The next-generation oral selective estrogen receptor degrader (SERD) camizestrant (AZD9833) is active against wild-type and mutant estrogen receptor-α

San Antonio Breast Cancer Symposium
December 6-10, 2022

Christopher J Morrow[1*], Larissa S Carnevalli[1*], Richard Baird[2*], Tim Brier[1], Carmela Ciardullo[1], Natalie Cureton[1], Mandy Lawson[1], Robert McEwen[1], Myria Nikolaou[1], Anne C Armstrong[3], Begoña Bermejo de las Heras[4], Emiliano Calvo[5], Eva María Ciruelos Gil[6], Javier Garcia-Corbacho[7], Erika Hamilton[8], Jason Incorvati[9], Peter Kabos[10], Mafalda Oliveira[11], Manish R Patel[12], Manuel Ruiz-Borregó[13], Nicholas Turner[14], Chris Twelves[15], Christos Vaklavas[16], Danielle Carroll[1], Steven Ching[17], Nevena Cvetesic[1], Michelle DuPont[18], Lisa Gibbons[1], Alastair Mathewson[1], Rhiannon Maudsley[1], Pablo Morentin Gutierrez[1], Avinash Reddy[18], Jaime Rodriguez-Canales[17], Susana Ros[1], Dhivya Sudhan[18], Andy Sykes[1], David Whitston[18], Teresa Klinowska[19**], Justin P O Lindemann[1**]

[1]Research and Early Development, Oncology R&D, AstraZeneca, Cambridge, UK; [2]Cancer Research UK, Cambridge Centre, Cambridge, UK; [3]The Christie NHS Foundation Trust and the Division of Cancer Sciences, The University of Manchester, UK; [4]Hospital Clínico Universitario de Valencia, Valencia, Spain; [5]START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; [6]Medical Oncology Department, 12 de Octubre University Hospital, Madrid, Spain; [7]Hospital Clinic Barcelona/IDIBAPs, Barcelona, Spain; [8]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA; [9]Fox Chase Cancer Center, Philadelphia, PA, USA; [10]Division of Medical Oncology, University of Colorado, CO, US; [11]Medical Oncology Department, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [12]Florida Cancer Specialists/Sarah Cannon Research Institute/Sarasota Memorial Hospital, Sarasota, FL, USA; [13]Department of Medical Oncology, University Hospital Virgen del Rocío, Seville, Spain; [14]Breast Cancer Now Toby Robins Research Centre, Institute of Cancer Research, London, UK; [15]St. James's Hospital and University of Leeds, UK; [16]Huntsman Cancer Institute, University of Utah, UT, USA; [17]Research and Early Development, Oncology R&D, AstraZeneca, Gaithersburg, Maryland, USA; [18]Research and Early Development, Oncology R&D, AstraZeneca, Waltham, Massachusetts, USA; [19]Late Development, Oncology R&D, AstraZeneca, Cambridge, UK.

*Joint lead authors **Joint senior authors

Introduction

- Endocrine therapy (ET) forms the backbone treatment for patients with estrogen receptor positive (ER+) tumors. Common ET options include aromatase inhibitors (AIs) and the selective estrogen receptor degrader (SERD) fulvestrant.[1–4]
- Mutation of *ESR1* – the gene encoding estrogen receptor α (ERα) – is a common mechanism of resistance to AIs and fulvestrant, leading to ligand-independent activity of ERα.[1,5,6]
- In ET-pretreated patients, presence of *ESR1* mutation *(ESR1m)* is often associated with continuing ER-dependent tumor growth.
- Camizestrant (AZD9833) is a next-generation oral SERD (ngSERD) and pure ER antagonist, designed to increase ER antagonism and degradation compared with fulvestrant, thereby enhancing clinical benefit for patients.
- Camizestrant has a broad clinical development program, including the Phase 1 study SERENA-1 (NCT03616587), the Phase 2 trial SERENA-2 (NCT04214288) and the Phase 3 trials SERENA-6 (NCT04964934) in patients with *ESR1*m tumors, and SERENA-4 (NCT04711252).[7–9]
- Here we report the preclinical and clinical activity of camizestrant in patients with *ESR1* wild-type (*ESR1*wt) and *ESR1*m tumors.

