LS What is the evidence for oncogenicity of variants in ERBB2 for breast cancer, and what inhibitors could I use to experimentally validate their importance in vitro from DGIdb?

I'll help you find evidence for ERBB2 oncogenicity in breast cancer and potential inhibitors for experimental validation. Let me query both CIViC and DGIdb databases.

L get_variant_evidence

L get_variant_evidence

Now let me get drug interactions for ERBB2 from DGIdb:

L get_drug_interactions_for_gene_list

Excellent! Now I have comprehensive information from both databases. Here's the summary:

## ERBB2 Oncogenicity Evidence in Breast Cancer

### CIViC Evidence for Oncogenicity

**ERBB2 G309A Variant** (EID:11490)

- **Evidence Level:** D (Preclinical)
- **Evidence Rating:** 4/5
- **Findings:** NIH 3T3 cells harboring the G309A variant showed increased colony formation in soft agar compared to wild-type ERBB2 and kinase-inactive D845A mutant, demonstrating transforming potential
- **Source:** PMID:22908275

### Clinical Evidence Supporting ERBB2 Amplification as Oncogenic Driver

The CIViC database contains extensive Level A (validated) clinical evidence demonstrating ERBB2 amplification drives breast cancer and predicts response to

ERBB2-targeted therapies, including landmark trials like HERA (EID:1122, PMID:16236737) and ExteNET (EID:1113, PMID:26874901).

## ERBB2 Inhibitors for In Vitro Validation (from DGIdb)

### FDA-Approved Small Molecule Inhibitors (Recommended for In Vitro Use)

| Drug | Type | Interaction Score | Notes |
|---|---|---|---|
| **Neratinib** | Irreversible TKI | 0.57 | Pan-ERBB inhibitor; excellent for cell-based assays |
| **Lapatinib** | Reversible TKI | 0.36 | Dual EGFR/ERBB2 inhibitor; widely used in research |
| **Tucatinib** | Selective TKI | 0.26 | Highly selective for ERBB2; minimal EGFR activity |
| **Afatinib** | Irreversible TKI | 0.25 | Pan-ERBB inhibitor |
| **Dacomitinib** | Irreversible TKI | 0.45 | Pan-ERBB inhibitor |

### Antibody-Based Inhibitors

| Drug | Type | Notes |
|---|---|---|
| **Trastuzumab** | Monoclonal Ab | Targets ERBB2 extracellular domain; requires Fc-mediated mechanisms |
| **Pertuzumab** | Monoclonal Ab | Blocks ERBB2 dimerization |
| **Margetuximab** | Monoclonal Ab | Fc-optimized anti-ERBB2 |

### Antibody-Drug Conjugates

| Drug | Type |
|---|---|
| **Trastuzumab deruxtecan (DS-8201)** | ADC |
| **Ado-trastuzumab emtansine (T-DM1)** | ADC |

## Recommendations for In Vitro Validation

For functional validation of ERBB2 variant oncogenicity, I recommend:

1. **Primary screen:** Use **lapatinib** or **neratinib** as they are well-characterized, potent, and widely used in research settings
2. **Selectivity control:** Include **tucatinib** (highly ERBB2-selective) to distinguish ERBB2-specific effects from pan-ERBB effects
3. **Experimental approach:**
   - Cell proliferation/viability assays (IC50 shifts)
   - Soft agar colony formation (as used in the G309A study)
   - Western blot for phospho-ERBB2 and downstream signaling (AKT, ERK)
4. **Cell models:** Introduce variants into Ba/F3 or NIH 3T3 cells to assess transforming activity, or use ERBB2-amplified breast cancer lines (SK-BR-3, BT-474) for drug sensitivity studies