PARIS 2022 ESMO congress

211MO: Giredestrant (GDC-9545) vs physician choice of endocrine monotherapy (PCET) in patients (pts) with ER+, HER2– locally advanced/metastatic breast cancer (LA/mBC): Primary analysis of the phase 2, randomised, open-label acelERA BC study

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Declaration of interests

Miguel Martín:

- Consulting/advisory roles for AstraZeneca, Daichii Sankyo, F. Hoffmann-La Roche Ltd/Genentech, Inc., Gilead, Lilly, Novartis, Pfizer and Seagen
- Speakers' bureaus for AstraZeneca, Daichii Sankyo, F. Hoffmann-La Roche Ltd/ Genentech, Inc., Gilead, Lilly/ImClone, Novartis, Pfizer, Pierre Fabre and Seagen
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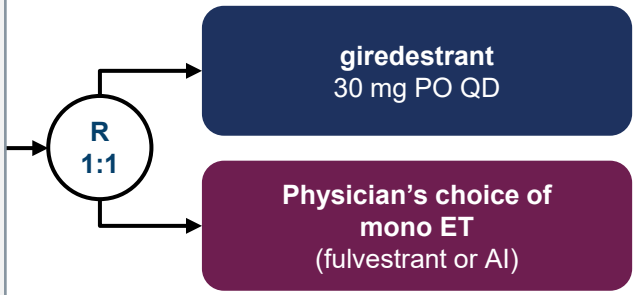
- For all author declarations, please see abstract

Study design: acelERA BC (NCT04576455)

- ER+/HER2– LA/mBC
- Post- or pre-/peri-menopausal women, and men*
- 1 or 2 prior lines of systemic therapy for LA/mBC:
  - 1 must be ET (≥ 6 months)
  - ≤ 1 targeted agent
  - ≤ 1 chemotherapy allowed

N = 303

Giredestrant is a highly potent, non-steroidal, oral selective SERD



Endpoints

1. PFS-INV by RECIST v1.1
2. OS, ORR, DoR, CBR, PFS by *ESR1*m status, safety, PROs

Stratification: Visceral vs non-visceral disease, prior CDK4/6i (yes/no) and prior fulvestrant (yes/no)

Statistical assumptions: 80% power; two-sided α = 0.05; target HR 0.647; MDD HR 0.738

PFS-BIRC: Sensitivity analysis performed on the full population

Clinical cut-off: 18 February 2022; median follow-up: 7.89 months. * Pre-/peri-menopausal women, and men, also received an LHRH agonist. AI, aromatase inhibitor; BC, breast cancer; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DoR, duration of response; ER+, oestrogen receptor-positive; *ESR1*m, *ESR1* mutation by baseline circulating tumour DNA; ET, endocrine therapy; HR, hazard ratio; HER2–, human epidermal growth factor receptor 2-negative; LA/mBC, locally advanced/metastatic breast cancer; LHRH, luteinising hormone-releasing hormone; MDD, minimum detectable difference; ORR, objective response rate; OS, overall survival; PFS-BIRC, progression-free survival by blinded independent review committee; PFS-INV, progression-free survival by investigator assessment; PO, oral; PROs, patient-reported outcomes; QD, once a day; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumors; SERD, selective oestrogen receptor antagonist and degrader.

Baseline characteristics and prior treatments

Demographic/ disease characteristic	giredestrant (n = 151)	PCET (n = 152)	All (N = 303)
Median age, years	60	59	60
Female sex, %	100	99.3	99.7
Post-menopausal, %	85	82	83
ECOG PS 0, %	50	54	52
Race: Asian / White, %	38 / 59	43 / 53	41 / 56
Region, %			
Asia	38	43	40
Europe	38	36	37
South America	19	14	16
North America	3	1	2
Disease status, %			
Visceral	69	68	68
Measurable	93	93	93
CNS involvement	2	2	2
Bone-only	9	9	9
PgR-negative	25	21	23
ESR1 status	n = 117	n = 115	n = 232
*ESR1*m detected, %	44	34	39

