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SPECIAL REPORT

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Optimizing dose selection in oncology: the rationale for the clinical dose selection of giredestrant, an oral selective estrogen receptor degrader

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ABSTRACT

Introduction: 'Maximum tolerated dose' (MTD) was historically used to maximize clinical efficacy. However, there is a drive to optimize dose selection to improve safety/tolerability, while maintaining efficacy. This paradigm is increasingly important in oncology clinical development, leading to a focus on careful early-phase trial design to ensure that appropriate dose – or exposure–response data are obtained to guide dose selection.

Areas covered: We describe the development pathway and risk–benefit considerations for clinical dose selection for giredestrant, a next-generation, highly potent, non-steroidal oral selective estrogen receptor antagonist and degrader, under development for estrogen receptor-positive breast cancer. This included evaluating low-grade adverse events to potentially improve tolerability, long-term compliance, and giredestrant combination therapy use; using pharmacodynamic markers for early drug activity assessment; and testing multiple dose levels during dose-escalation and -expansion phases. Data were leveraged from preclinical and phase I/II studies in metastatic and early breast cancer, as a single agent with palbociclib, to inform giredestrant dose selection.

Expert opinion: Our learnings challenge the MTD paradigm in drug development, particularly in targeted therapies, and demonstrate the importance of basing dose selection on the totality of evidence, including preclinical data, and may help inform the clinical development of future targeted therapies.

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Breast cancer; dose optimization; giredestrant; pharmacodynamic markers; phase I/II studies; risk–benefit assessment; safety and tolerability; selective estrogen receptor antagonist and degrader

1. Introduction

Historically, oncology drug development has used the 'maximum tolerated dose' (MTD) paradigm, assuming higher doses yield greater efficacy despite increased toxicity. This approach was mainly driven by the narrow therapeutic window of cytotoxic chemotherapies expected to be dosed over short time periods (Figure 1(A)) [1,2]. The MTD approach may be less applicable to modern targeted therapies or immunotherapies, which have a wider therapeutic window and are dosed longer than chemotherapy (Figure 1(B)). For these therapies, higher doses may not increase efficacy and often worsen safety outcomes [3] and monitoring dose-limiting toxicities (DLTs) in Cycle 1 per the MTD approach may not be suitable for adverse events (AEs) affecting long-term tolerability and compliance. Instead, the optimal biological or biological effective dose may be more relevant. Recently, academia, industry, regulatory agencies (e.g. the United States Food and Drug Administration's [FDA's] Project Optimus [4]), and patient advocacy groups have driven a new paradigm, emphasizing thorough dosage assessments. This ensures that recommended doses provide tolerable, effective therapeutic intervention while maintaining quality of life (QoL) [1,2,5].

Targeted therapies, typically administered until disease progression in metastatic settings and for longer durations than chemotherapies in early disease settings, require several important considerations for optimizing the dose. These include mechanisms of anti-tumor activity, tumor pathophysiology, robust biomarker availability, treatment combinability, long-term tolerability, drug adherence, QoL, and patient preference [6]. Shifting from the MTD approach necessitates careful early clinical study design to obtain data for characterizing dose – or exposure–response relationships to guide dose selection.

In hormone receptor-positive (HR+) breast cancer (BC), tamoxifen and aromatase inhibitors (AIs) have formed the therapeutic backbone for over 3 decades [7,8]. However, relapse due to acquired resistance remains a concern. *ESR1* mutations are a common resistance mechanism, occurring in approximately 50% of endocrine-resistant cases [9]. Furthermore, extended AI treatment can increase bone pain, osteoporosis, arthralgia, and cardiotoxicity risk [10]. Observational studies have reported AEs as one of the primary reasons for AI non-adherence [11–13]. To address the unmet needs in patients with HR+ BC, interest grew in developing

