1017

Safety and activity of single-agent giredestrant (GDC-9545) from a phase Ia/b study in patients (pts) with estrogen receptor-positive (ER+), HER2-negative locally advanced/metastatic breast cancer (LA/mBC)

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Background

- Targeting ER activity and/or estrogen synthesis is a mainstay of ER+ BC treatment, but many pts relapse during/after adjuvant ET or develop resistance via *ESR1* mutations that drive estrogen-independent transcription and proliferation.
- Most tumors remain ER signaling-dependent and pts may respond to second-/third-line ET after PD on prior therapies.[1,2]
- Giredestrant, a highly potent, nonsteroidal oral selective ER degrader, achieves robust ER occupancy, is active despite *ESR1* mutations, and was well tolerated alone and in combination with palbociclib; showing encouraging antitumor activity in the nonrandomized, open-label, dose-escalation and -expansion, phase Ia/b GO39932 study (NCT03332797).[3,4]
- We present updated interim data from the dose-escalation and -expansion single-agent giredestrant cohorts (clinical cutoff: Jan 31, 2021).

Click to view study design

Conclusions

- Single-agent giredestrant was well tolerated at all doses, with no DLTs.
- AEs were generally low grade.
- Based on the overall activity, safety, and pharmacokinetics (see poster 577 also[5]), giredestrant 30 mg is under evaluation in ongoing phase III studies (NCT03916744, NCT04546009 [see poster TPS1103][6])
  - Sinus bradycardia was uncommon at 30 mg and assessed as not related to giredestrant.
- Promising clinical activity was encouraging and observed at all dose levels and in all patient subgroups, independent of whether an *ESR1* mutation was detected or whether pts received prior chemotherapy in the mBC setting, prior fulvestrant, or a prior CDK4/6i.
- Activity in pts with mutated *ESR1* is notable, as it shows that an ET resistance mechanism has been overcome.
- Pharmacokinetic data support QD dosing.

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Results

Click to view baseline characteristics/demographics

Safety

Pts (%) with ≥1 AE*	Giredestrant dose: 10 mg n=6	30 mg n=41	90/100 mg ± LHRH n=55	250 mg ± LHRH n=9	All single-agent cohorts N=111
Any grade	6 (100)	33 (80)	47 (85)	9 (100)	95 (86)
Grade ≥3	1 (17)	5 (12)	14 (25)	1 (11)	21 (19)
Serious	0	4 (10)	6 (11)	0	10 (9)
Grade 5	0	1 (2)†	1 (2)‡	0	2 (2)
Leading to dose interruption	0	6 (15)	9 (16)	1 (11)	16 (14)
Leading to dose reduction	0	1 (2)	2 (4)	0	3 (3)

* Treatment-emergent (onset or worsened from Cycle 1, Day 1) regardless of attribution. Multiple occurrences of the same AE in one pt are counted once. † Pleural effusion due to PD. ‡ Duodenal perforation after stopping giredestrant due to PD and beginning a new line of therapy with paclitaxel.

The most common AEs were fatigue, arthralgia, and back pain (largely grade 1/2). Click to view data

- No DLTs occurred; MTD was not reached; related grade 3 AEs were infrequent (five pts; 5%; no grade 4/5 per investigator assessment); one AE led to study drug withdrawal.
- Nine pts (8%) had sinus bradycardia.
  - 30 mg: One (2%; unrelated per investigator assessment); 100 mg: Six (11%); 250 mg: Two (22%).
  - All grade 1 except one grade 2 at 250 mg.
  - No treatment interruptions/dose reductions were required.
  - At clinical cutoff, bradycardia had resolved or was resolving in seven out of nine patients and remained ongoing in two out of nine.

