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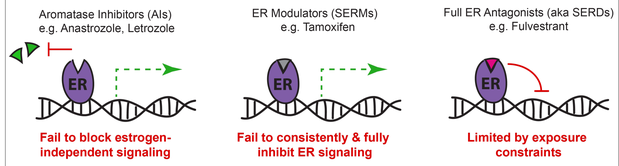
Giredestrant immobilizes the Estrogen Receptor to potently suppress ER-active breast cancers

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BACKGROUND

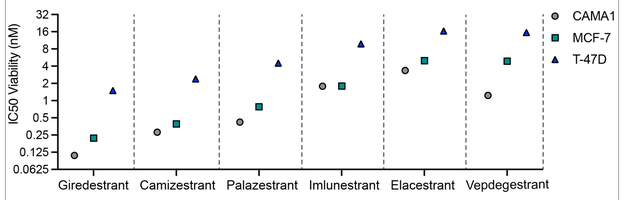
- Approximately 70% of all breast cancers (BC) express the Estrogen Receptor (ER), a ligand-stimulated multi-domain transcription factor.
- The advent of endocrine-based therapies transformed the treatment of ER+ BC, however, a high unmet need remains, with up to one third of patients eventually relapsing after adjuvant treatment in early BC, and metastatic BC being currently incurable.
- Endocrine therapies either prevent estrogen synthesis (e.g. aromatase inhibitors, AIs), bind to ER to modulate its function (e.g. tamoxifen), or act as selective ER degraders (SERDs) and full ER antagonists (e.g. fulvestrant).



- Giredestrant was designed as an exquisitely potent next-generation oral SERD and full ER antagonist, aiming to overcome the liabilities of existing endocrine agents to drive deep and sustained inhibition of ER signaling, irrespective of *ESR1* mutation status[1].
- Giredestrant has a broad clinical development plan across the ER+ BC treatment continuum. In the recently disclosed evERA BC and lidERA Phase III trials, giredestrant demonstrated significant and clinically meaningful advances over standard of care therapy in combination and as a single agent.

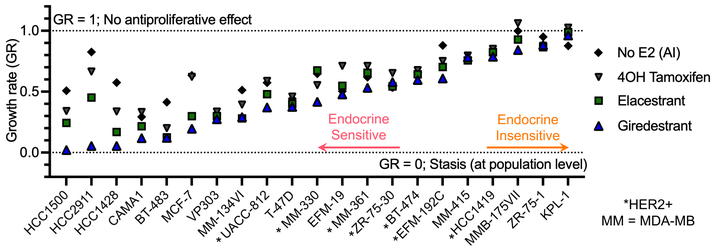
RESULTS

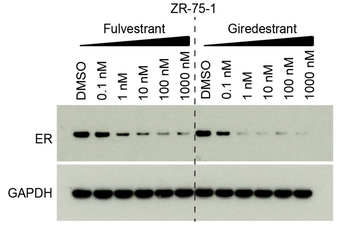
Giredestrant is exceptionally potent against ER+ breast cancer cells *in vitro,* compared to other oral ER therapeutics



Methods: Cell viability was determined using CellTiterGlo after 7 to 10 days of treatment. Cells were grown in standard, hormone-replete serum; relative IC50s are shown.

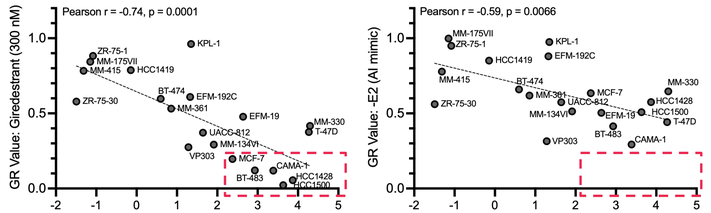
Endocrine therapies exhibit a range of antiproliferative activity against *ESR1* wildtype breast cancer cells; in endocrine-sensitive models, giredestrant outperforms tamoxifen & estrogen withdrawal (-E2, mimicking aromatase inhibition)





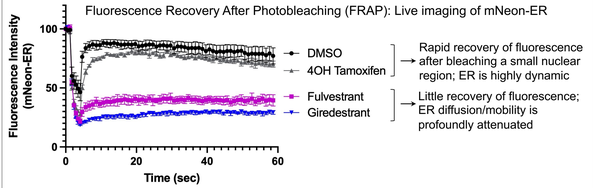
The lack of antiproliferative activity of giredestrant against endocrine-insensitive *ESR1* wildtype ZR-75-1 cells is not explained by a failure to deplete ER protein;
i.e. **lack of sensitivity is likely not a pharmacology-driven phenomenon.**