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Article highlights

- Optimization of targeted oncology therapy dose selection to improve safety/tolerability, while maintaining efficacy, is increasingly important, and has led to a focus on careful early clinical study design.
- The dose-selection process for giredestrant, a next-generation, non-steroidal oral selective estrogen receptor antagonist and degrader under development for estrogen receptor-positive breast cancer, is detailed here.
- Evaluation of low-grade adverse events, long-term treatment compliance, combination therapy partners, pharmacodynamic markers, and assessment of multiple dose levels were critical factors in the dose-escalation and dose-expansion phases of the giredestrant clinical studies.
- These key factors highlight the importance of basing dose selection on the totality of evidence and overall risk–benefit considerations.
- The giredestrant recommended clinical dose (30 mg) will be assessed in multiple phase III studies in estrogen receptor-positive early and metastatic breast cancer.
- Learnings from the process may help inform the clinical development of future targeted therapies.

novel and improved therapies, including selective estrogen receptor antagonists and degraders (SERDs). The first-generation SERD, fulvestrant, was approved in 2002, but has poor solubility, requiring intramuscular administration, which limits dose delivery [14–16]. Furthermore, associated injection site-related reactions include sciatica, neuralgia, neuropathic pain, and peripheral neuropathy [15]. Evidence suggests that patients prefer oral oncology drugs due to their perceived efficacy, past treatment experience, and the potential for at-home administration [17]. Giredestrant, a next-generation, potent, non-steroidal oral SERD, is being developed to treat estrogen receptor-positive (ER+) BC [18]. Table 1 shows SERD dose-selection approaches. For all SERDs, MTDs were not reached in phase I studies; dose rationales were based on pharmacokinetics, pharmacodynamics, anti-tumor activity, safety, and tolerability [19–45].

We describe the drug development pathway and risk–benefit considerations for giredestrant clinical dose selection, which may help inform future targeted therapy development.

2. Dose selection of giredestrant

Phase I clinical trials investigated giredestrant as a single agent at multiple dose levels and with the cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6i) palbociclib in advanced breast cancer (aBC) and early breast cancer (eBC) (Table 2). Clinical and preclinical data guided initial dose selection for giredestrant. Clinical pharmacology, safety, and efficacy data described herein supported the 30-mg dose for further development in patients with ER+ eBC or aBC.

2.1. Key considerations for the first-in-human dose-finding study

The first-in-human dose-escalation studies of giredestrant used a 10-mg starting dose taken orally once daily (QD) in 28-day cycles, which preclinical studies projected would be efficacious and well tolerated [54]. This was 10-fold lower than the maximum recommended starting dose of 96 mg QD, as determined in Good Laboratory Practice repeat-dose toxicity studies in rats (Genentech, data on file). Given the large safety margin, dose escalation in ≤200% increments were allowed until the first DLT, then in ≤100% increments [55]. This is in contrast to more traditional dose-escalation methods that use incrementally smaller dose increases for each new cohort [56]. Giredestrant's half-life (8–24 hours) and oral bioavailability (~17–55%) in preclinical studies supported once-daily dosing in humans [18].

2.2. Pharmacokinetics

The first-in-human phase Ia/b GO39932 study (NCT03332797) in ER+ aBC assessed multiple dose levels during dose escalation (10, 30, 90, and 250 mg QD; 3 + 3 design) and expansion (30, 100, and 250 mg QD) [19]. Although the MTD was not reached, enrollment for the 250-mg dose was halted in nine patients to focus on lower doses. All cohorts had sufficient pharmacokinetic and pharmacodynamic assessments, and no DLTs were identified during dose escalation [19]. Giredestrant (30 mg) demon-