Clinical activity

Click to view swimlane plot

Click to view waterfall plot

	Giredestrant dose: 10 mg n=6	30 mg n=41	90/100 mg ± LHRH n=55	250 mg ± LHRH n=9
Median treatment duration, days (range)	56.5 (16–475)	168.0 (29–699)	166.0 (1–853)	167.0 (27–815)
Median cycles, n (range)	2 (1–17)	6 (1–24)	6 (1–30)	6 (1–30)
Median progression-free survival, months (95% CI)	5.3 (1.7–15.6)	7.2 (1.9–22.1)	7.4 (3.7–14.3)	5.4 (1.7–23.0)
Investigator-assessed clinical benefit rate, n/N (%); clinical-benefit-evaluable pts*				
Overall	1/6 (17)	22/40 (55)	27/52 (52)	3/9 (33)
CR	0	0	0	0
PR	1 (17)	6 (15)	5 (9)	0
SD	2 (33)	15 (37)	28 (51)	5 (56)
PD	2 (33)	15 (37)	13 (24)	3 (33)
Prior fulvestrant	0/2	3/8 (38)	3/13 (23)	0/0
Prior CDK4/6i	1/4 (25)	11/26 (42)	10/30 (33)	2/7 (29)
Prior chemotherapy in the mBC setting	1/2 (50)	4/6 (67)	5/8 (63)	0/1
ESR1 mutation detected	0/4	13/17 (76)	11/19 (60)	2/6 (33)
Responders in pts with baseline measurable disease	1/4 (25)	6/30 (20)	5/41 (12)	0/6

* Confirmed CR, PR, + SD ≥6 months in pts with confirmed CR, PR, pts who discontinued the study, or pts staying on study for ≥6 months since Cycle 1, Day 1 of giredestrant.

Pharmacokinetics

Click to view data

- Plasma exposures increased proportionally with dose from 10 mg to 250 mg.
- Geometric mean (%CV) terminal half life ranged from 25.8 hours (16.2%) to 43.0 hours (14.7%) at these dose levels, supporting QD dosing.

References

1. Di Leo A, *et al. J Clin Oncol* 2010; 28: 4594–600; 2. Baselga J, *et al. N Engl J Med* 2012; 366: 520–9; 3. Jhaveri KL, *et al.* SABCS 2019; PD7-05; 4. Lim E, *et al.* 2020 ASCO Virtual Congress; 1023; 5. Moore HM, *et al.* 2021 ASCO Virtual Congress; 577; 6. Turner N, *et al.* 2021 ASCO Virtual Congress; TPS1103.

Abbreviations

AE, adverse event; BC, breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; CR, complete response; CV, coefficient of variation; DLT, dose-limiting toxicity; ECG, electrocardiogram; ER, estrogen receptor; ET, endocrine therapy; LA, locally advanced; LHRH, luteinizing hormone-releasing hormone; mBC, metastatic breast cancer; MTD, maximum tolerated dose; PD, disease progression; PR, partial response; pt, patient; QD, daily; SD, stable disease.

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Conflicts of interest

KLJ: Consultant/Advisory Board (self): Novartis, Genentech, Inc., Lilly Pharmaceuticals, Taiho Oncology, Jounce Therapeutics, AstraZeneca, Spectrum Pharmaceuticals, ADC Therapeutics, Pfizer, BMS, AbbVie, Seattle Genetics, Blueprint Medicines. Research Funding (Institution): Novartis, Pfizer, Clovis Oncology, Genentech, Inc., AstraZeneca, ADC Therapeutics, Novita Pharmaceuticals, Debio Pharmaceuticals, Puma Biotechnology, Zymeworks, Immunomedics. Research (medical writing support): F. Hoffmann-La Roche Ltd. Please refer to the abstract for all author conflicts of interest. This study is sponsored by Genentech, Inc.

