Poster B115

Vepdegestrant, an Oral PROTAC, is a Robust ER Degrader Leading to Improved ER Degradation and Antitumor Activity Relative to SERDs in Preclinical ER+ Breast Cancer Models

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Objective

- To evaluate estrogen receptor (ER) degradation and antitumor activity by vepdegestrant, an investigational PROteolysis TArgeting Chimera (PROTAC) ER degrader, FDA-approved selective estrogen receptor degraders (SERDs; elacestrant, imlunestrant, and fulvestrant), or investigational oral SERDs (giredestrant, camizestrant, and amcenestrant) in preclinical models.

Key Findings

- Vepdegestrant induced greater maximal ER degradation than investigational oral SERDs, imlunestrant or elacestrant in vitro.
- Vepdegestrant led to greater ER degradation and antitumor activity in the MCF7 cell-line derived xenograft (CDX) model compared with fulvestrant.
- Vepdegestrant resulted in greater ER degradation and antitumor activity than fulvestrant or elacestrant in ER1 gene (*ESR1*)-mutated preclinical models.

Conclusions

- Consistent with other reports,[1,2] vepdegestrant induced greater maximal ER degradation in vitro than elacestrant or fulvestrant in wild type (WT) ER+ breast cancer cell lines.
- Vepdegestrant also demonstrated greater tumor growth inhibition (TGI) and ER degradation in vivo compared with fulvestrant in a WT ER+ breast cancer CDX model.
- Vepdegestrant induced greater maximal degradation of clinically relevant ER mutants (ER^{Y537S} and ER^{D538G}) than elacestrant or fulvestrant in vitro and in vivo and greater TGI than elacestrant or fulvestrant in an ER^{Y537S} mutant PDX model.

References

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Background

- Vepdegestrant is an oral PROTAC ER degrader.[3] Unlike SERDs, which are competitive ER antagonists that induce conformational changes in the ER and indirectly induce ER degradation, vepdegestrant forms a trimer complex with an E3 ligase and ER, leading to direct ubiquitination and proteasomal degradation of WT ER and clinically relevant ER mutants[3].
- Our previous studies demonstrated greater ER degradation and antitumor activity than fulvestrant in ER^{WT} and ER^{Y537S} hormone insensitive breast cancer PDX models[3,4].
- In the Phase 3 VERITAC-2 trial, vepdegestrant treatment significantly prolonged progression-free survival compared with fulvestrant among patients with *ESR1*-mutated ER+/HER2- advanced breast cancer[5].
- Here, we report preclinical ER degradation and antitumor activity of vepdegestrant compared with FDA-approved SERDs (fulvestrant, elacestrant, and imlunestrant) and investigational oral SERDs (giredestrant, camizestrant, and amcenestrant).

Methods

Lysate generation & immunoblotting

- T47D or MCF7 cells were treated for 24 hours with indicated drugs and subsequently lysed in radioimmunoprecipitation assay (RIPA) buffer. Protein concentrations in lysates were determined using a bicinchoninic acid (BCA) assay; protein levels were normalized across samples with RIPA buffer and run on ProteinSimple™ JESS (Figure 1A, 2A) or western blots (Figure 1B, 3A).
- Blots were probed with primary antibodies for ER or β-actin and imaged using JESS or ChemiDoc systems (Bio-Rad). Western blot band intensity was quantified using ImageLab (Figure 1B) or ImageJ (Figure 3A).
- Experiments in T47D stably expressing clustered regularly interspaced short palindromic repeats (CRISPR) knock-in ER Y537S or ER D538G were conducted as previously reported[3].