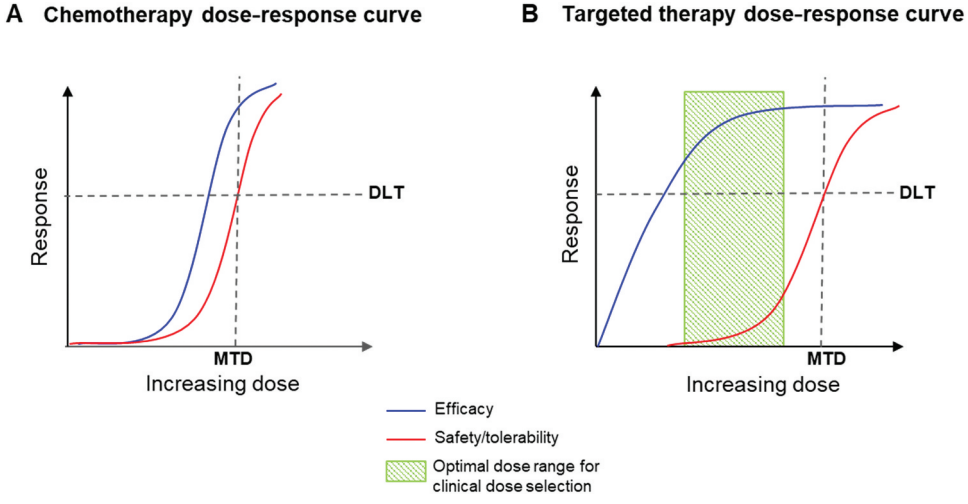

Figure 1. Typical dose–response curves for a (A) chemotherapy drug versus (B) targeted drug.
Abbreviations: DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

Table 1. Summary of dose ranges tested and dose rationales of several oral SERD drugs.

Drug	References	Dose range tested in dose-escalation phase (QD)	Dose range tested in dose-expansion phase (QD)	MTD	Phase III clinical dose (QD)	Dose rationale
Giredestrant (GDC-9545)	[19]	10–250 mg as single agent ($n = 111$); 100 mg in combination with palbociclib ($n = 64$)	30, 90/100, 250 mg as single agent; 100 mg in combination with palbociclib	Not reached	30 mg	30 mg QD was selected based on preclinical data and the evaluation of low-grade adverse events, long-term treatment compliance, combination therapy partners, pharmacodynamic markers, and assessment of multiple dose levels in the dose-escalation and dose-expansion phases of the giredestrant clinical studies. Single-agent giredestrant showed promising clinical activity at all doses (10, 30, 90/100, and 250 mg). The maximal clinical benefit was observed at 30 mg, with no additional clinical benefit observed at >30 mg. The 30-mg dose of giredestrant is currently being investigated with multiple combination partners.
Amcenestrant (SAR439859)	[20–23]	20–600 mg ($n = 16$) as single agent; 200 and 400 mg ($n = 15$) in combination with palbociclib	400 mg as single agent ($n = 49$); 200 mg in combination with palbociclib ($n = 30$)	Not reached	200 mg	Amcenestrant induces CYP3A at therapeutic dose levels and decreases palbociclib exposure. The 200-mg QD dose was selected in combination with palbociclib as a result of the DDI between amcenestrant and palbociclib. Based on PD activity and safety results from phase I and II dose-finding studies, the 200-mg QD dose of amcenestrant was selected in combination with tamoxifen.
Camizestrant (AZD9833)	[24–27]	25–450 mg as single agent ($n = 108$)	75, 150, and 300 mg as single agent ($n = 108$); 75 mg in combination with palbociclib ($n = 25$)	Not reached	75 mg	The safety, PK, PD (ERα, PgR, Ki67, and *ESR1*m ctDNA VAF), and clinical efficacy observed in SERENA-1 established 75, 150, and 300 mg QD as doses of interest for the phase II dose-finding studies. No increases in clinical efficacy were noted at camizestrant dose levels above 75 mg. In the SERENA-2 study, both camizestrant 75-mg and 150-mg QD doses demonstrated statistically significant and clinically meaningful PFS benefit over fulvestrant. In the SERENA-3 WOO study, camizestrant at 75, 150, and 300 mg QD demonstrated similar ER degradation and Ki67 suppression, at 12–15 days exposure.
Elacestrant (RAD1901)	[28–30]	200–600 mg as single agent ($n = 50$)	400 mg ($n = 50$)	Not reached (no DLTs reported up to 600 mg; however, upper GI events observed at 600 mg raised concerns regarding long-term tolerability)	400 mg	In the RAD1901-005 study, the 600-mg QD dose was deemed not tolerable, primarily due to upper gastrointestinal events. In the RAD1901-106 study, both 200/400-mg and 400-mg QD doses demonstrated a high degree of ER occupancy as measured by FES- PET with low-dose CT. The 400-mg QD dose was selected as the phase III dose based on safety, PK, PD, and anti-tumor activity.
Imlunestrant (LY3484356)	[31–34]	200–1200 mg as single agent ($n = 114$ aBC, $n = 24$ EEC)	200 ($n = 21$) and 400 ($n = 51$), ≥600 mg ($n = 42$) as single agent ($n = 114$); 400 ($n = 80$) and 800 mg ($n = 5$) in combination with or without aromatase inhibitor	Not reached	400 mg	400 mg was selected based on favorable safety and PK properties, along with preliminary efficacy.