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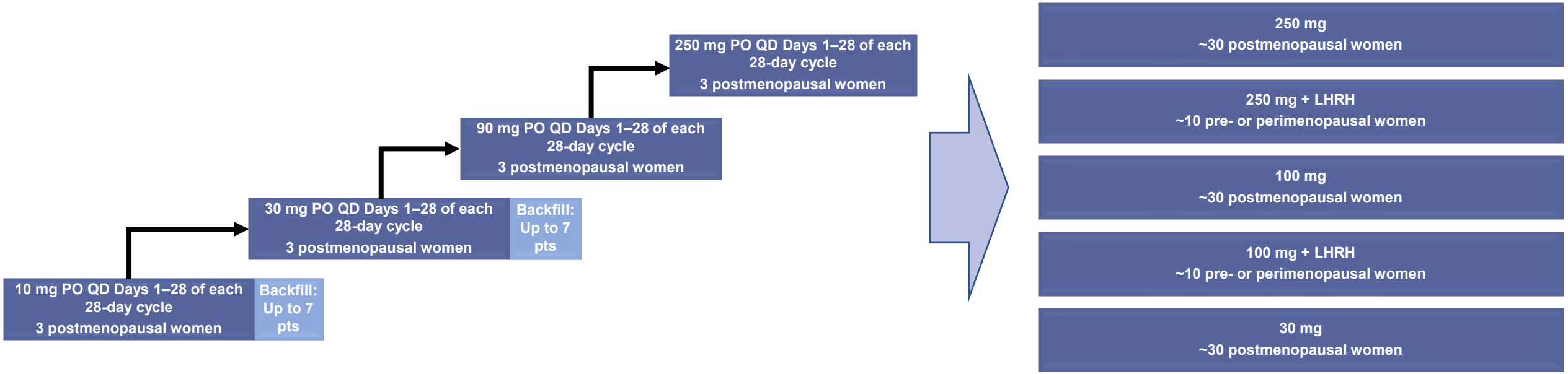
Supplementary: Study design

- Pts had ≤2 prior therapies in the LA/mBC setting with disease recurrence/disease progression while being treated with adjuvant ET for ≥24 months and/or ET in the LA/mBC setting, and derived a clinical benefit from therapy (tumor response/stable disease ≥6 months).
- Pts were postmenopausal (medical menopause on LHRH agonists was allowed with ≥100 mg giredestrant).
- Tumor assessments were conducted every 8 weeks.



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Abbreviations

ER, estrogen receptor; ET, endocrine therapy; LA, locally advanced; mBC, metastatic breast cancer; LHRH, luteinizing hormone-releasing hormone; PO, oral; pt, patient; QD, daily.

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Supplementary: Demographics and baseline characteristics

	Giredestrant dose				
	10 mg n=6	**30 mg n=41**	**90/100 mg ± LHRH n=55**	**250 mg ± LHRH n=9**	**All single-agent cohorts N=111**
Median age, years (range)	57 (42–73)	60 (35–87)	58 (33–76)	57 (38–74)	58 (33–87)
Visceral disease at baseline, pts (%)	3 (50)	30 (73)	35 (64)	4 (44)	72 (65)
Measurable disease at baseline, pts (%)	4 (67)	30 (73)	41 (75)	6 (67)	81 (73)
Median lines of prior metastatic therapies, n (range)	1.5 (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–3)
Prior use of fulvestrant, pts (%)	2 (33)	8 (20)	13 (24)	0	23 (21)
Prior use of CDK4/6i, pts (%)	4 (67)	27 (66)	33 (60)	7 (78)	71 (64)
Prior chemotherapy in the mBC setting, pts (%)	2 (33)	7 (17)	8 (15)	1 (11)	18 (16)
Baseline *ESR1* mutation status, pts (%)*					
Mutation not detected	2 (33)	19 (46)	32 (58)	3 (33)	56 (50)
Mutation detected	4 (67)	21 (51)	21 (38)	6 (67)	52 (47)
Unknown	0	1 (2)	2 (4)	0	3 (3)

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ESR1 mutation status determined from pre-treatment ctDNA by a central, digital PCR BEAMing assay.

Abbreviations
BEAMing, beads, emulsion, amplification, magnetics; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumor DNA; ER, estrogen receptor; LA, locally advanced; LHRH, luteinizing hormone-releasing hormone; mBC, metastatic breast cancer; PCR, polymerase chain reaction; pt, patient.