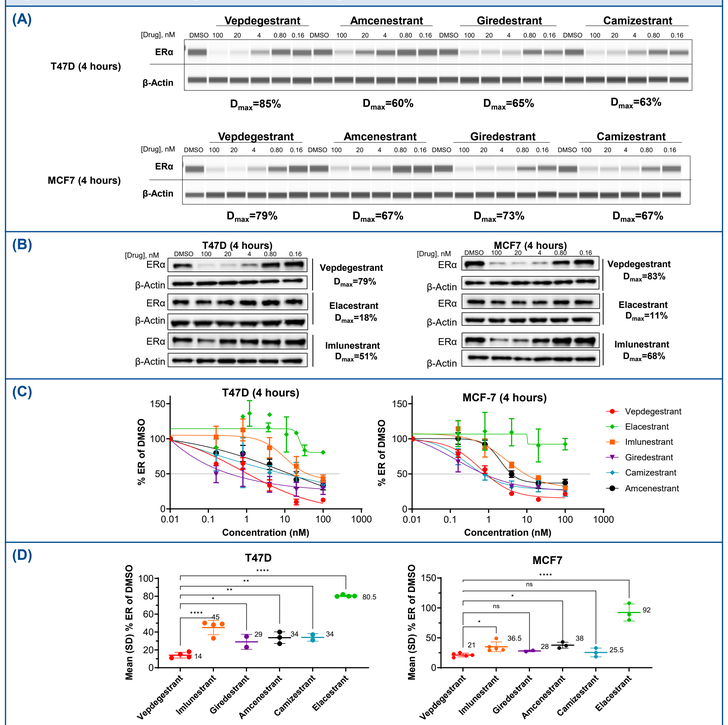
In vivo studies

- 6-8 week old female nonobese diabetic/severe combined immunodeficiency (NOD/SCID) mice were subcutaneously implanted with a 0.36-mg, 90-day release 17β-estradiol pellet; 5 million MCF7 cells in Matrigel were injected orthotopically 1-2 days later.
- When mean tumor volume reached approximately 200 mm^3, mice were assigned to treatment groups and dosed with vehicle, oral vepdegestrant 30 mg/kg once daily or subcutaneous fulvestrant 200 mg/kg twice in the first week and weekly thereafter; all mice received treatment for 26 days, after which they were sacrificed and harvested tissue was snap-frozen.
- Tumors were lysed in RIPA buffer and homogenized using a Qiagen Tissue Lyser II. A BCA assay was performed, and protein concentration was normalized across lysates. Protein samples were run on western blots, probed for ER or β-actin and imaged on a ChemiDoc system. Western blot band intensity was quantified using ImageLab software.
- The ST941 patient-derived xenograft (PDX) model study was conducted as previously reported[3].

Results

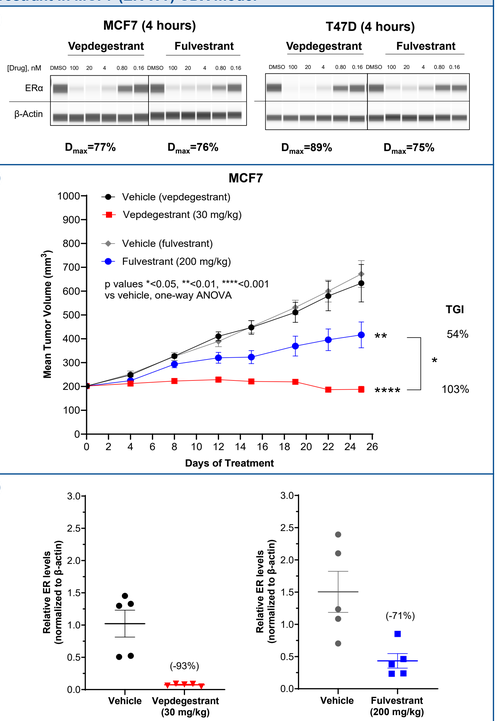
- In vitro, vepdegestrant treatment in MCF7 and T47D cell lines led to deeper degradation of WT ER (79%–86%) compared with investigational oral SERDs (55%–74.5%; **Figure 1A,C,D**), approved oral SERDs (8%–68%; **Figure 1B-D**), or fulvestrant (73%–74%; **Figure 2A**) after 4 hours of treatment.
- In the WT ER MCF7 CDX model, vepdegestrant displayed greater antitumor activity (103% TGI) than fulvestrant (54% TGI) at day 26 of treatment (**Figure 2B**). Vepdegestrant treatment led to a 93% decrease in ER protein levels compared to a 71% decrease with fulvestrant in tumor lysates collected at day 26 relative to vehicle-treated tumors (**Figure 2C**).
- Our previous studies[3] demonstrated greater maximal degradation of clinically relevant ER mutants (ER^{Y537S} and ER^{D538G}; 79%–85%) compared with fulvestrant (47–66%; **Figure 3A**) or elacestrant (9–62%) in vitro.
- Vepdegestrant displayed greater antitumor activity (107% TGI) than fulvestrant (62% TGI) or elacestrant (96% TGI) in the mutant ER^{Y537S} PDX (ST941; **Figure 3B**).
- Mean ER protein levels decreased by 88% with vepdegestrant, decreased by 63% with fulvestrant and increased by 11% with elacestrant relative to vehicle-treated tumors in tumor lysates collected at day 27 (**Figure 3C**).