(*Continued*)

Table 1. (Continued).

Drug	References	Dose range tested in dose-escalation phase (QD)	Dose range tested in dose-expansion phase (QD)	MTD	Phase III clinical dose (QD)	Dose rationale
Palazestrant (OP-1250)	[35–39]	30–300 mg as single agent; 30 ($n = 3$), 60 ($n = 3$), 90 ($n = 3$), and 120 mg ($n = 3$) in combination with palbociclib; 30 ($n = 3$), 60 ($n = 3$), and 120 mg ($n = 3$) in combination with ribociclib	60 ($n = 37$) and 120 mg ($n = 37$) as single agent; 120 mg in combination with ribociclib ($n = 41$)	Not reached	90 or 120 mg (TBD)	The tolerability, encouraging anti-tumor efficacy, and favorable PK support the recommended phase II dose range of 60 mg to 120 mg QD.
Vepdegestrant (ARV-471)	[40–45]	30–700 mg ($n = 83$) as single agent	200 ($n = 35$) and 500 mg ($n = 36$) as single agent; 180 ($n = 2$), 200 ($n = 21$), 400 ($n = 3$), and 500 mg ($n = 20$) in combination with palbociclib	Not reached	200 mg	PK showed dose-dependent exposure for 30–500 mg. The expansion cohort of the VERITAC study tested 200 and 500 mg QD. The 200 mg QD was selected as the phase III single-agent dose based on comparable efficacy and favorable tolerability versus 500 mg QD and robust ER degradation. At the 200-mg dose, vepdegestrant appears to increase palbociclib exposure and serious neutropenia rate when compared with historical palbociclib data. To mitigate the DDI finding, vepdegestrant 200 mg QD plus palbociclib 100 mg QD or 75 mg QD are being tested in the phase III VERITAC-3 study.

Abbreviations: aBC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CT, computed tomography; ctDNA, circulating tumor DNA; CYP3A, cytochrome P450 3A; DDI, drug–drug interaction; EEC, endometrial endometrioid carcinoma; ER, estrogen receptor; *ESR1*m, *estrogen receptor 1* mutant; FES-PET, fluorine 18 fluoroestradiol positron emission tomography; Ki67, antigen Kiel 67; MTD, maximum tolerated dose; PD, pharmacodynamics; PFS, progression-free survival; PgR, progesterone receptor; PK, pharmacokinetics; QD, once daily; SERD, selective estrogen receptor degrader; VAF, variant allele frequency; WOO, window-of-opportunity.

strated linear pharmacokinetics with a geometric mean half-life of 43.0 hours, supporting once-daily dosing [55]. Early assessments showed no impact of food intake or race on giredestrant exposure. The study demonstrated adequate exposure separation between dose levels. Giredestrant exposures exceeded those of fulvestrant, even at 10 mg, indicating better oral giredestrant bioavailability at lower doses compared with intramuscular fulvestrant [55]. Notably, several oral SERDs have demonstrated clinically relevant drug–drug interactions (DDIs) with CDK4/6is. For example, amcenestrant required dose reduction when co-administered with palbociclib due to amcenestrant's CYP3A enzyme activity induction [20]. Conversely, vepdegestrant, a potent small-molecule proteolysis-targeting chimera degrader of the estrogen receptor (ER), increased palbociclib concentrations and neutropenia rates, necessitating palbociclib dose reduction in phase III testing [40,57]. The GO39932 study also investigated the combinability of giredestrant with palbociclib during dose escalation and expansion [19]. Unlike other oral SERDs, no clinically relevant DDIs were observed with palbociclib [19], and no dose adjustment was needed when palbociclib was co-administered with giredestrant [20]. Similarly, no clinically relevant DDIs with giredestrant were seen when combined with abemaciclib or ribociclib in the phase Ib/II MORPHEUS BC study (NCT04802759) in ER+ metastatic BC (mBC) [46].