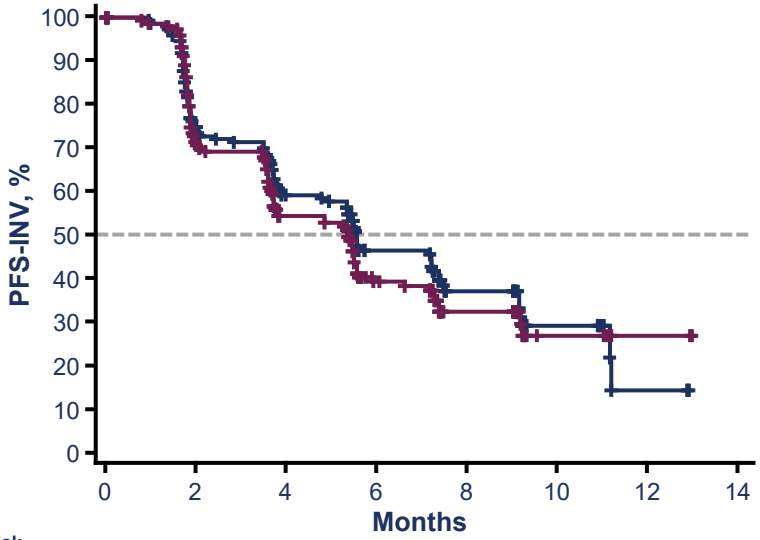
Prior treatments for LA/mBC	giredestrant (n = 151)	PCET (n = 152)	All (N = 303)
Prior lines, %			
1	68	74	71
2	31	25	28
AI, %	81	73	77
Fulvestrant, %	20	18	19
Tamoxifen, %	13	21	17
Targeted, %	48	44	46
CDK4/6i, %	43	41	42
Last prior line	37	35	36
Chemotherapy, %	31	32	32
Last prior line	23	26	24

PCET control arm split:

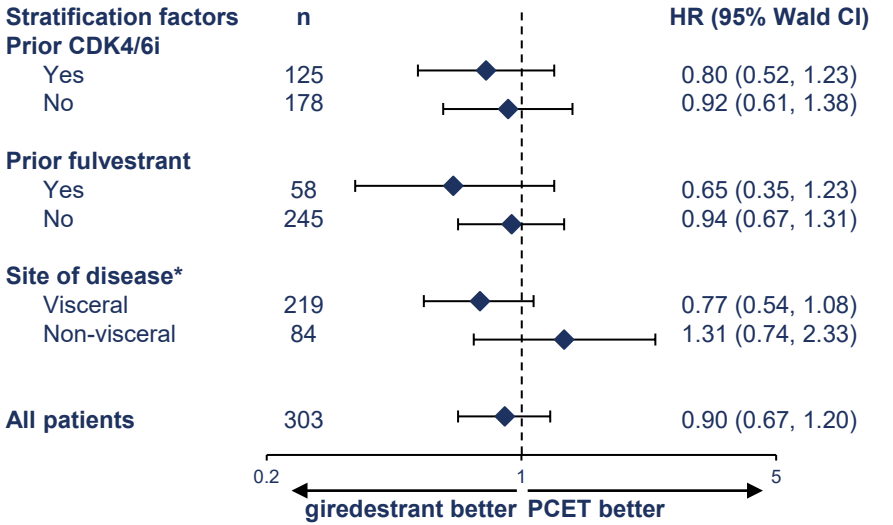
- Fulvestrant: 75%
- AI: 25% (mostly exemestane and letrozole)

Clinical cut-off: 18 February 2022; median follow-up: 7.89 months.
AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; *ESR1*m, *ESR1* mutation by baseline circulating tumour DNA; LA/mBC, locally advanced/metastatic breast cancer; PCET, physician's choice of endocrine therapy; PgR, progesterone receptor.

