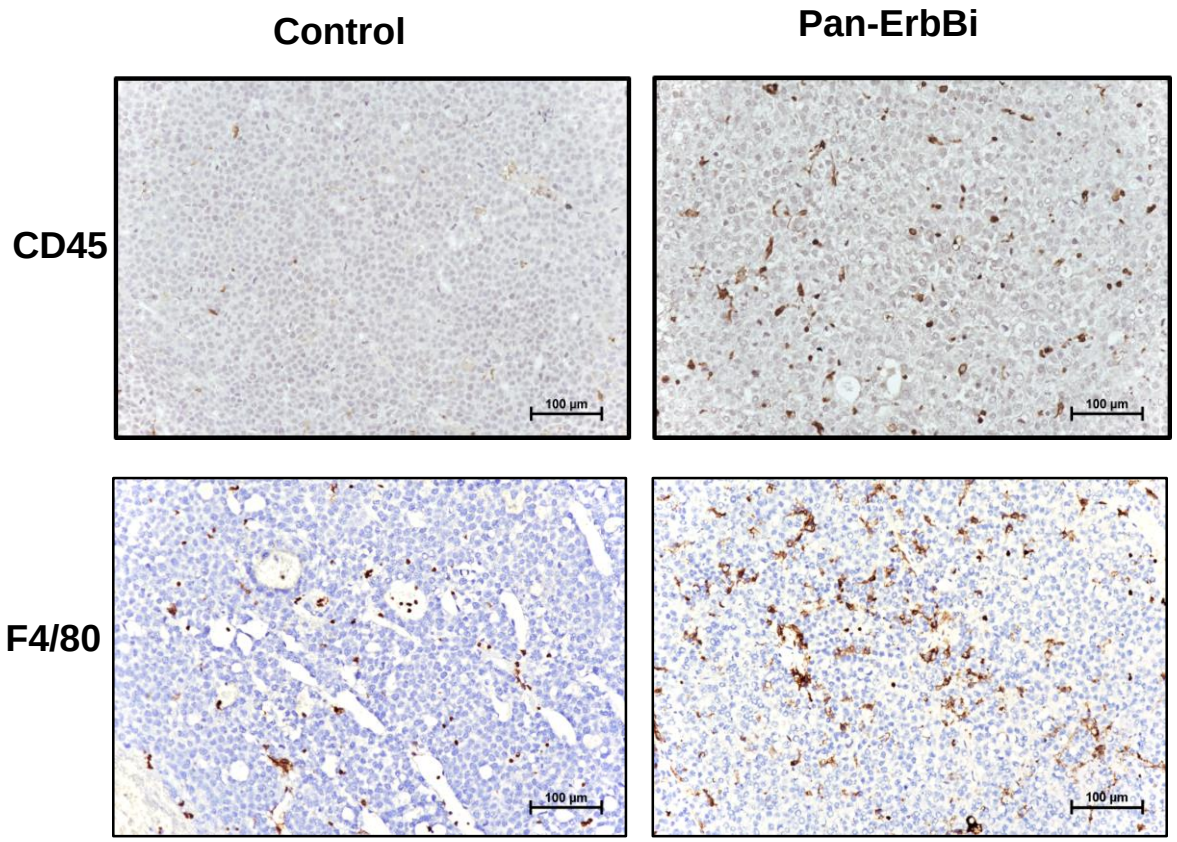
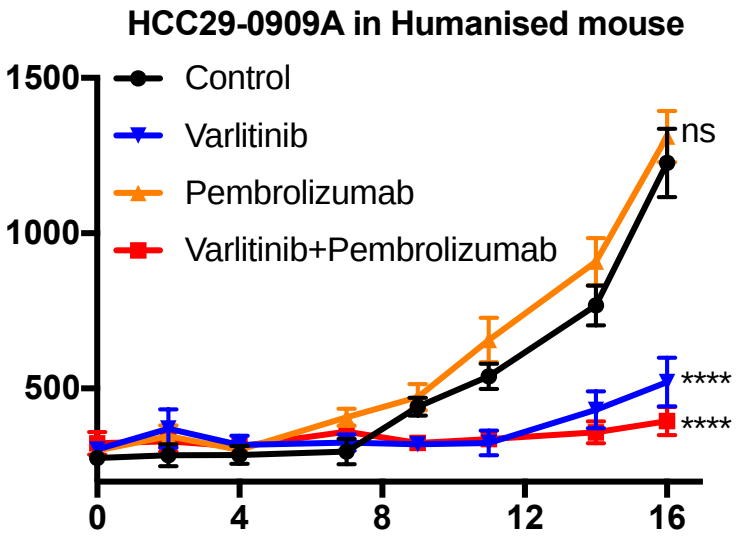
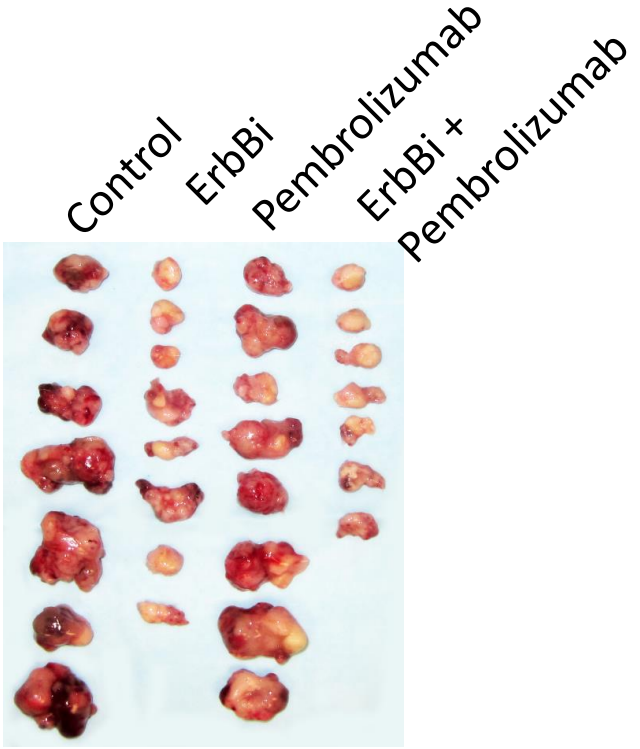
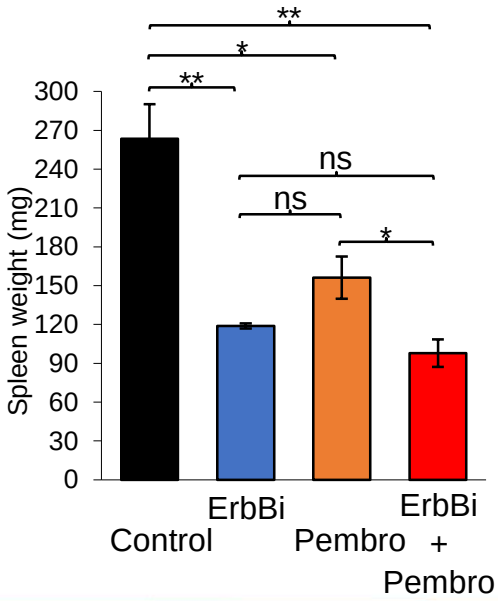