Supplementary: AEs in more than 10% of patients overall

	Giredestrant dose				
Pts (%) with ≥1 event	10 mg n=6	30 mg n=41	90/100 mg ± LHRH n=55	250 mg ± LHRH n=9	All single-agent cohorts N=111
Fatigue	2 (33)	7 (17)	12 (22)	3 (33)	24 (22)
Arthralgia	2 (33)	8 (20)	11 (20)	3 (33)	24 (22)
Back pain	2 (33)	7 (17)	12 (22)	1 (11)	22 (20)
Nausea	2 (33)	8 (20)	10 (18)	0	20 (18)
Diarrhea	1 (17)	5 (12)	8 (15)	2 (22)	16 (14)
Cough	1 (17)	3 (7)	9 (16)	1 (11)	14 (13)
Constipation	2 (33)	5 (12)	6 (11)	0	13 (12)
Pain in extremity	0	3 (7)	8 (15)	1 (11)	12 (11)

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Abbreviations
AE, adverse event; ER, estrogen receptor; LA, locally advanced; LHRH, luteinizing hormone-releasing hormone; mBC, metastatic breast cancer; pt, patient.

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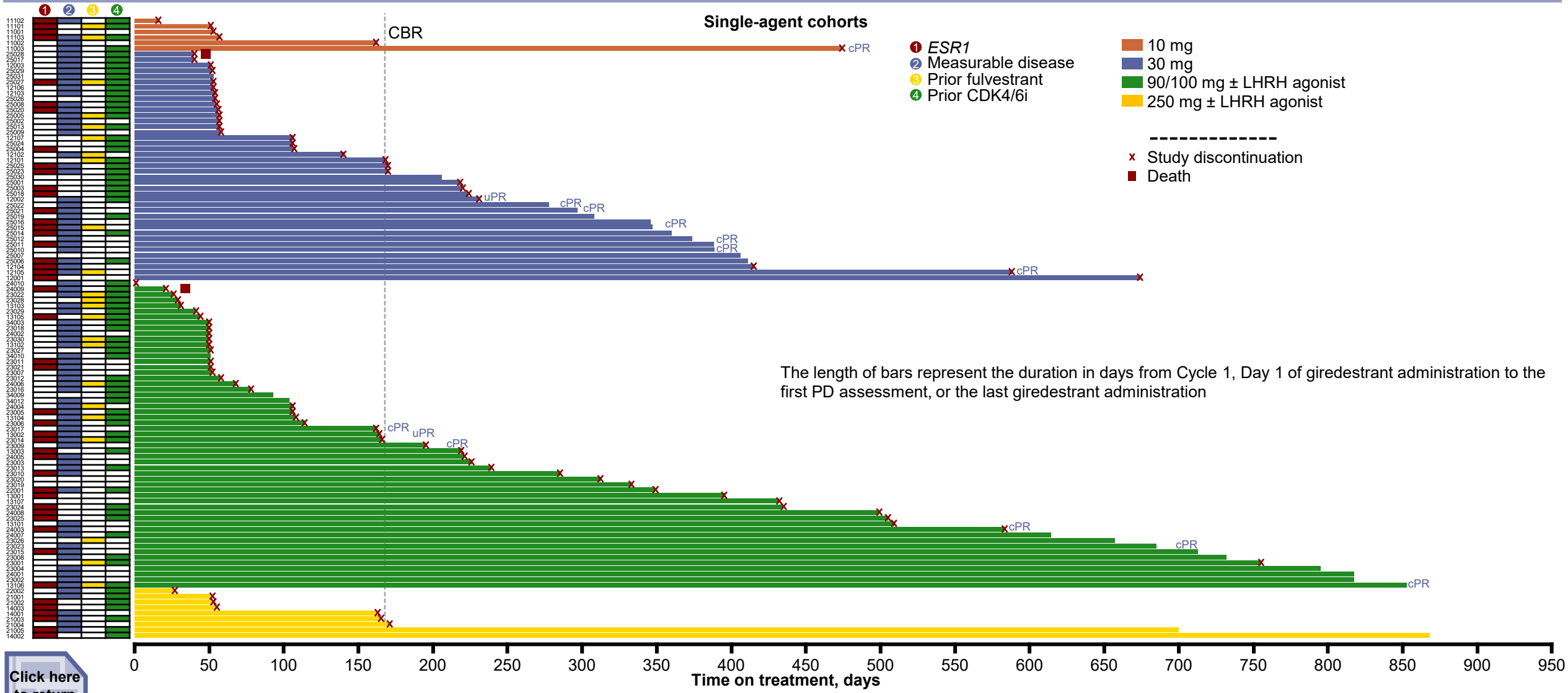
Supplementary: Duration of treatment to date of first PD



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Abbreviations

c, confirmed; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CR, complete response; ER, estrogen receptor; LA, locally advanced; LHRH, luteinizing hormone-releasing hormone; mBC, metastatic breast cancer; PD, disease progression; PR, partial response; pt, patient; u, unconfirmed.