2.3. Efficacy

Single-agent giredestrant demonstrated promising clinical activity across all doses (10–250 mg) and patient subgroups, including those previously treated with chemotherapy, fulvestrant, or CDK4/6is, and those with *ESR1*-mutated tumors [19,58,59]. In GO39932, the objective response rate (ORR) was 20% ($n = 16/81$) and the clinical benefit rate (CBR; confirmed complete or partial responses, or first occurrence of progressive disease after 24 weeks of treatment) was 49% ($n = 54/111$) across cohorts [19]. Clinical benefit plateaued at 30 mg, with no added efficacy observed at higher doses [19]. Exposure–response analyses supported these observations [60], suggesting an efficacy plateau within the evaluated ranges. No significant association was found between exposure and efficacy (ORR or CBR) at doses of 10–250 mg, regardless of *ESR1* mutation status, with no improved efficacy above 30 mg [60].

Promising clinical activity was observed across all subgroups receiving 100-mg giredestrant with 125-mg palbociclib, with or without luteinizing hormone-releasing hormone agonist [19,59]. In the giredestrant plus palbociclib subgroups in GO39932, the ORR was 48% ($n = 27/56$) and the CBR was 81% ($n = 52/84$) [19].

Once-daily 30-mg giredestrant was also investigated in phase II trials, including as a single agent versus physicians' choice of endocrine therapy (PCET) in locally advanced (LA)/mBC in acelERA BC (NCT04576455) [47], and as a single agent or with palbociclib versus anastrozole ± palbociclib in eBC in coopERA BC (NCT04436744) [48]. Although acelERA BC did not meet its primary endpoint of investigator-assessed progression-free survival (PFS) with giredestrant versus PCET, the

numerical PFS improvement observed was more pronounced in patients with *ESR1*-mutated tumors [47].

2.4. Pharmacodynamics

Fulvestrant studies show that incomplete target engagement or residual ER availability, measured by [^{18}F]-fluoroestradiol (FES) positron emission tomography (PET), is linked to early progression in ER+ mBC [61]. Various pharmacodynamic biomarkers were used to assess giredestrant's early single-agent activity at different doses [19,49,59,61,62]. In the GO39932 study, 11 of 14 patients (79%) receiving single-agent giredestrant (10, 30, 90, or 250 mg) with FES-avid disease showed complete or near-complete (>90%) suppression of FES uptake [19], including those with *ESR1*-mutated tumors. Although FES-PET is approved to detect ER+ disease sites in BC, its utility in SERD dose-selection studies is limited by near-saturation levels across all giredestrant doses studied [19,63].

In GO39932, baseline circulating tumor DNA (ctDNA) was assessed for *ESR1* mutations. Most patients with detectable *ESR1* mutations showed *ESR1* variant allele frequency reduction by Cycle 1, Day 15, or Cycle 2, Day 1, after single-agent giredestrant treatment. Additionally, 65% of patients with *ESR1*-mutated tumors had undetectable *ESR1* variant allele frequency at doses ≥30 mg, whereas reductions were less consistent at 10 mg ($n = 6$ patients) [19]. The lack of further ctDNA reduction at higher doses and inconsistent effects at 10 mg supported the 30-mg dose for patients with ER + BC [19].

Ki67 response to preoperative endocrine therapy is prognostic in ER+ eBC [64]. In a window-of-opportunity (WOO) study (NCT03916744) in ER+ eBC, 14 days of pre-surgery giredestrant (10, 30, or 100 mg) led to a 78% geometric mean reduction in Ki67 and a 55% complete cell-cycle arrest rate across the three doses tested [49]. All doses decreased ER and progesterone receptor levels, confirming intratumoral ER degradation and inhibition of ER signaling. ER activity was further evaluated through gene expression assessment (transcriptional profiling by RNA sequencing) with pre- and on-treatment biopsies scored for ER activity using a curated gene signature, validated in patient-derived xenograft models, and cross-referenced with The Cancer Genome Atlas [65]. Using this ER activity gene signature, the greatest suppression of ER activity was observed at 30 mg, with no further decreases in ER activity at 100 mg [49]. Therefore, these pharmacodynamic endpoints and biomarkers informed dose selection for aBC and eBC. A limitation of the neoadjuvant eBC study is the low baseline prevalence of *ESR1* mutations; however, because *ESR1* mutations are known to drive resistance to current therapies and considering the inconsistent ctDNA reduction at 10 mg, this supported the rationale for doses >10 mg despite apparent pharmacodynamic saturation.