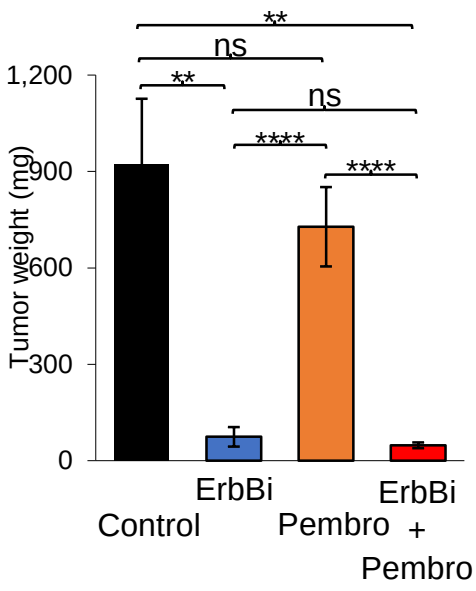


Pan-ErbBi + Anti-PD1 antibody in humanised liver cancer model









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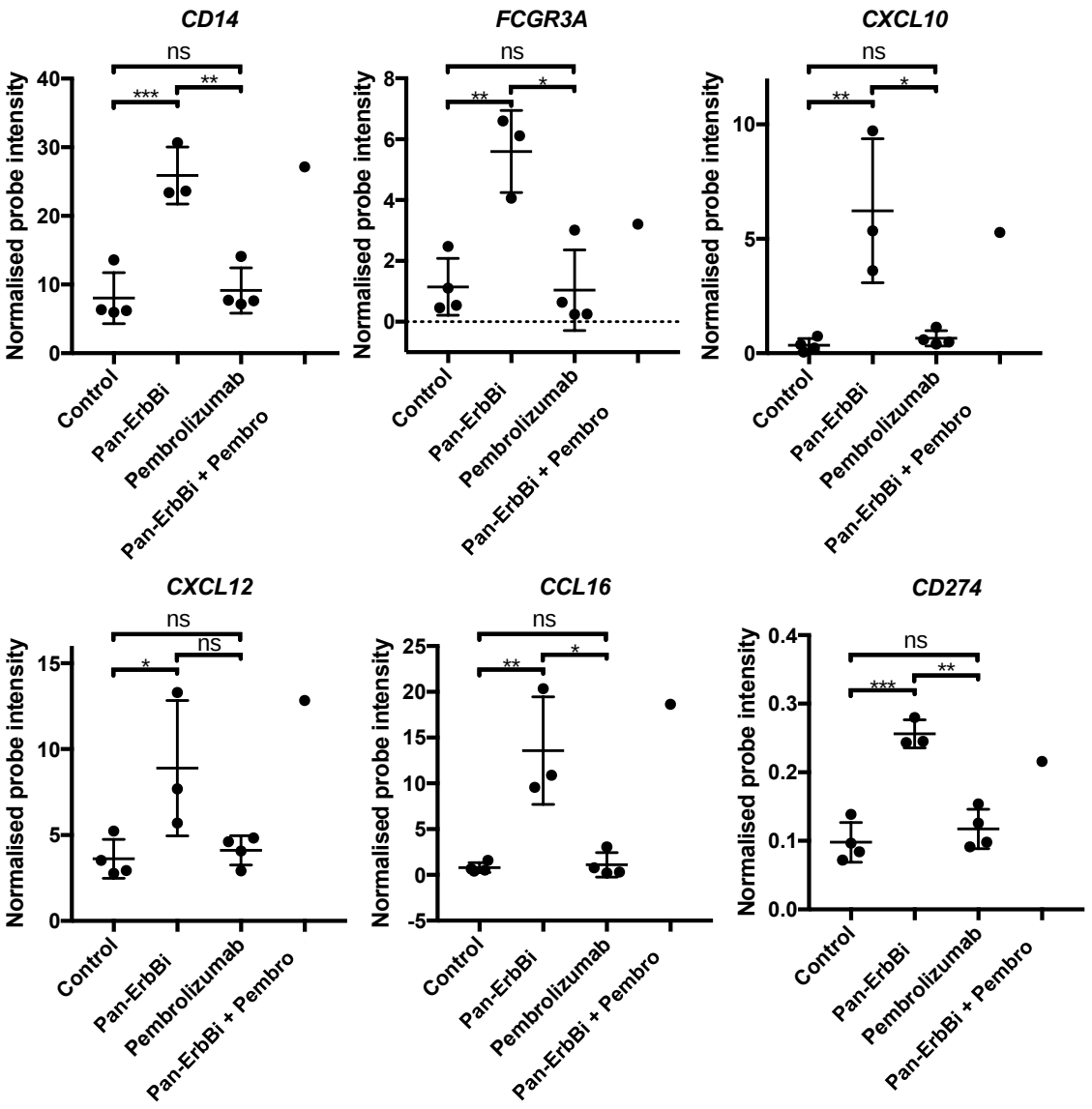
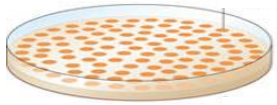
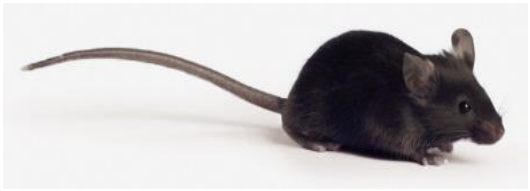