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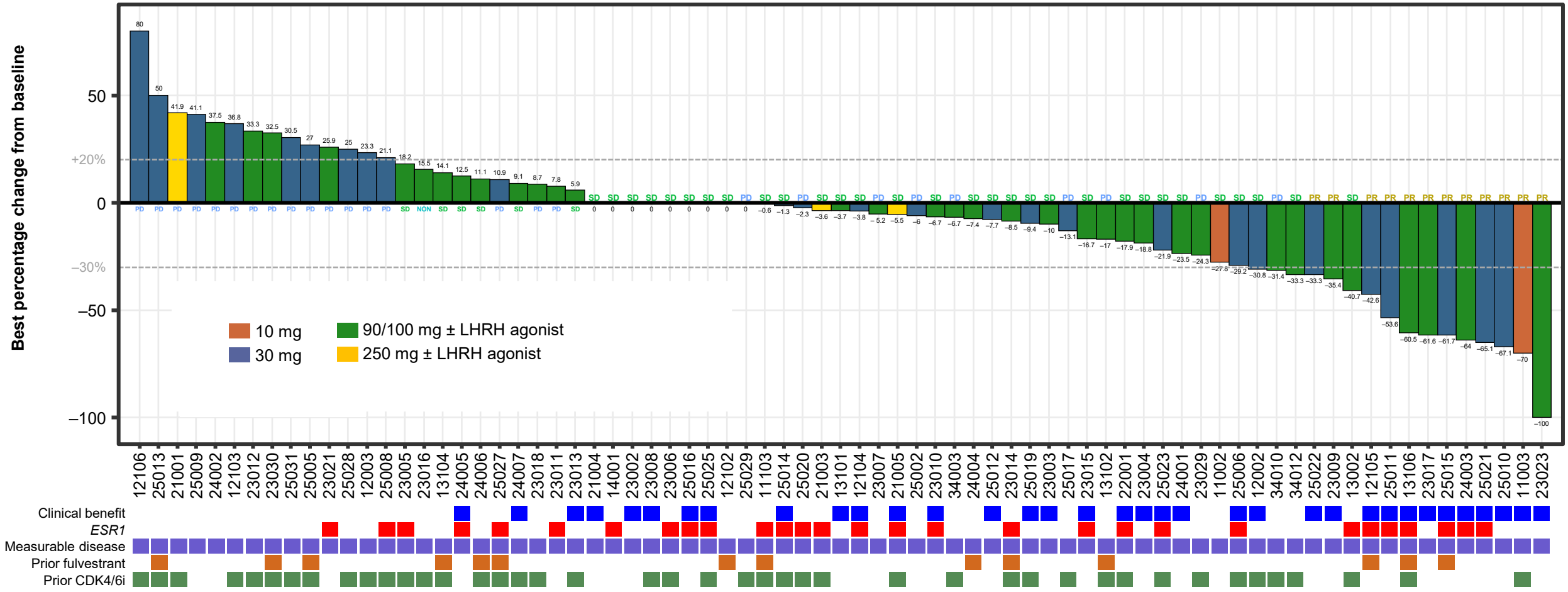
Supplementary: Best percent change from baseline in tumor sum of diameters



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Abbreviations

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; LA, locally advanced; LHRH, luteinizing hormone-releasing hormone; mBC, metastatic breast cancer; PD, disease progression; PR, partial response; pt, patient; SD, stable disease.