Primary endpoint: PFS-INV



	giredestrant (n = 151)	PCET (n = 152)
HR (95% CI)	**0.81** (0.60, 1.10)	
p-value (log-rank)	0.1757	
mPFS, months	5.6	5.4
PFS rate at 6 months, %	46.8	39.6
Patients with event, n (%)	90 (59.6)	92 (60.5)

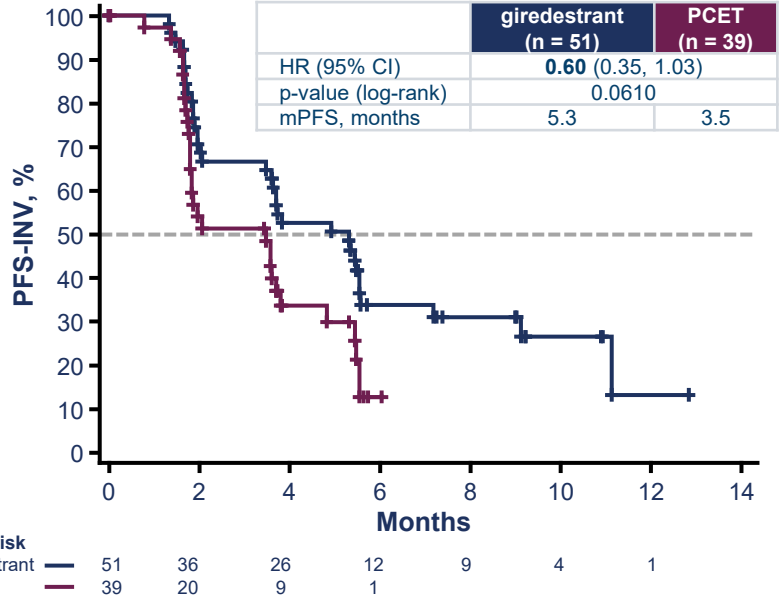


Sensitivity analysis (PFS-BIRC): HR 0.92 (95% CI = 0.64, 1.33)

Clinical cut-off: 18 February 2022; median follow-up: 7.89 months.
Primary endpoint: Stratified HR. Subgroups: Unstratified HRs. * Assessed locally.
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; HR, hazard ratio; m, median;
PCET, physician's choice of endocrine therapy; PFS, progression-free survival;
PFS-BIRC, progression-free survival by blinded independent review committee;
PFS-INV, progression-free survival by investigator assessment.

Secondary efficacy endpoints

PFS-INV: *ESR1*m subgroup



	giredestrant (n = 51)	PCET (n = 39)
HR (95% CI)	**0.60** (0.35, 1.03)	
p-value (log-rank)	0.0610	
mPFS, months	5.3	3.5

PFS-INV in complementary subgroup of *ESR1*m not detected: HR 0.88 (95% CI = 0.54, 1.42)

