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First-in-human Phase 1A study of RGT-419B, a next generation CDK4 inhibitor, in patients (pts) with HR+/HER2- ABC who progressed on prior CDK4/6 inhibitors

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Conclusions

- In phase 1A single agent dose escalation study, RGT-419B was safe, well-tolerated and demonstrated encouraging single agent efficacy in the heavily pretreated HR+/HER2- ABC pts who had progressed on CDK4/6is and ET.
- The PK of RGT-419B was dose proportional with long half-life and low C_{max} to C_{trough} ratio.
- RGT-419B demonstrated single agent activity in CDK4/6i resistant breast cancer models, providing preclinical data support for the emerging single agent clinical efficacy.
- The current data on RGT-419B monotherapy dose-escalation support further evaluation of RGT-419B as a single agent, as well as in combination therapy with ET in HR+/HER2- ABC pts who have progressed on the CDK4/6is +ET. Further evaluation is underway.

References
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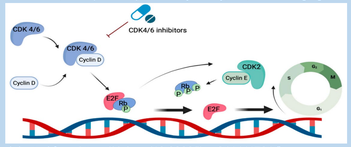
Background

- Breast cancer (BC) is the most common cancer worldwide, and approximately 70% of BCs are hormone receptor positive (HR+), and human epithelial growth factor receptor 2 negative (HER2-). [1,2]
- Cyclin-dependent kinases 4/6 inhibitors (CDK4/6is) suppress cell cycle progression in estrogen receptor positive (ER+) BC cells (**Figure 1**). [3] CDK4/6is plus endocrine therapy (ET) is the standard of care for first-line treatment of HR+/HER2- advanced BC (ABC). [4] However, both intrinsic and acquired resistance to CDK4/6is are common and there is a large unmet need. [3]
- RGT-419B is a novel next generation CDK4+ inhibitor (**Table 1**). It has robust potency against CDK4 plus significant activity against CDK2 and high selectivity over CDK6 to improve efficacy, overcome resistance and reduce toxicity. Preclinical work demonstrated that RGT-419B fully suppressed the proliferation of ER+ BC cells that were resistant to the approved CDK4/6is, and the activity was further augmented when administered in combination with ET and inhibitors of the phosphoinositide 3-kinase (PI3K) signaling pathway.[5]
- This is a Phase 1, first-in-human (FIH), open-label, multicenter, dose-escalation study to evaluate the safety, tolerability, pharmacokinetic (PK) profile, and preliminary efficacy of RGT-419B administered orally in pts with HR+/HER2- ABC (NCT05304962). Herein, we report the preliminary safety, PK, and emerging efficacy data from this study.



Adapted from https://doi.org/10.3390/ijms241411791 [6]

Figure 1. Cell cycle regulation and resistant mechanisms

Table 1. K_i values of RGT-419B against CDKs

Biochemical Ki (nM)	CDK4	CDK6	CDK2
RGT-419B	0.3	7.1	4.6

RGT-419B is a selective CDK4 inhibitor with significant activity against CDK2 and high selectivity over CDK6.

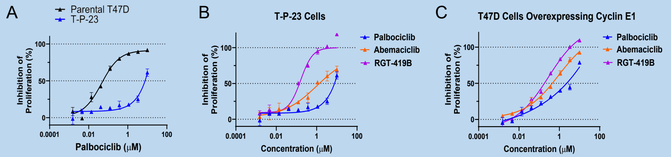
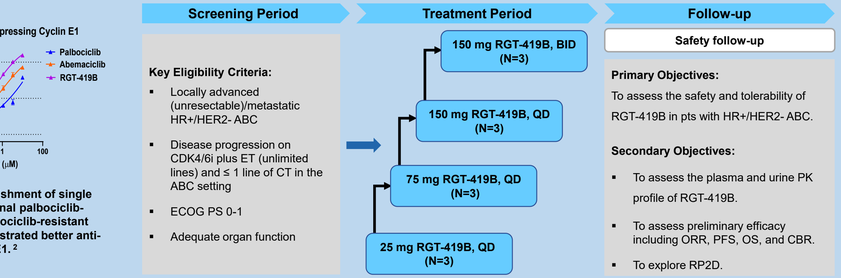