Pan-ErbBi + Anti-PD1 antibody in humanised liver cancer model



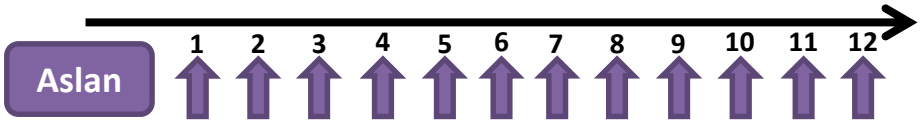
Pan-ErbBi + Anti-PD1 antibody in immunocompetent liver cancer model

Hepa1-6 cell line





Immunocompetent mouse



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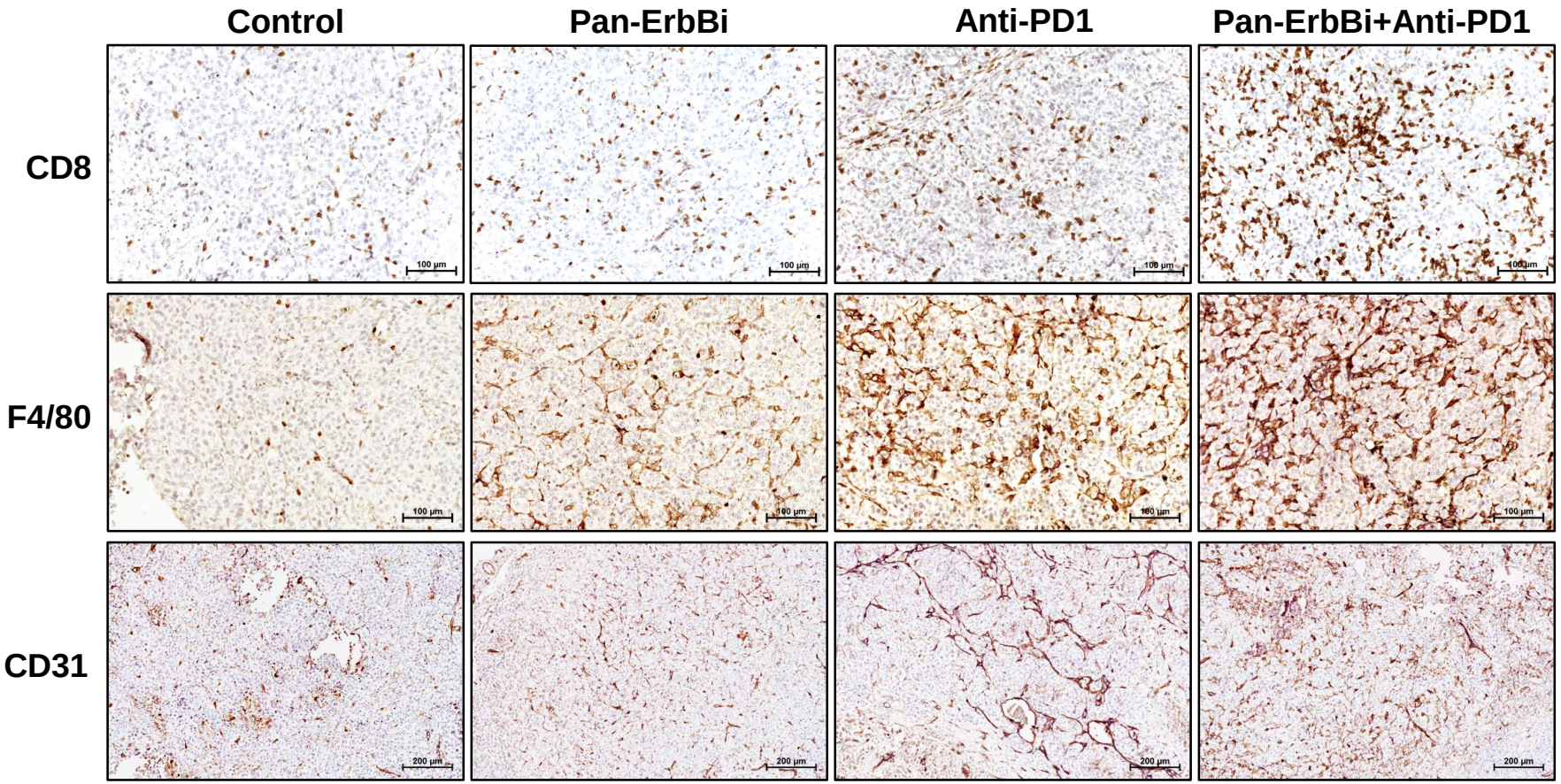
