First-in-human, phase 1a/b study of GDC-4198 (RGT-419B), a next generation CDK4/2 inhibitor, in patients with HR+ HER2- locally advanced/metastatic breast cancer (LA/mBC) who progressed on prior CDK4/6 inhibitors

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BACKGROUND

- Combining a cyclin-dependent kinase (CDK)4/6 inhibitor with endocrine therapy (ET) is a key pillar of hormone receptor positive (HR+) metastatic BC treatment and a recommended option in patients with high-risk HR+ early BC[1,2]
- Despite the clinical success of approved CDK4/6 inhibitors, resistance is a major challenge that limits clinical benefit in patients with HR+ human epidermal growth factor receptor 2 negative (HER2-) BC[3-5]
  - A key resistance mechanism involves the compensatory activity of CDK2, which drives cell cycle progression despite CDK4/6 inhibition [see preclinical GDC-4198 poster #PS2-11-28]
  - Overexpression of CCNE1 mRNA, which activates CDK2, has been associated with worse prognosis on CDK4/6 inhibitor therapy in metastatic BC patients[6,7]
- CDKs are a family of kinases that pair with cyclins to regulate cell cycle progression
  - CDK4 and CDK6 bind cyclin D to initiate the cell cycle, but they have distinct roles, with CDK4 driving HR+ BC growth and CDK6 playing a critical role in hematopoiesis[8,9]
  - CDK2, in complex with cyclin E or cyclin A, hyperphosphorylates Rb to promote cell cycle progression and can compensate for loss of CDK4/6 activity[8-13]
- GDC-4198 (formerly known as RGT-419B) is a next-generation CDK4/2 inhibitor, which induces durable cell cycle arrest and overcomes CDK2-driven adaptation to CDK4 inhibition (Figure 1)

Figure 1. GDC-4198 Mechanism of Action

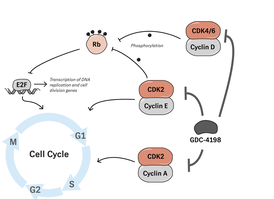
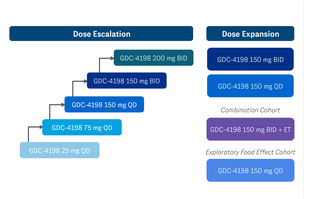


Figure 2. Study Design



- Here we present interim data from a phase 1, first-in-human, multicenter trial of GDC-4198 as a monotherapy or in combination with ET in patients with HR+ HER2- LA/mBC

OBJECTIVES

Primary Objective

- Assess the safety and tolerability of different dose levels and schedules of GDC-4198, to identify the maximum tolerated dose (MTD) when given as monotherapy

Secondary Objectives

- Secondary objectives included assessing the PK profile and exploratory efficacy of GDC-4198

METHODS

- Adults with HR+ HER2- LA/mBC who have previously progressed during or after ET and CDK4/6 inhibitor therapy were eligible for this study (NCT05304962)
- GDC-4198 monotherapy was administered orally in continuous 28-day cycles across five cohorts (25, 75, 150 mg once daily [QD], 150 mg twice daily [BID] and 200 mg BID) using a standard 3+3 dose escalation design in a fasted state to identify the MTD and recommended dose for expansion (RDE) (Figure 2)
- Patients in the combination therapy cohort received GDC-4198 150 mg BID + ET (aromatase inhibitor)
- Impact of food on GDC-4198 PK was assessed within the food effect (FE) cohort where a single 150 mg QD dose was administered with/without food. FE was assessed under the high fat, high calorie (HFHC) diet with an adequate washout window of 7 days between the 2 doses and then 150 mg QD dosing was administered continuously
- Baseline ESR1 and PIK3CA mutation status were determined using pre-treatment circulating tumor DNA (ctDNA) with the exception of one patient who had PIK3CA status determined with tissue, using FoundationOneCDx

RESULTS

- As of October 1, 2025, 42 patients (38 monotherapy; 4 in combination with ET) received GDC-4198 (Table 1)
- The median age was 62 years (range 39-80); all patients were female (100%) and most were White (93%)
- All patients were ECOG 0 or 1 and the median number of previous lines of therapy for LA/mBC was 3 (range 1, 8)
- All patients received prior CDK4/6i and ET (100%), most of whom (79%) had received treatment with a CDK4/6 inhibitor for longer than 12 months
- The most common (occurring in ≥20% of patients) treatment-emergent adverse events (TEAEs; all causality) are shown in Table 2