Giredestrant activity is dictated by ER activity levels prior to treatment, and is superior to E2 withdrawal in ER activity-high models

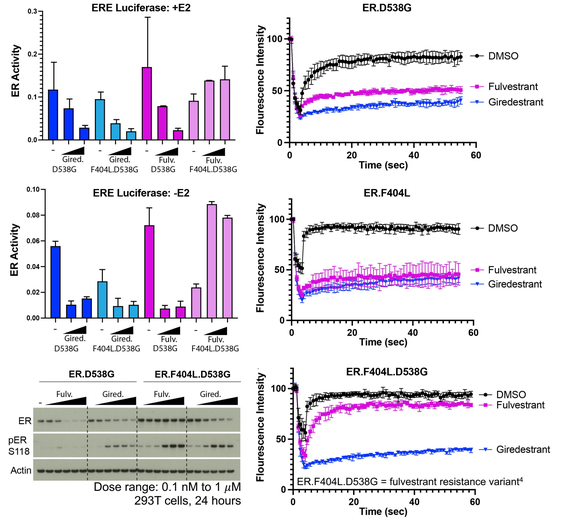


Methods: In the top panel, cell viability was determined using CyQuant, after 8 days of treatment. Cells were grown in charcoal-stripped serum supplemented with estrogen (E2), except in the case annotated as –E2, intended to mimic aromatase inhibition. GR values for ER antagonists are shown at maximally active concentrations. Data is displayed using a previously described growth rate (GR) method, enabling cross-cell line comparisons[2]. For ER western blots, cells were grown in charcoal-stripped stripped serum and treated as shown for 24 hours. ER activity levels were derived using a previously published gene expression signature[3].

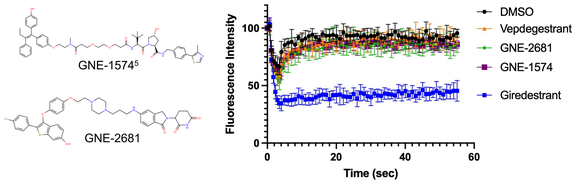
Giredestrant, like fulvestrant[3], immobilizes ER



The ER immobilizing capability of giredestrant & fulvestrant correlates with their capacity for ER inhibition & turnover

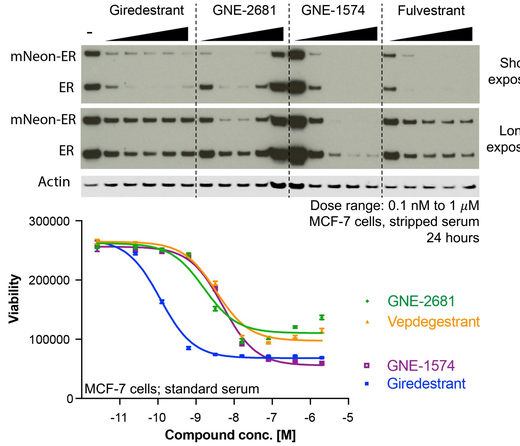


CRBN & VHL-recruiting ER PROTACs do not immobilize ER



Methods: FRAP and ERE luciferase reporter assays are conducted as in Guan, Zhou et al (2019)

ER PROTACs potently and efficiently degrade ER; however, giredestrant maintains superior potency and activity in suppressing ER+ cancer cell proliferation



SUMMARY

- Giredestrant is an exceptionally potent ER antagonist, with the lowest measured IC50 values amongst the current investigational and recently approved endocrine agents, in cell viability assays
- Differentiation of ER-targeted endocrine therapies, with respect to relative efficacy, occurs specifically in contexts where ER signaling is active
- Giredestrant exhibits superiority versus estrogen withdrawal, intended to mimic aromatase inhibition, and tamoxifen, in *ESR1* wildtype ER activity-high breast cancer cell lines
- Giredestrant immobilizes ER, which associates with its ability to potently and robustly suppress ER signaling, and which we hypothesize to be a key driver of ER suppression
- ER PROTACs potently and efficiently degrade ER protein, but do not immobilize ER; giredestrant maintains superior potency and activity relative to ER PROTACs in antiproliferative assays
- **Preclinical and clinical data together support that giredestrant has the potential to become a new endocrine backbone in all ER-active patient segments, independent of *ESR1* mutation status**

References: **1**) Liang J, *et al. J Med Chem* 2021; **64**:11841–11856 **2**) Hafner M, *et al. Nat. Methods* 2016 **13**: 521-527 **3**) Guan J, Zhou W, *et al. Cell* 2019; **178**:949–963 **4**) Kingston B, et al. *Cancer Discov.* 2024; **14**:247-289 **5**) Dragovich P, *et al. Bioorg. Med. Chem. Lett.* 2020; **30**:126907