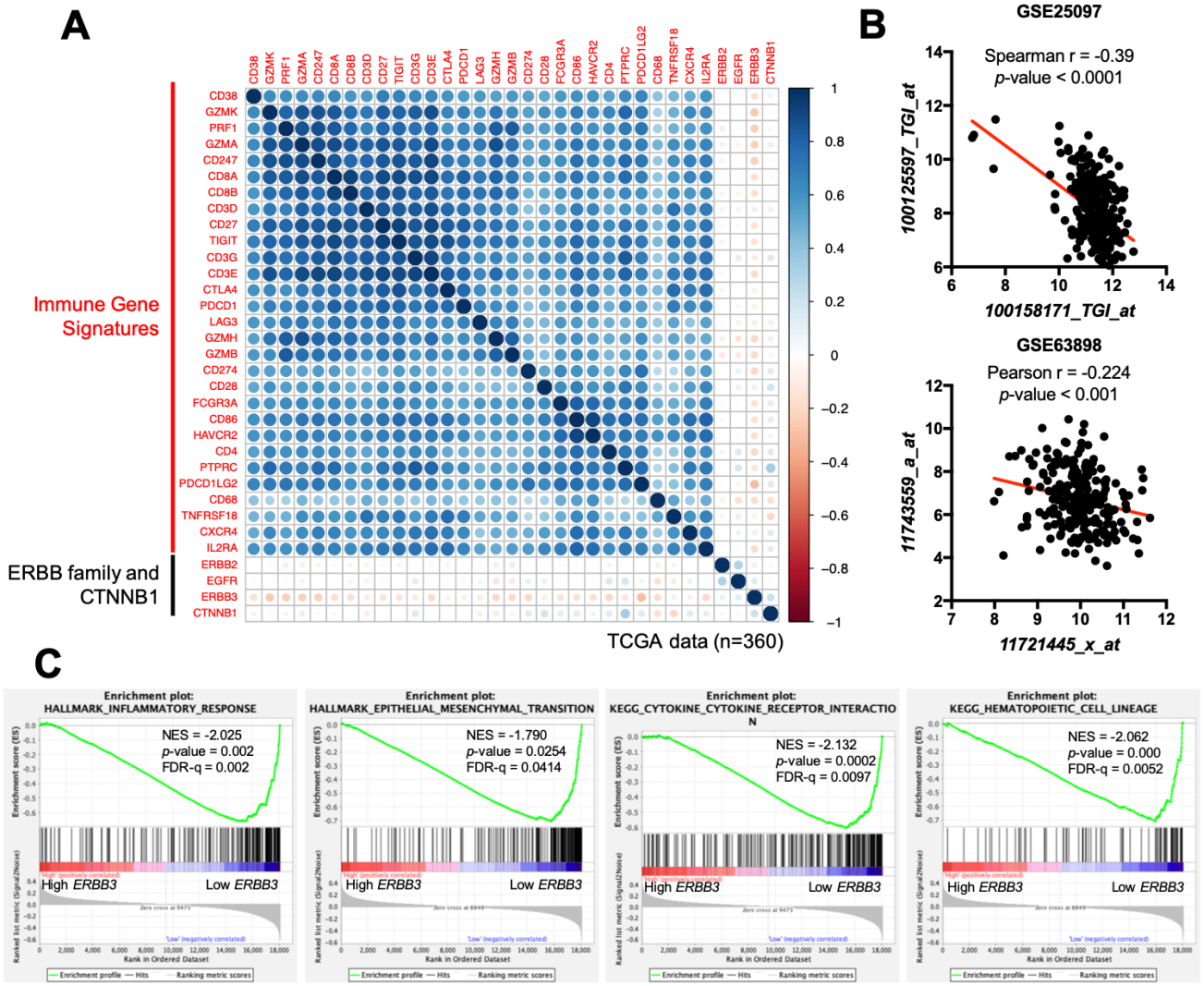
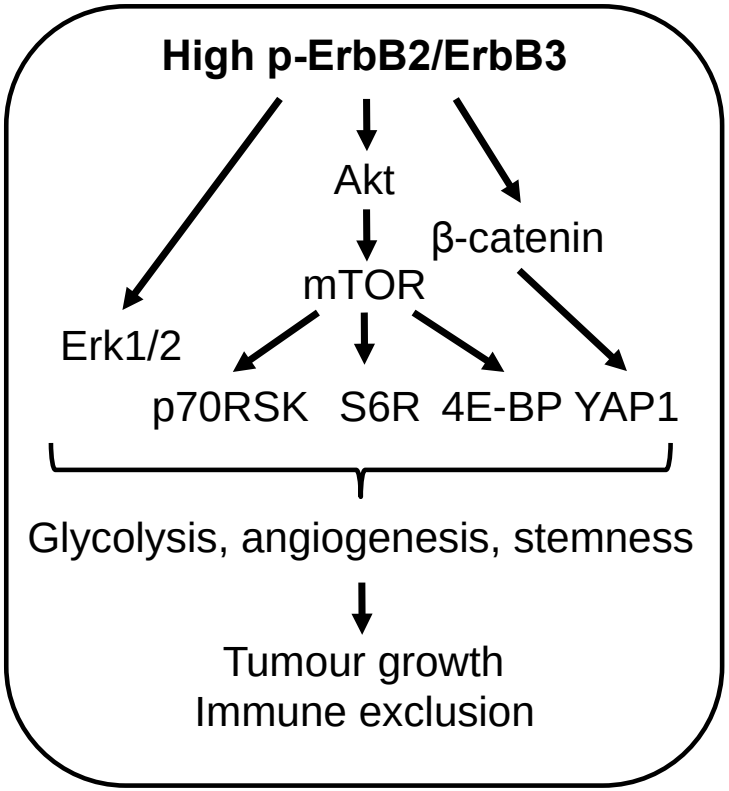


ERBB3 is negatively correlated with immune infiltration