Table 1. Patient Demographics and Baseline Characteristics

	GDC-4198 25 mg QD (n=3)	GDC-4198 75 mg QD (n=3)	GDC-4198 150 mg QD (n=17)	GDC-4198 150 mg BID (n=11)	GDC-4198 200 mg BID (n=4)	All mono (n=38)	GDC-4198 150 mg BID + ET (n=4)	All patients (N=42)
Age, years, median (range)	74.0 (65, 80)	62.0 (58, 69)	64.0 (39, 79)	60.0 (49, 77)	51.5 (39, 64)	62.0 (39, 80)	61.5 (60, 68)	62.0 (39, 80)
Most common sites of metastasis[1]								
Liver	0 (0)	2 (67)	14 (82)	11 (100)	4 (100)	31 (82)	3 (75)	34 (81)
Lung	1 (33)	0 (0)	6 (35)	3 (27)	1 (25)	11 (29)	1 (25)	12 (29)
Bone	2 (67)	2 (67)	12 (71)	8 (73)	3 (75)	27 (71)	4 (100)	31 (74)
Lymph node	0 (0)	0 (0)	8 (47)	2 (18)	1 (25)	11 (29)	1 (25)	12 (29)
Brain	0 (0)	0 (0)	0 (0)	1 (9)	0 (0)	1 (3)	1 (25)	2 (5)
Other	1 (33)	1 (33)	6 (35)	2 (18)	1 (25)	11 (29)	2 (50)	13 (31)
No. lines of therapy, median (range)	2.0 (1, 3)	3.0 (1, 7)	3.5 (1, 8)	2.5 (1, 6)	4.0 (1, 7)	3.0 (1, 8)	3.0 (1, 5)	3.0 (1, 8)
Prior chemo in LA/mBC setting, n (%)	2 (67)	1 (33)	6 (35)	5 (45)	1 (25)	15 (39)	2 (50)	17 (40)
Prior CDK4/6 inhibitor, n (%)	3 (100)	3 (100)	17 (100)	11 (100)	4 (100)	38 (100)	4 (100)	42 (100)
Palbo	3 (100)	2 (67)	12 (71)	7 (64)	1 (25)	25 (66)	4 (100)	29 (69)
Ribo	0 (0)	0 (0)	3 (18)	3 (27)	3 (75)	9 (24)	0 (0)	9 (21)
Abema	0 (0)	1 (33)	6 (35)	2 (18)	0 (0)	9 (24)	0 (0)	9 (21)

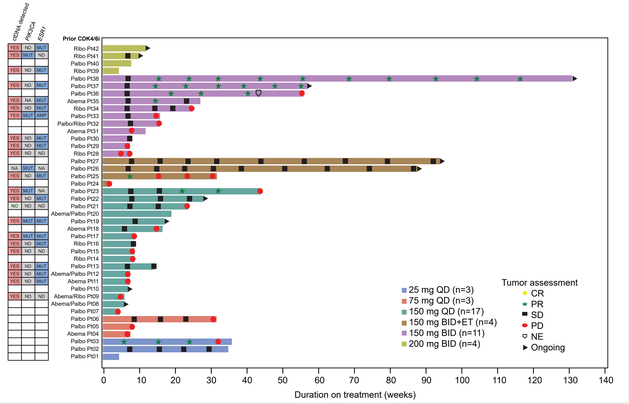
[1]Categories are not mutually exclusive; a subject may be counted in more than one row.

Table 2. Summary of TEAEs in ≥20% of Patients (All Grades) Regardless of Attribution

n (%)	GDC-4198 25 mg QD (n=3)	GDC-4198 75 mg QD (n=3)	GDC-4198 150 mg QD (n=17)	GDC-4198 150 mg BID (n=11)	GDC-4198 200 mg BID (n=4)	All mono (n=38)	GDC-4198 150 mg BID + ET (n=4)	All patients (N=42)
No. patients with TEAE	3 (100)	3 (100)	16 (94)	11 (100)	4 (100)	37 (97)	4 (100)	41 (98)
Nausea	3 (100)	0 (0)	13 (76)	7 (64)	2 (50)	25 (66)	3 (75)	28 (67)
Diarrhea	1 (33)	1 (33)	10 (59)	7 (64)	3 (75)	22 (58)	2 (50)	24 (57)
Vomiting	1 (33)	0 (0)	10 (59)	7 (64)	3 (75)	21 (55)	3 (75)	24 (57)
White blood cell count decreased	1 (33)	1 (33)	6 (35)	7 (64)	0 (0)	15 (39)	2 (50)	17 (40)
Fatigue	1 (33)	1 (33)	5 (29)	6 (55)	3 (75)	16 (42)	0 (0)	16 (38)
Headache	2 (67)	1 (33)	5 (29)	5 (45)	1 (25)	14 (37)	1 (25)	15 (36)
Neutrophil count decreased	1 (33)	0 (0)	4 (24)	6 (55)	1 (25)	12 (32)	2 (50)	14 (33)
Blood alkaline phosphatase increased	0 (0)	0 (0)	7 (41)	3 (27)	0 (0)	10 (26)	0 (0)	10 (24)
Constipation	1 (33)	0 (0)	6 (35)	1 (9)	2 (50)	10 (26)	0 (0)	10 (24)
Hyperglycemia	2 (67)	0 (0)	1 (6)	4 (36)	0 (0)	7 (18)	2 (50)	9 (21)