In the phase II coopERA BC study (NCT04436744), neoadjuvant 30-mg giredestrant (both alone or with palbociclib) showed a greater Ki67 reduction and a higher rate of complete cell cycle arrest compared with anastrozole [48]. Based on GO39932 results and with the supporting coopERA efficacy data, the ongoing persevERA BC study (NCT04546009) is evaluating 30-mg giredestrant with 125-mg palbociclib in the first-line aBC setting [50].

Collectively, the results from the first-in-human GO39932, acelERA, WOO, and coopERA BC studies [19,48,49] suggest that giredestrant's clinical benefit can be obtained at 30-mg doses, supporting further evaluation of this dose in aBC and eBC.

2.5. Safety

Giredestrant, as a single agent or combined with palbociclib, was well tolerated at all doses tested (10–250 mg). In the first-in-human GO39932 study single-agent cohorts (10, 30, 90, and 250 mg), no DLTs were observed and the MTD was not reached [19,54]. Giredestrant dose selection also considered low-grade AEs identified in phase I trials (e.g. asymptomatic bradycardia) to potentially improve adherence to and tolerability of long-term therapy, and to allow combination of giredestrant with other agents [19,54,58,60,62,66]. At clinical cutoff, the median treatment duration was 5.6 months (range, 1–36); 19 patients (17.1%) remained on treatment. In the 30-mg single-agent giredestrant arm of the GO39932 study, only three (7.3%) patients had giredestrant-related AEs leading to giredestrant modification/interruption, and only one (2.4%) had a giredestrant-related serious AE (Grade 2 transient ischemic attack that resolved within 24 hours). No patients had giredestrant-related AEs leading to giredestrant discontinuation or with a fatal outcome [19]. Exposure–response analysis showed that increasing giredestrant exposure did not significantly increase the incidence of any-grade or Grade ≥3 AEs, AEs of special interest, or bradycardia [60]. Since low-grade asymptomatic bradycardia is an identified risk of giredestrant, detailed cardiovascular assessments were conducted with 100-mg giredestrant. However, despite the exposure–response relationship for bradycardia not being significant [60], clinically asymptomatic bradycardia AEs were seen more frequently at doses ≥90 mg as compared with 30 mg [19]. Cardiac safety assessments, including routine electrocardiograms, 24-hour Holter monitoring, and exercise testing revealed no relevant cardiac effects at 100-mg giredestrant [66]. Although exposure–response analyses indicated heart rate decreases at steady state [67], bradycardia increases were non-significant [60]. Higher exposure may increase the probability of hepatic events (i.e. liver function abnormalities), but clinically relevant hepatic events were rare at 30 mg [60]. Tolerability of single-agent giredestrant at 10, 30, and 100 mg was further supported by the WOO study, showing no AE-related treatment discontinuations, no Grade 3 or serious giredestrant-related AEs, and no Grade 4/5 AEs in generally healthy patients with eBC [49]. Overall, single-agent 30-mg giredestrant was well tolerated and manageable and was not associated with an appreciable increase in the incidence of AEs [19]. In GO39932, 100-mg giredestrant with palbociclib was well tolerated, with few giredestrant-related AEs requiring dose modification/interruption/discontinuation, and no serious or Grade 5 giredestrant-related AEs [19].

The MORPHEUS BC study showed that 30-mg giredestrant combined with everolimus (10 mg) or inavolisib (9 mg) resulted in promising efficacy and no significant DDIs [68,69]. Furthermore, 30-mg giredestrant with abemaciclib or

Table 2. Summary of clinical trials discussed in this review.