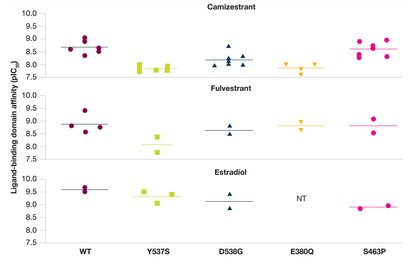
ERα mutations impact binding, ERα degradation, antagonism, and anti-tumor activity of camizestrant and fulvestrant compared with wt ERα

- Camizestrant, fulvestrant, and estradiol exhibited reduced binding to clinically relevant mutant forms of ERα compared with wt ERα. In general, the Y537S mutation had the greatest impact on binding (Figure 1).
- Greater concentrations of camizestrant and fulvestrant are required to degrade and antagonize mutated ERα and to impact cellular proliferation in MCF-7 cells expressing Y537S *ESR1*m compared with those expressing *ESR1*wt (Figure 2).
- Furthermore, while a 3 mg/kg dose of camizestrant achieved a maximal anti-tumor effect in an *ESR1*wt patient-derived xenograft (PDX) model, 10 mg/kg was required for maximal effect in a D538G *ESR1*m model (Figure 3).

PK/PD modeling of camizestrant activity against *ESR1*m

- Camizestrant PK and ERα expression in mice bearing the *ESR1*m D538G CTC174 PDX model was analyzed by western blot to generate a concentration–response model (Figure 4A).
- Comparison of the level of residual ERα and the anti-tumor activity of different doses of camizestrant suggested maximum anti-tumor effect is reached at doses that caused an 87% reduction in ERα (Figure 4B).
- A PK/PD model accounting for human PK predicted that doses >20 mg should cause an 87% reduction in ER when measured by western blot. This equates to an ~50% reduction in ER when measured by immunohistochemistry H-score (Figure 4C).
- The predicted human PK for a 75 mg dose of camizestrant closely matches the observed PK in SERENA-1 (Figure 4D).

Figure 1. Binding affinity of camizestrant, fulvestrant, and estradiol was lower in mutant than in wt ERα ligand-binding domains



NT= not tested

Figure 2. Compared with parental cells expressing wt ERα, camizestrant and fulvestrant show reduced potency for degradation and antagonism of ER, and for inhibition of proliferation in Y537S MCF-7 cells

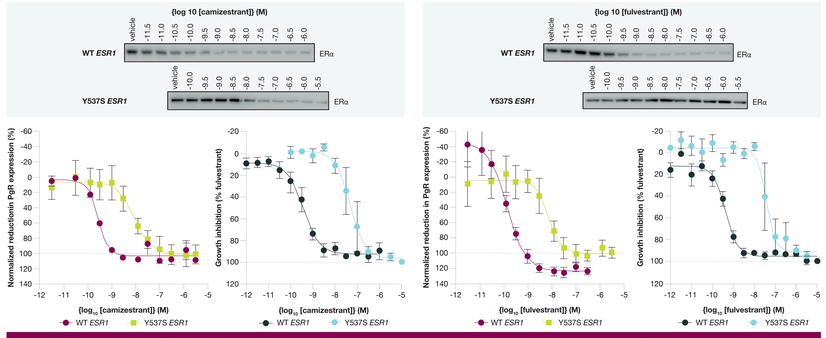
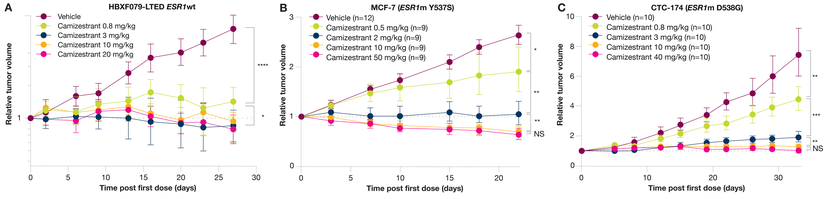


Figure 3. Compared with wt ERα xenografts, higher doses of camizestrant are needed to achieve maximal anti-tumor activity in D538G and Y537S mutant ERα xenografts