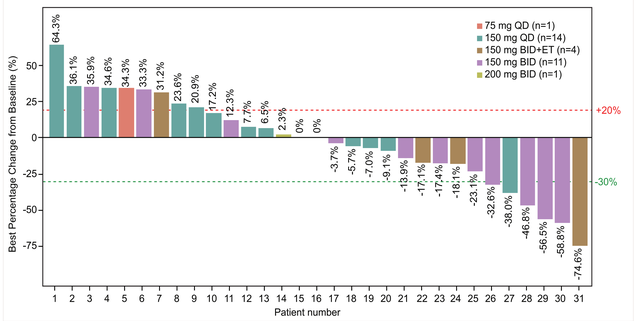
- The incidence of Grade ≥3 treatment-related adverse events (TRAEs) was low (24%); the most common (≥5%) events were neutrophil count decreased (7%), lymphocyte count decreased (5%), and neutropenia (5%)
- All gastrointestinal AEs (eg, nausea, diarrhea) considered related to treatment with single-agent GDC-4198 were low-grade (Grade 1 or 2)
- Three patients discontinued treatment due to AEs; one patient treated at 150 mg BID with an ongoing history of Grade 1 neuropathy has discontinued GDC-4198 after over 6 months of treatment due to collective mild/moderate TRAEs including Grade 2 peripheral neuropathy
- There were no treatment-related serious AEs and no fatal AEs were reported
- No DLTs have been observed and the MTD has not been reached

Figure 3. Time on Treatment in Safety Population and Responses in Efficacy Measurable Population with Mutation Status



AMP, amplification; MUT, mutation; NA, not available; ND, not done.

Figure 4. Change in Tumor from Baseline in Efficacy Measurable Population



- In the monotherapy cohorts among patients with measurable disease and at least 1 post-baseline tumor assessment (n=27), 4 patients had confirmed partial responses (1 at 150 mg QD; 3 at 150 mg BID) and 11 patients achieved a best response of SD, resulting in a disease control rate of 56% (95% CI, 35–75) (Figures 3 and 4)
- While interpretation of clinical activity with GDC-4198 plus ET is limited due to the small number of patients treated with this combination (n=4), 2 patients had SD for more than 20 months
- Partial responses were observed in patients both with and without detectable ESR1 or PIK3CA alterations (as shown in Figure 3)
- Responses with single-agent GDC-4198 appeared durable, with a median DOR of 8.9 months (range 3-23 months)
- No significant impact of food was observed on GDC-4198 PK; the point estimates for both $C_{max}R$ and $AUCR_{0\text{-}24h}$ exposures (fed/fasted) were observed to be 1.10 and 1.12 respectively (Table 3)

Table 3. Food Effect on PK Parameters

Analyte	Food Condition	n	T_{max} (hr)	C_{max} (ng/mL)	$C_{max}R$ (fed/fasted)	$AUC_{0\text{-}24h}$ (ng*hr/mL)	$AUCR_{0\text{-}24h}$ (fed/fasted)
			Median (range)	Geomean (geo %CV)	Geomean (90%CI)	Geomean (geo %CV)	Geomean (90%CI)
GDC-4198	Fed	6	6 (4, 8)	86.04 (83.4%)	1.10 (0.88, 1.38)	1150 (79.2%)	1.12 (0.85, 1.49)
	Fasted	6	5 (2, 6)	77.5 (83.4%)		1019 (67.8%)	

CONCLUSIONS

- GDC-4198, with potent and selective activity against CDK4 and CDK2, was well-tolerated both as a single agent and in combination with ET
- GDC-4198 monotherapy has demonstrated preliminary evidence of disease control in a post-CDK4/6i setting with sustained responses in a heavily pre-treated patient population
- Based on the preliminary FE results, no significant impact of food was observed on GDC-4198 PK
- Further dose escalation with GDC-4198 as a single agent is ongoing
- Evaluation of GDC-4198 with giredestrant in a phase 1b/2 study has been initiated (NCT07100106)

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