Study	References	Phase	Treatment arms	Eligibility criteria	Sample size	Outcome measures
GO39932 (NCT03332797)	[19]	Ia/b	GDC-9545 alone or in combination with palbociclib and/or LHRH agonist	Patients with ER+, HER2– LA/mBC	175	Primary: Safety Secondary: Includes PK, PD, and efficacy
MORPHEUS BC (NCT04802759)	[46]	Ib/II	Multiple combinations of treatments	Patients with inoperable, LA/mBC, ER+ BC	510 (estimated)	Primary: Safety, ORR Secondary: Includes PFS, OS, CBR, DCR, DOR, and PK
acelERA BC (NCT04576455)	[47]	II	Giredestrant compared with physician's choice of endocrine single agent	Patients with ER+, HER2– who have received 1 or 2 prior lines of systemic therapy in LA/mBC	303	Primary: PFS Secondary: Includes OS, ORR, DOR, CBR, and INV-PFS
coopERA BC (NCT04436744)	[48]	II	Giredestrant compared with anastrozole (in the WOO phase) and giredestrant plus palbociclib compared with anastrozole plus palbociclib (in the neoadjuvant phase)	Postmenopausal women with ER+ and HER2– untreated eBC	221	Primary: Relative change in Ki67 scores from BL Secondary: Includes ORR, CCCA, and safety
Short-term preoperative WOO (NCT03916744)	[49]	I	Giredestrant single agent	Postmenopausal women with stage I–III operable, ER+ BC	75	Primary: Relative change in Ki67 scores from BL Secondary: Safety
persevERA BC (NCT04546009)	[50]	III	Giredestrant combined with palbociclib compared with letrozole combined with palbociclib	Patients with ER+, HER2– LA/mBC	992	Primary: PFS Secondary: Includes OS, ORR, and CBR
pionERA BC (NCT06065748)	[51]	III	Giredestrant compared with fulvestrant, both combined with a CDK4/6 inhibitor	Patients with ER+, HER2– aBC with acquired adjuvant ETR	1050 (estimated)	Primary: PFS in the *ESR1* m subgroup + FAS Secondary: Includes PFS in *ESR1*nmd subgroup, OS, and cORR
evERA BC (NCT05306340)	[52]	III	Giredestrant plus everolimus compared with the physician's choice of endocrine therapy plus everolimus	Patients with ER+, HER2–, LA/mBC	320 (estimated)	Primary: PFS Secondary: Includes OS, ORR, DOR, and CBR
lidERA BC (NCT04961996)	[53]	III	Adjuvant giredestrant compared with physician's choice of adjuvant endocrine single agent	Patients with ER+, HER2– eBC	4200 (estimated)	Primary: IDFS Secondary: Includes OS, IDFS, and DFS

Abbreviations: aBC, advanced breast cancer; BC, breast cancer; BL, baseline; CBR, clinical benefit rate; CCCA, complete cell cycle arrest; CDK4/6, cyclin-dependent kinase 4/6; cORR, complete objective response rate; DCR, disease control rate; DFS, disease-free survival; DOR, duration of response; eBC, early breast cancer; ER, estrogen receptor; *ESR1*m, *estrogen receptor 1* mutation; *ESR1*nmd, *ESR1* no mutation detected; ETR, endocrine treatment resistant; FAS, full analysis set; FIH, first-in-human; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease-free survival; INV-PFS, invasive progression-free survival; LA, locally advanced; LHRH, luteinizing hormone-releasing hormone; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; WOO, window-of-opportunity.

ribociclib was well tolerated, with safety consistent with the known profiles of each treatment, and no clinically relevant DDIs [46]. As a potential backbone endocrine therapy, giredestrant shows promising safety profiles in combination with targeted therapies.

3. Conclusion

Optimizing giredestrant's clinical dose highlighted the importance of evidence-based dose selection and of weighing risk–benefit considerations across multiple studies in aBC and eBC. The design and planned analyses for the GO39932 and WOO studies enabled the recommended dose to be selected using this holistic approach rather than following the traditional MTD paradigm. Though implemented before FDA guidance, the approach aligns with FDA oncology dose-optimization recommendations, including robust pharmacokinetic/pharmacodynamic assessments, multiple-dose-level evaluations in early trials, and thorough safety signal evaluations [4]. Additionally, the 30-mg dose of giredestrant has been tested with multiple combination partners, supporting it as the appropriate dose to minimize overlapping toxicities or DDIs [46]. With comparable target engagement, biologic activity, and maximal clinical benefit observed at ≥30 mg, and a favorable safety profile, the 30-mg once-daily dose was chosen for further clinical development in phase II/III eBC and aBC studies. These results support the co-administration of 30-mg giredestrant with palbociclib, which is studied in patients with HR+ aBC in the ongoing phase III persevERA BC study [50], with investigator's choice of CDK4/6i (palbociclib, abemaciclib, or ribociclib) in the ongoing pionERA BC study (NCT06065748) [51], or with everolimus in the ongoing evERA BC study (NCT05306340) [52], all being conducted in patients with ER+ aBC. Additionally, the ongoing lidERA BC study (NCT04961996), is investigating single-agent 30-mg giredestrant versus PCET in patients with ER+ eBC [53].