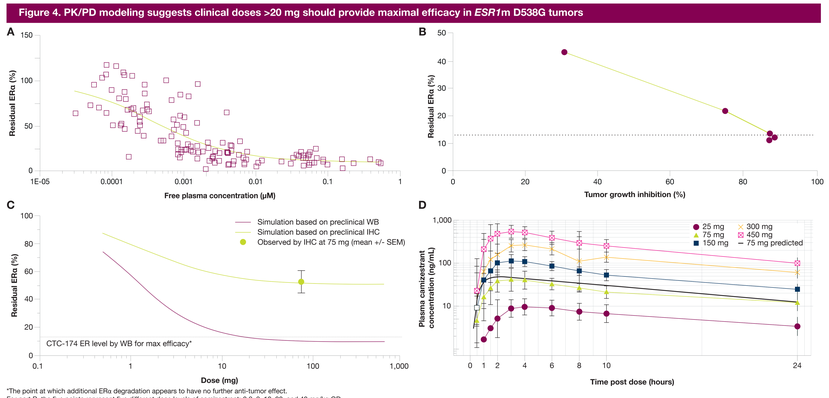


Camizestrant dosed daily PO achieved maximal anti-tumor effect in (A) the *ESR1*wt PDX model HBXF079-LTED at 3 mg/kg. A dose of 10 mg/kg was required for (B) the *ESR1*m Y537S MCF-7 xenograft model, and (C) the *ESR1*m D538G CTC174 PDX model. Tumor growth inhibition was dose dependent.

Statistical analysis was performed by one-tailed, unequal variance t-test *versus* log (change in tumor volume) compared with vehicle control at the final day of treatment.

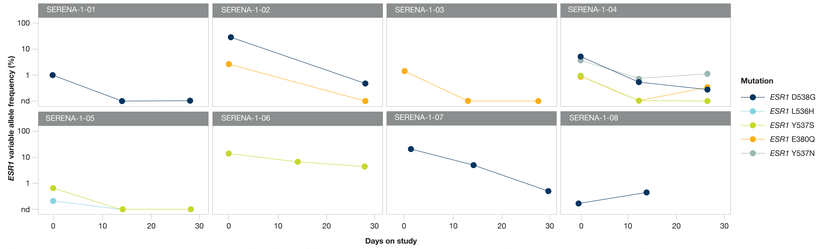
*p<0.05,**p<0.01, ***p<0.001, ****p<0.0001. NS=not significant.

Figure 4. PK/PD modeling suggests clinical doses >20 mg should provide maximal efficacy in *ESR1*m D538G tumors



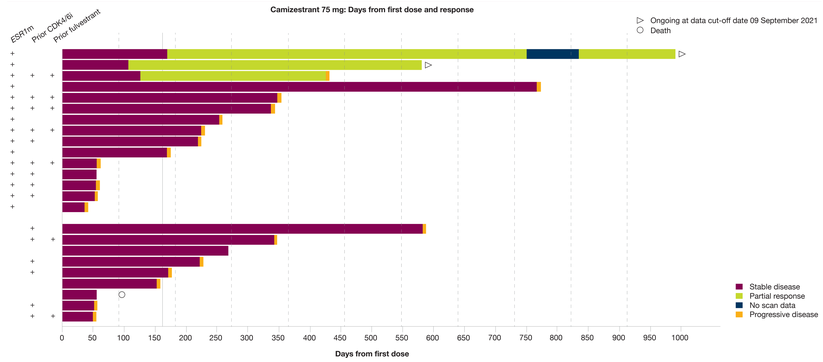
*The point at which additional ERα degradation appears to have no further anti-tumor effect.
For part B, the five points represent five different dose levels of camizestrant: 0.8, 3, 10, 20, and 40 mg/kg QD.