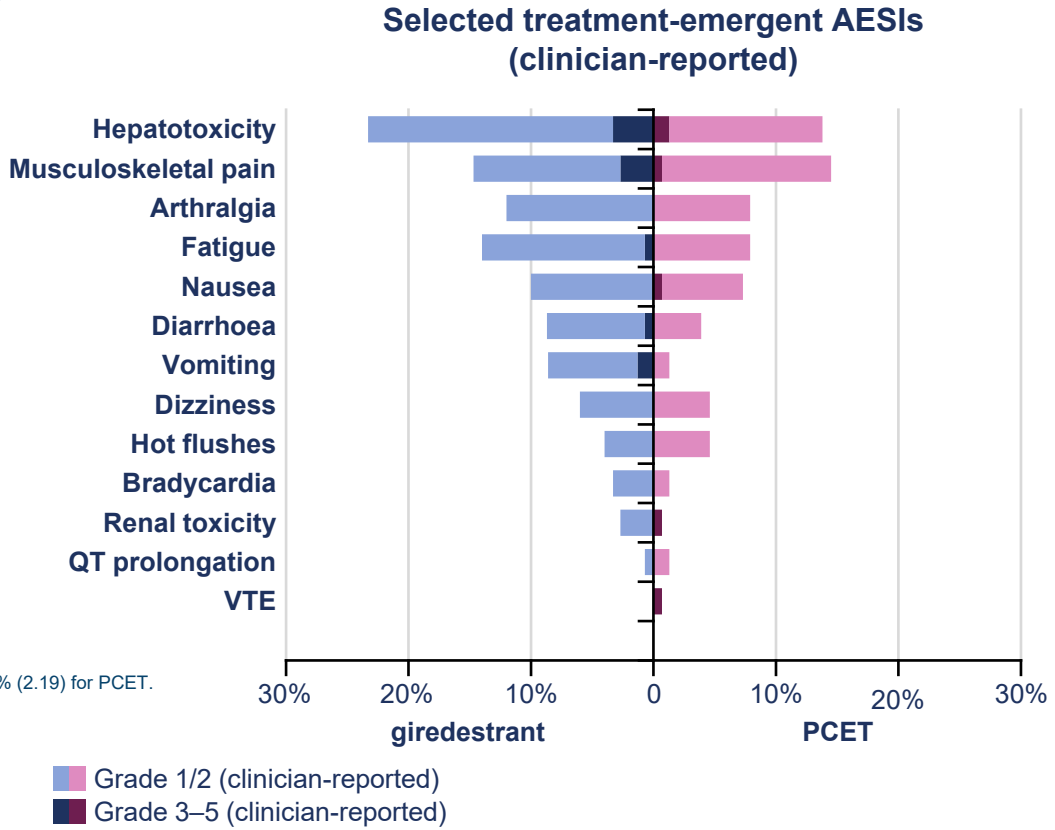
	giredestrant (n = 151)	PCET (n = 152)
cORR, % (95% CI)	**12.6** (7.75, 18.95)	**7.2** (3.67, 12.58)
Odds ratio (95% CI)	1.87 (0.86, 4.07)	
DoR	n = 19	n = 11
mDoR, months (95% CI)	**NR** (5.55, NE)	**7.39** (7.39, NE)
Range, months	2.0* to 8.9*	2.8* to 9.3*
CBR, % (95% CI)	**31.8** (24.46, 39.85)	**21.1** (14.87, 28.40)
Odds ratio (95% CI)	1.79 (1.06, 3.04)	
OS: Deaths, n (%)	**18 (11.9)**	**11 (7.2)**
PD, n	12	9
Grade 5 AE, n†	1	1
Other (post-treatment), n‡	5	1

Patients without any post-baseline tumour assessment or with non-measurable disease at baseline were considered non-responders. CBR included all patients with confirmed PR/CR or SD of ≥ 6 months as determined by the investigator per RECIST v1.1.
* Censored value. † giredestrant: Ischaemic stroke; PCET: Pulmonary embolism.
‡ Unrelated – outside of AE reporting period (> 30 days post-treatment discontinuation); giredestrant: Three COVID-19-related, two septic shocks; PCET: One septicaemia.

Clinical cut-off: 18 February 2022; median follow-up: 7.89 months. Stratified analyses. AE, adverse event; CBR, clinical benefit rate; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DoR, duration of response; *ESR1*m, *ESR1* mutation by baseline circulating tumour DNA; HR, hazard ratio; m, median; NE, non-estimable; NR, not reached; OS, overall survival; PCET, physician's choice of endocrine therapy; PD, disease progression; PFS, progression-free survival; PFS-INV, progression-free survival by investigator assessment; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Safety summary

% patients with ≥ 1	giredestrant (n = 150)	PCET (n = 152)
AE	85	71
Grade 3/4 AE	17	12
Grade 3/4 TRAE	4	3
Serious AE	9	8
Serious TRAE	2	1
Grade 5 AE*	1	1
AETD	1	2



Clinical cut-off: 18 February 2022; median follow-up: 7.89 months.
Mean dose intensity was 96.98% (SD = 9.60) for giredestrant and 99.57% (2.19) for PCET.
* giredestrant: Ischaemic stroke; PCET: Pulmonary embolism.
AE, adverse event; AESI, adverse event of special interest;
AETD, adverse event leading to treatment discontinuation;
PCET, physician's choice of endocrine therapy; SD, standard deviation;
TRAE treatment-related adverse event; VTE, venous thromboembolism.