4. Expert opinion

As oncology drug development moves from chemotherapy to targeted agents, dose selection increasingly requires a patient-centered approach that considers both efficacy and tolerability. Before the FDA's Project Optimus [4], giredestrant's early clinical development highlighted the importance of basing dose selection on pharmacokinetics, pharmacodynamics, efficacy, and safety, rather than toxicity alone. Giredestrant dose selection benefited from carefully designed phase I/II studies that allowed adaptation to emerging safety and efficacy data, while capturing relevant pharmacokinetic, pharmacodynamic, and clinical activity data across dose levels. This approach can inform future targeted therapy development. While GO39932 used a traditional 3 + 3 dose-escalation design, future studies could leverage model-based or model-assisted designs [70]. Given the extended duration of treatment of ER+ BC, particularly in the adjuvant setting, it is essential to identify AEs with a focus on patient-reported outcomes, long-term tolerability, and adherence. Equally important is identifying a dose that ensures sufficient target inhibition across the changing receptor landscape, encompassing both *ESR1*-mutant and *ESR1*-wildtype, which occurs with tumor evolution and treatment pressure. Furthermore, leveraging pharmacodynamic markers (e.g. changes in ER protein levels, pathway activity, and Ki67) and rapidly developing ctDNA-based surrogate clinical endpoints alongside standard oncology endpoints, such as OBR, CBR, and PFS, may inform future dose-selection decisions.

Changes to the dose-optimization paradigm can realistically be implemented into clinical research, offering the potential to significantly enhance the development of new treatments. However, challenges exist in striking a balance between the urgency to bring transformative medicines to patients and ensuring the robustness of the dose-optimization process. This balance is crucial to maintain the integrity and value of clinical trials while also addressing the pressing needs of patients awaiting innovative therapies.

The dose optimization process described herein for giredestrant does have some limitations. The pharmacodynamic markers described here may not be relevant to all oncology therapies. For giredestrant, the availability of FES-PET imaging to measure target engagement, along with the ability to assess multiple biomarkers, such as ER degradation, in neoadjuvant tumor tissue, represents a unique strength. Furthermore, dose optimization based on clinical, pharmacokinetic, and pharmacodynamic parameters introduces some uncertainty around efficacy when selecting lower drug doses. It also remains difficult to predict whether an efficacy curve will follow a hyperbolic pattern with a broad therapeutic index, a more sigmoidal relationship with an expanded index, or a profile more typical of conventional chemotherapeutic agents. Additionally, this approach may be difficult to apply to drugs with non-linear pharmacokinetics, as dose adjustments may not lead to proportional changes in exposure, posing a challenge for predicting a patient's response to a given dose [70].

Dose-finding study design optimization is expected to continue evolving, with a focus on incorporating novel endpoints such as ctDNA clearance and patient-reported outcomes. Tools such as the ER-signaling readout, evaluated during giredestrant development, may have potential as future biomarkers, although they remain to be fully validated [71]. Additional tools such as the clinical utility index [72,73] or multiple-dose randomized trial design [71] will become more prevalent. However, dose optimization remains challenging given the diversity of drug mechanisms, patient populations, available pharmacodynamic markers, and treatment combinations. Over the next 5 years, a consensus is expected to emerge on how to streamline dose optimization through collaboration between the pharmaceutical industry, health authorities, and the medical community. In the longer term, advanced quantitative tools will likely enable real-time, patient-specific dose decisions, further advancing precision oncology and improving therapeutic outcomes.

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Data sharing statement

For eligible studies, qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing, this request platform is Vivli (https://vivli.org/ourmember/roche/). For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked because of a potential increase in risk of patient reidentification.

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