Figure 5. Camizestrant 75 mg reduced the variant allele frequency of *ESR1*m ctDNA at C1D15 and C2D1 in patients in SERENA-1



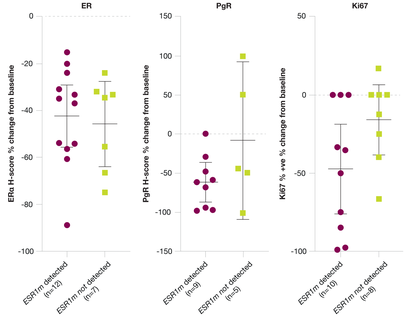
*ESR1*m was assessed in plasma samples collected from patients at screening, C1D1, C1D15 and C2D1. All patients with longitudinal data available were included. The variant allele frequency of the indicated *ESR1*m was determined at the indicated timepoint by targeted NGS. Observed PD effects of camizestrant match predictions: camizestrant reduces *ESR1*m ctDNA. nd=not detected.

Figure 6. Progression-free survival was longer in heavily pretreated patients with *ESR1*m tumors *versus* tumors without *ESR1*m detected



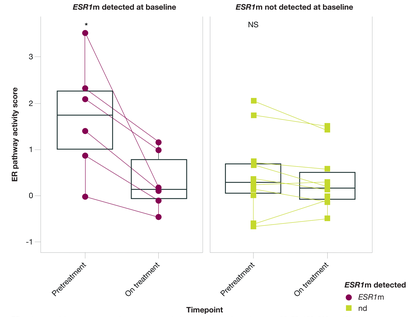
*Data cut-off 09 September 2021.

Figure 7. Paired immunohistochemistry: Equivalent reductions in ERα seen in *ESR1*m detected and not detected, but greater reductions in Ki67 in *ESR1*m-detected subgroups



Pathologist scores from paired biopsies were collected at screening and C2D1 after treatment with camizestrant: 25, 75, 150, 300, or 450 mg. Cases were excluded if baseline ER or PgR H-score was <10, or Ki67 % +ve was <5.

Figure 8. Paired whole transcriptome sequencing: ERα activity was higher at baseline in *ESR1*m-detected patients and was reduced on treatment



ER pathway activity score assessed at screening and after treatment with camizestrant: 25, 75, 150, 300, or 450 mg. p-values represent two-sided Wilcoxon paired test.*p<0.05; NS=not significant, nd=not detected.

Clinical and pharmacodynamic activity with camizestrant in patients with *ESR1*m detected *versus* *ESR1*m not detected in SERENA-1

- Analysis of *ESR1*m ctDNA levels in heavily pretreated patients from SERENA-1 showed a clear treatment effect with camizestrant 75 mg (Figure 5):
  - >2-fold reduction in *ESR1*m variant allele frequency in 12/13 cases (92%).
  - Complete clearance of *ESR1*m ctDNA in 7/13 cases (54%), including D538G, Y537S, and E380Q.
- Clinical activity of camizestrant was greater in heavily pretreated patients with *ESR1*m tumors than in those with *ESR1*m not detected.
  - With 75 mg, median progression-free survival was 8.3 months in patients with *ESR1*m tumors and 5.6 months in those with *ESR1*m not detected (Figure 6).*
- Camizestrant-induced ERα degradation was seen in both groups (mean H-score reduction of 42% in *ESR1*m tumors [n=12 evaluable pairs] and 46% in tumors without *ESR1*m detected [n=7]; Figure 7).
- Consistent with the clinical activity data, camizestrant reduced cell proliferation more profoundly in *ESR1*m tumors than in *ESR1*m not detected tumors (as seen by greater reductions of Ki67+ tumor cells), suggesting *ESR1*m as an enrichment marker of continuing ER-drive (Figure 7).
- Whole transcriptome analysis revealed higher ERα activity at baseline in *ESR1*m tumors compared with *ESR1*m not detected, consistent with the presence of *ESR1*m being a biomarker of ER-dependent tumors; significant reductions in ERα activity after treatment with camizestrant were only seen in the *ESR1*m-detected group (Figure 8).