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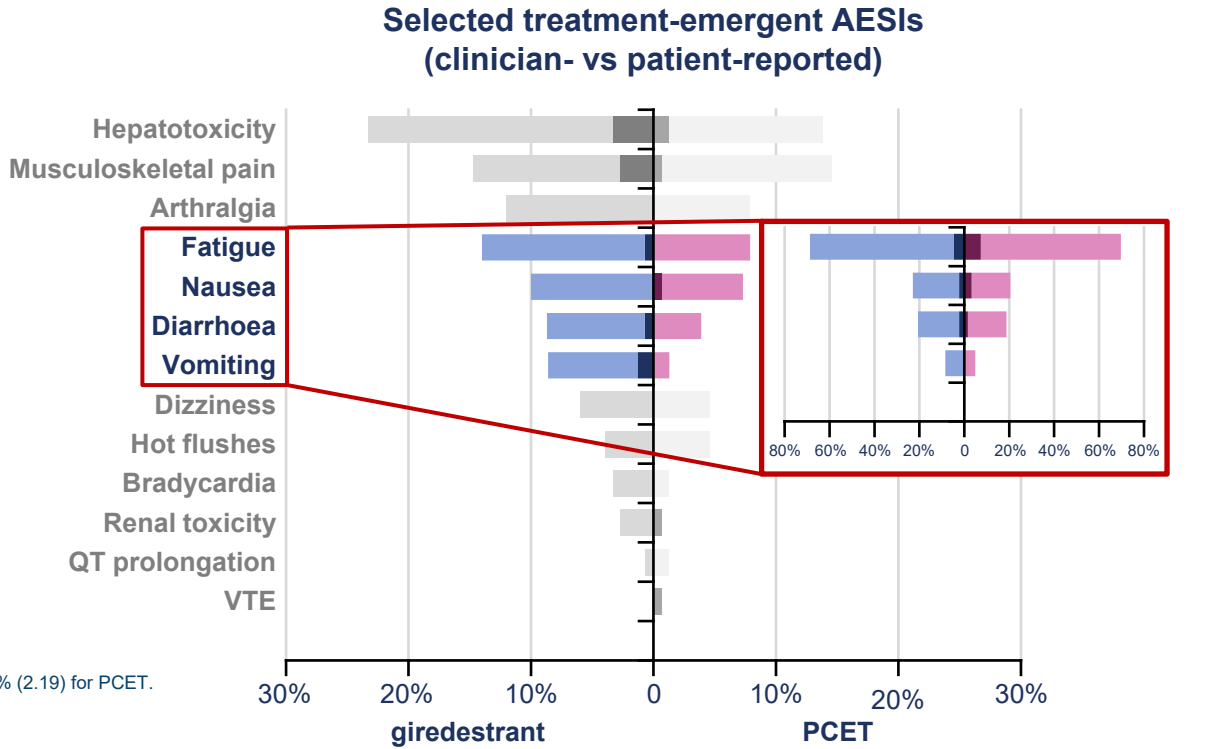

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Conclusions

- While the phase 2 acelERA BC study did not reach statistical significance for its primary endpoint of PFS-INV, giredestrant showed a numerical improvement vs PCET (HR 0.81; 95% CI = 0.60, 1.10; p = 0.1757), with a consistent treatment effect across most key subgroups and a more pronounced effect in patients with *ESR1*-mutated tumours (HR 0.60; 95% CI = 0.35, 1.03)

- Secondary efficacy endpoints numerically favoured giredestrant in terms of CBR (31.8% vs 21.1% with PCET) and ORR (12.6% vs 7.2%); DoR and OS were immature at the time of the primary analysis

- Giredestrant was well tolerated, with a safety profile comparable to PCET and consistent with known ET risks. Grade 3/4 TRAEs, serious AEs and discontinuations due to AEs were balanced across arms

- Overall, these data support the continued investigation of giredestrant in other studies

AE, adverse event; BC, breast cancer; CBR, clinical benefit rate; CI, confidence interval; DoR, duration of response; ET, endocrine therapy; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PCET, physician's choice of endocrine therapy; PFS-INV, progression-free survival by investigator assessment; TRAE, treatment-related adverse event.

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Presentation

https://bit.ly/acelERAESMO22oral

Lay summary

https://bit.ly/acelERAESMO22lay