Figure 1: In vitro ER WT degradation with vepdegestrant and oral SERDs



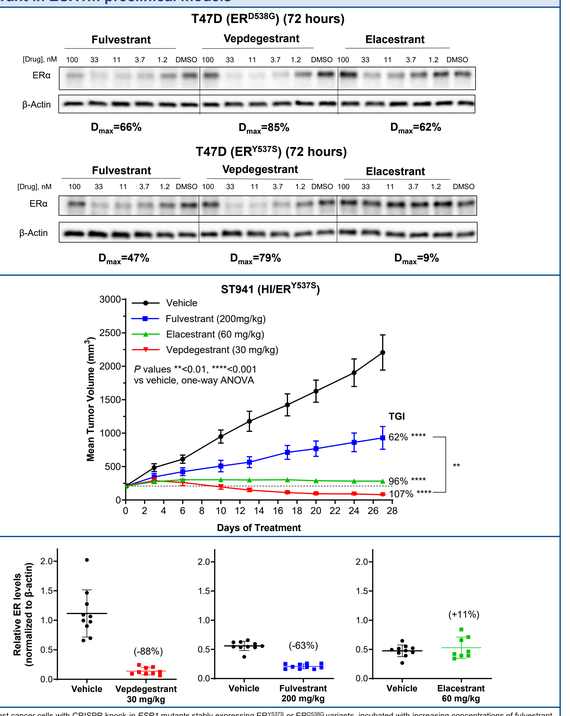
(**A-B**) Dose-dependent in vitro ER protein degradation with vepdegestrant, elacestrant, imlunestrant and investigational oral SERDs (giredestrant, camizestrant, amcenestrant) at concentrations ranging from 0.16 to 100 nM in MCF7 and T47D cells, after 4 hours of treatment by (**A**) SimpleWestern™ and (**B**) immunoblot. (**C**) Quantified ER levels in T47D and MCF7 cells from (A and B). (**D**) Mean % ER remaining in T47D or MCF7 cells treated with 100 nM vepdegestrant or the indicated oral SERD. ER protein levels were normalized to β-actin levels and expressed as a percentage of ER levels in DMSO treated cells. Values shown are means of 3 independent experiments (2 experiments for giredestrant [MCF-7, T47D] and camizestrant [T47D]). Dots represent values from independent experiments.
P values: *<0.05, **<0.01, ****<0.0001 vs vepdegestrant treatment, one-way ANOVA with Dunnett's multiple comparisons test
ANOVA = analysis of variance; D_{max}=maximal degradation; DMSO=dimethyl sulfoxide; ER=estrogen receptor; SEM=standard error of the mean; WT=wild type.

Figure 2: ER degradation and antitumor activity of vepdegestrant vs fulvestrant in MCF7 (ER WT) CDX model



(A) Vepdegestrant and fulvestrant dose-dependent in vitro degradation of WT ER after 4-hour treatment of MCF7 and T47D by SimpleWestern™. (B) In vivo efficacy of vepdegestrant in Orthotopic MCF7 CDX model. Mice were dosed with vepdegestrant at 30 mg/kg orally once daily for 28 days, or 200 mg/kg fulvestrant subcutaneously twice per week for 2 weeks and once weekly thereafter. (C) ER protein levels at 16 hours post-last dose in tumor lysates harvested on day 28 from (B), determined by western blot (not shown) and densitometry analysis.
ANOVA=analysis of variance; CDX=cell line-derived xenograft; ER=estrogen receptor; WT=wild type.

Figure 3: ER degradation and antitumor activity of vepdegestrant vs fulvestrant and elacestrant in *ESR1*m preclinical models



(A) T47D breast cancer cells with CRISPR knock-in *ESR1* mutants stably expressing ER^{Y537S} or ER^{D538G} variants, incubated with increasing concentrations of fulvestrant, vepdegestrant, or elacestrant for 72 hours. (B) *In vivo* efficacy of vepdegestrant in the START ST941/HI ER^{Y537S} mutant PDX model. Mice were dosed with oral vepdegestrant 30 mg/kg once daily for 27 days, elacestrant 60 mg/kg orally once daily for 27 days, or subcutaneous fulvestrant 200 mg/kg twice per week for 2 weeks and once weekly thereafter. (C) ER protein levels relative to vehicle control in tumor lysates of the ST941/HI ERY537S PDX efficacy study shown in B (n=10/arm). ER protein levels were determined by western blot and densitometry analysis. Figure 3 (vepdegestrant and fulvestrant data) is adapted from Gough SM, et al Clin Cancer Res. 2024;30(16):3549-63.
ANOVA=analysis of variance; CRISPR=clustered regularly interspaced short palindromic repeats; ER=estrogen receptor; ESR1=ER 1 gene; PDX=patient derived xenograft; START=South Texas Accelerated Research Therapeutics.