Conclusions

- Preclinical work demonstrates that higher concentrations of camizestrant are required for efficacy in *ESR1*m tumors compared with *ESR1*wt tumors.
- PK/PD modeling predicts the clinical exposure achieved with camizestrant 75 mg is sufficient to achieve maximal efficacy in *ESR1*m tumors.
- Data from SERENA-1 demonstrate the activity of camizestrant 75 mg in patients with *ESR1*m tumors.
- Clinical activity, along with degradation of ERα and inhibition of ER signaling, is also seen in patients with tumors in which *ESR1* mutations are not detected.
- In this heavily pretreated, Phase 1 patient population from SERENA-1, *ESR1*m may be a predictive biomarker to enrich for patients with ER-dependent tumors.
- With clear evidence of clinical benefit in patients with *ESR1*wt and *ESR1*m disease, camizestrant may provide a valuable treatment option for patients by overcoming mechanisms of resistance to current endocrine therapies.
- SERENA-6 is investigating the efficacy and safety of camizestrant in combination with CDK4/6 inhibition in patients with metastatic breast cancer and detectable *ESR1*m.[8]

References

1. Jeselsohn R, Buchwalter G, De Angelis C *et al. ESR1* mutations – a mechanism for acquired endocrine resistance in breast cancer. *Nat Rev Clin Oncol* 2015; **12:** 573–83.
2. Robertson J. IC1 182,780 (Fulvestrant) – the first oestrogen receptor down-regulator – current clinical data. *Br J Cancer* 2001; **85 (Suppl 2):** 11–14.
3. Di Leo A, Jerusalem G, Petruzelka L *et al.* Results of the CONFIRM Phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. *J Clin Oncol* 2010; **28:** 4594–600.
4. Kuter I, Gee JMW, Hegg R *et al.* Dose-dependent change in biomarkers during neoadjuvant endocrine therapy with fulvestrant: results from NEWEST, a randomized Phase II study. *Br Cancer Res Treat* 2012; **133:** 237–46.
5. Dustin D, Gu G, Fuqua SAW. *ESR1* mutations in breast cancer. *Cancer* 2019; **125:** 3714–728.
6. Clarke R, Liu MC, Bouker KB *et al.* Antiestrogen resistance in breast cancer and the role of estrogen receptor signaling. *Oncogene* 2003; **22:** 7316–39.
7. ClinicalTrials.gov. A comparative study of AZD9833 plus palbociclib versus anastrozole plus palbociclib in patients with ER-positive HER2 negative breast cancer who have not received any systemic treatment for advanced disease (SERENA-4). Available at: https://clinicaltrials.gov/ct2/show/NCT04711252. [Accessed 28/09/2022].
8. ClinicalTrials.gov. Phase III study to assess AZD9833+ CDK4/6 inhibitor in HR+/HER2-MBC with detectable ESR1m before progression (SERENA-6). Available at: https://clinicaltrials.gov/ct2/show/NCT04964934. [Accessed 28/09/2022].
9. ClinicalTrials.gov. A comparative study of AZD9833 versus fulvestrant in women with advanced ER-positive HER2-negative breast cancer (SERENA-2). Available at: https://clinicaltrials.gov/ct2/show/NCT04214288. [Accessed 28/09/2022].

Abbreviations

C1D15: Cycle 1 Day 15
C2D1: Cycle 2 Day 1
IC_{50}: half-maximal inhibitory concentration
NGS: next-generation sequencing
PDX: patient-derived xenograft
SERD: selective estrogen receptor degrader

Disclosures and acknowledgements

- This study was funded by AstraZeneca. AstraZeneca develops and markets treatments for breast cancer. Camizestrant is an investigational medical product with no currently approved indication.
- CM, LC, TB, CC, NC, ML, RMc, MN, DC, SC, NC, MD, LG, RM, PBG, AR, JR-C, SR, DS, AS, DW, TK, and JPOL are employees of AstraZeneca and may own stock or stock options. All other authors submitted relevant disclosures to SABCS during the submission process.
- AM is director of Munro Clinical Projects Ltd, contracted by AstraZeneca to provide clinical study management support, and also owns stock.
- We sincerely thank the volunteers, the investigators, and the site staff who participated in this study.
- We thank Alice Kirk, MSc, on behalf of InterComm International, who provided medical writing support for this poster funded by AstraZeneca.

Abstract number: P3-07-13

This presentation is the intellectual property of the author/presenter.
Contact them at Christopher.Morrow@astrazeneca.com for permission to reprint and/or distribute.