# Boosting immune surveillance by low-dose PI3K inhibitor facilitates early intervention of breast cancer

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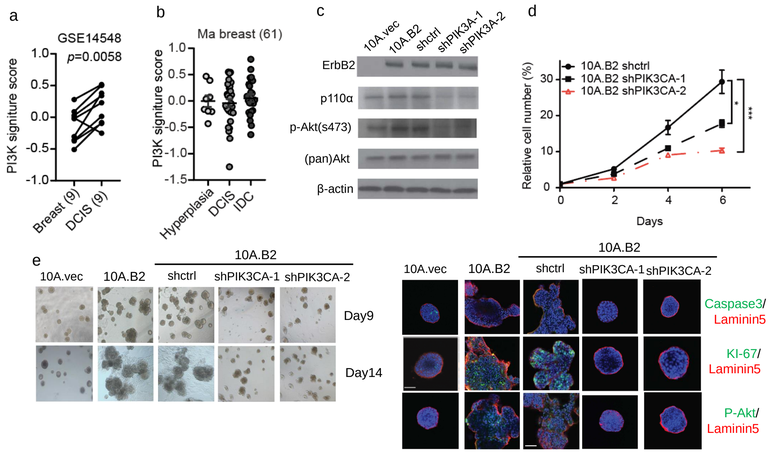
## ABSTRACT

- **Background:** Prevention of estrogen receptor–negative (ER-) breast cancer is an unmet challenge, although tamoxifen and aromatase inhibitors can successfully decrease the incidence of ER-positive (ER+) breast cancer.
- **Hypothesis:** Blocking PI3K pathway by genetic knockdown or using a clinically applicable PI3K inhibitor (GDC-0941) can inhibit ER- tumor initiation and progression.
- **Results:**
  - PI3K pathway is significantly activated in premalignant ER- breast lesions compared with paired normal tissues of patients.
  - Genetic knockdown of PI3K and low dose GDC-0941 intervention reversed the disorganized 3-dimensional growth of semi-transformed human ER- mammary epithelial cells *in vitro*.
  - Low-dose GDC-0941 treatment significantly delayed mammary tumor initiation in the MMTV-neu mouse model without exhibiting discernable adverse effects.
  - Increased CD8+/GZMB+ T-cells were detected in mammary tissue after GDC-0941 treatment, suggesting enhanced immune surveillance.
  - Mechanistically, elevated expression of potent T-cell chemo-attractants, including CCL5 and CXCL10, were detected both in vitro and in vivo after GDC-0941 treatment. Inhibition of PI3K significantly increased T-cell recruitment in a CCL5/CXCL10–dependent manner.

## RESULTS

Figure 1. Blocking PIK3CA prevents the dysplasia phenotype of 10A.B2 mammary epithelial cells.

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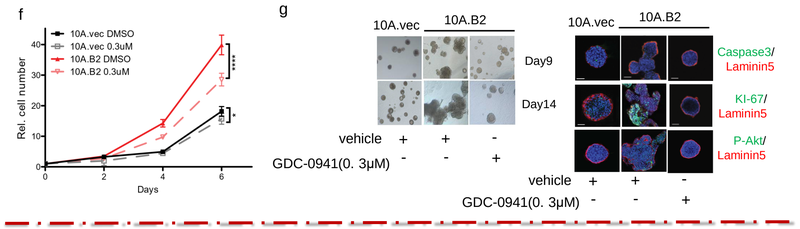



Figure 2. Targeting PI3K/Akt by GDC-0941 inhibited tumor initiation in MMTV-neu mice.

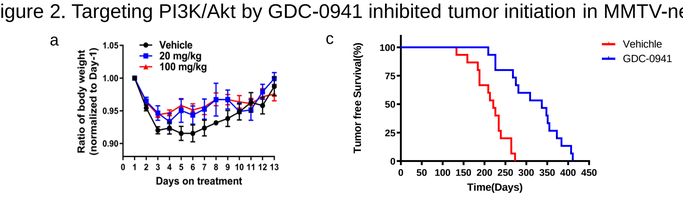



Figure 3. Low-dose GDC-0941 increases T-cell infiltration in mammary tissues of MMTV-neu mice.

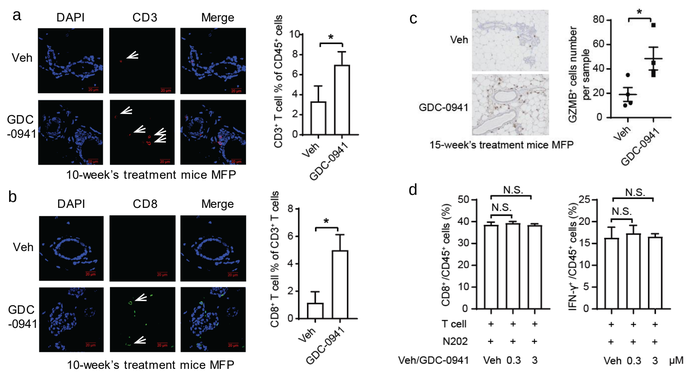
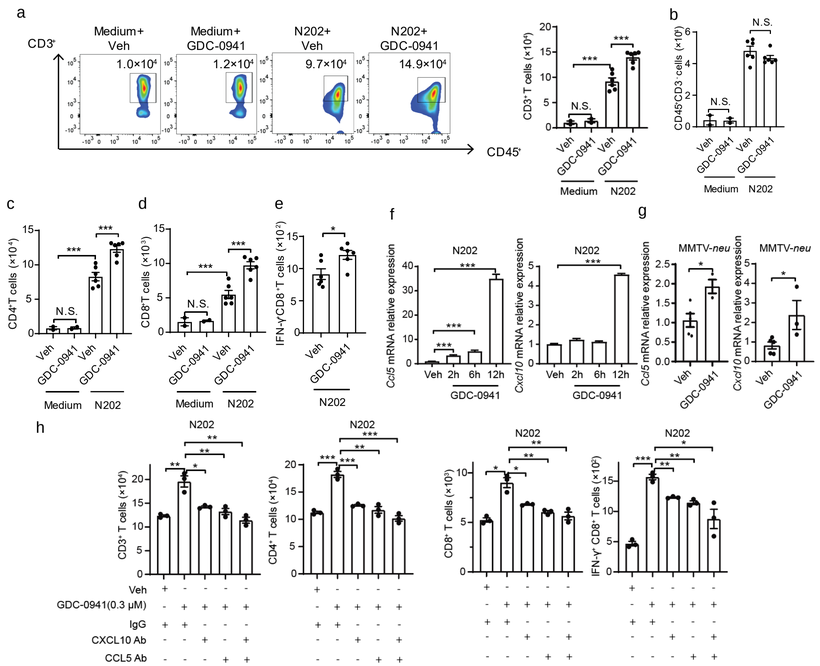



Figure 4. GDC-0941 enhances T-cell migration via CCL5/CXCL10.




## CONCLUSIONS

- Our study demonstrated that PI3K/Akt activation as a potential target for ER- breast cancer prevention and showed that inhibiting the PI3K/Akt pathway by low-dose GDC-0941 effectively suppressed abnormal acini growth of semi-transformed mammary epithelial cells in vitro and delayed ER- mammary tumor initiation in vivo.
- Low dose of PI3K inhibitor also significantly enhanced T-cell recruitment in a CCL5 and CXCL10–dependent manner.

## REFERENCES

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