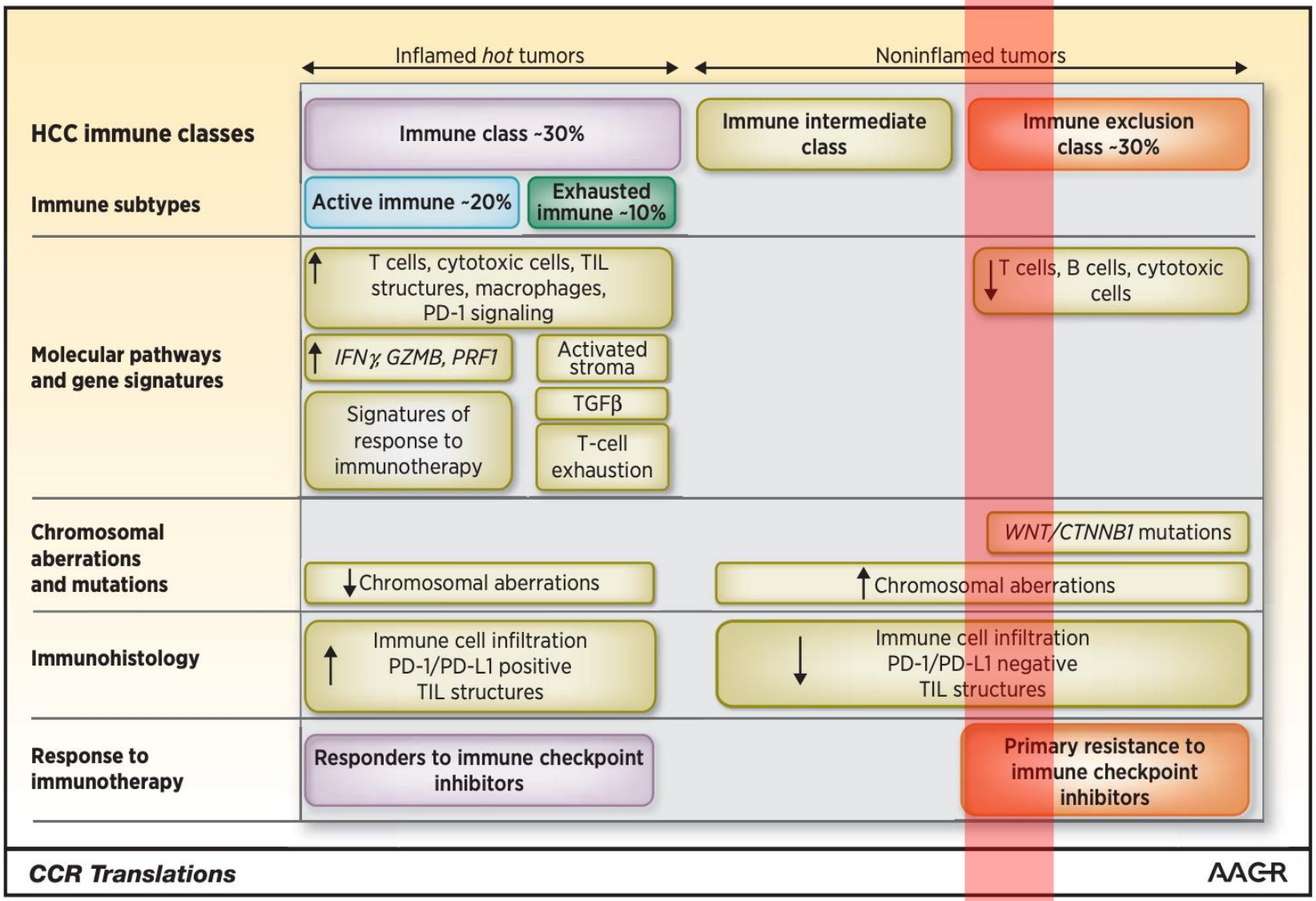


Proposed Pan-ErbB Targeting in HCC



ErbB family

Figure 1:



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