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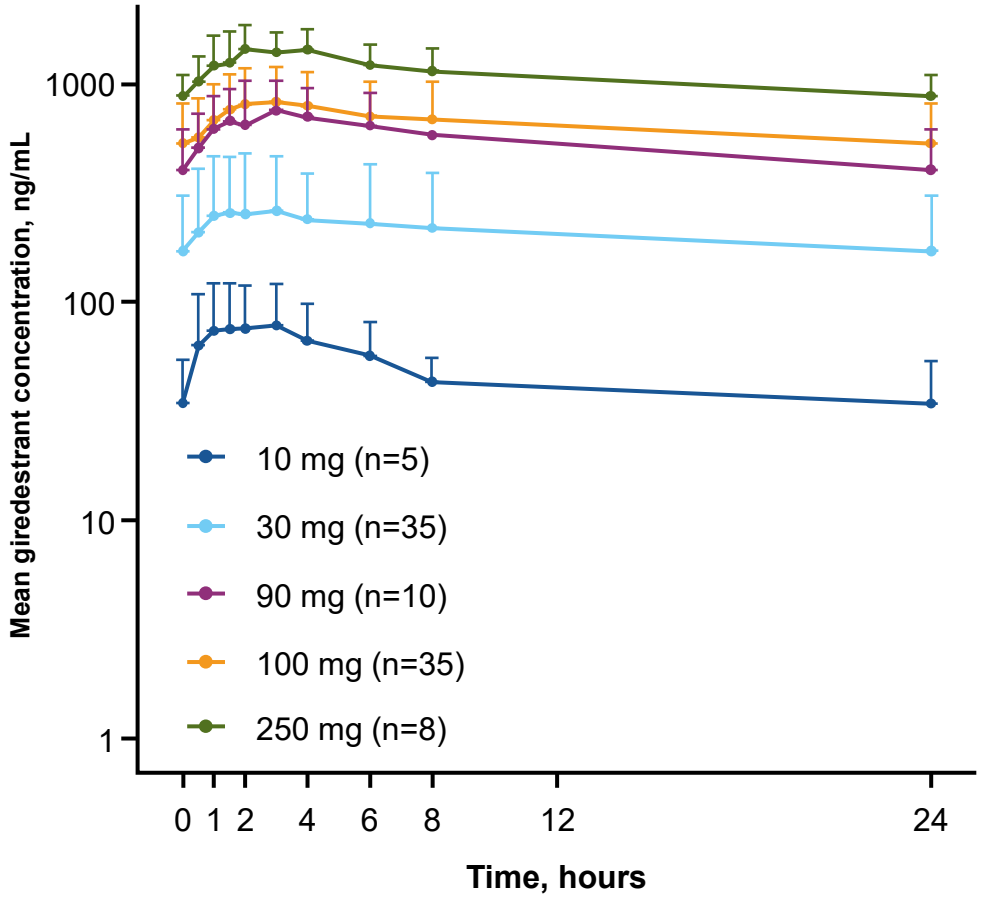
Supplementary: Pharmacokinetics



	Giredestrant dose				
	10 mg n=5	**30 mg n=35**	**90 mg n=10**	**100 mg n=35**	**250 mg n=8**
Median $T_{max,ss}$, hour (range)	1.50 (0.967–3.55)	2.50 (0–8.00)	3.02 (1.50–3.98)	3.00 (1.02–8.07)	2.83 (2.00–4.08)
GMR (%CV) $C_{max,ss}$, ng/mL	72.8 (49.7)	231 (79.7)	718 (44.3)	792 (62.2)	1540 (22.0)
GMR (%CV) $AUC_{0–24,ss}$, hour·ng/L	1090 (50.0)	3850 (80.9)	11500 (58.4)	13400 (72.3)	25800 (25.4)

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Abbreviations

$AUC_{0–24,ss}$, area under the concentration–time curve from 0 to 24 hours at steady state; $C_{max,ss}$, maximum serum concentration at steady state; CV, coefficient of variation; ER, estrogen receptor; GMR, geometric mean ratio; LA, locally advanced; mBC, metastatic breast cancer; pt, patient; $T_{max,ss}$, time to maximum serum concentration at steady state.