Figure 2. RGT-419B suppressed the proliferation of CDK4/6 inhibitor-resistant T47D cells. (A) Establishment of single clonal T47D cells resistant to palbociclib (T-P-23). Single-cell clone T-P-23 was isolated from polyclonal palbociclib-resistant T47D cells. (B) RGT-419B potently suppressed the proliferation of single clonal T-P-23 palbociclib-resistant T47D cells. Abemaciclib did not fully suppress the proliferation of T-P-23 cells. (C) RGT-419B demonstrated better anti-proliferation activity than either abemaciclib or palbociclib in the T47D cells overexpressing cyclin E1. [2]

Study Design

- The study consists two arms, Arm A (RGT-419B monotherapy) and Arm B (doublet therapy of RGT-419B+ET). Each Arm is to advance in a 3+3 design.
- The study population is patients with HR+/HER2- ABC progressed on CDK4/6i treatment plus ET.
- As of the data cutoff (September 26, 2023), 4 dose levels in Arm A were evaluated as shown in **Figure 3**.
- Arm B is now open for recruitment.



Abbreviations: BID, twice daily; QD, once daily; ECOG, Eastern Cooperative Oncology Group; HER2-, human epithelial growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, objective response rate; PS, performance status; PFS, progression free survival; OS, overall survival; CBR, clinical benefit rate; RP2D, recommended Phase 2 dose; CT, chemotherapy.

Figure 3. Schematic study design for RGT-419B monotherapy

Results

Demographics and Baseline Characteristics

- At the data cut-off (September 26, 2023), 12 pts were enrolled in 4 dose-escalation cohorts, 3 into each dose level.
- All pts were female with a median age of 63.5 (50-80) years.
- The pts were heavily pretreated with median of 3.5 (range: 2-9) prior lines of treatment. All pts received prior treatments of both CDK4/6i +ET, 7 (58%) pts had received prior chemotherapy. Eight (67%) pts had visceral metastases (**Table 2**).

Table 2. Baseline demographics and characteristics

	Total (N=12)
Age, median (range)	63.5 (50-80)
Female, n (%)	12 (100)
ECOG PS, n (%)	
0/1	7 (58)/5 (42)
Race, n (%)	
White	11 (92)
Black or African American	1 (8)
Visceral metastases, n (%)	8 (67%)
Prior Lines of Treatment, median (range)	3.5 (2-9)
Prior Treatment Type, n (%)	
CDK 4/6 inhibitors#	12 (100)
Endocrine Therapy	12 (100)
AI	11 (92)
SERD	8 (67)
Chemotherapy	7 (58)
Others*	3 (25)

#Include palbociclib, abemaciclib, and ribociclib.
*Others including PI3K inhibitors and mTOR inhibitors.
Abbreviations: AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6; ECOG, Eastern Cooperative Oncology Group; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; PS, performance status; SERD, selective estrogen receptor degrader.

Safety

- As of cut-off date, no dose limiting toxicities (DLTs) were observed and the maximum tolerated dose (MTD) has not been identified.
- Treatment emergent adverse events (TEAEs) in ≥3 pts are presented in **Table 3**.
- Treatment-related adverse events (TRAEs) were reported in 10 pts, with the most reported (≥3 pts) being white blood cell count decreased, nausea, and diarrhea. No G3 or above TRAEs reported.
- No serious TRAEs were reported. One pt with brain metastasis discontinued the treatment due to vomiting, which was not related to RGT-491B.

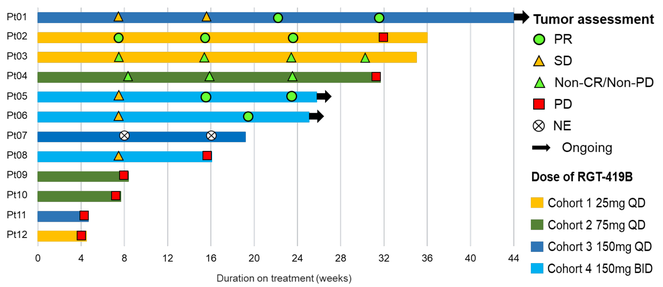
Table 3. TEAEs in ≥3 pts in the full analysis set by PT

	Grade 1	Grade 2	Grade ≥3*	All Grades
Any TEAE	1 (8)	8 (67)	3 (25)	12 (100)
TEAEs in ≥3 pts, n (%)				
White blood cell count decreased	3 (25)	4 (33)	0	7 (58)
Nausea	2 (17)	4 (33)	0	6 (50)
Diarrhoea	4 (33)	0	0	4 (33)
Hyperglycaemia	3 (25)	0	1 (8)	4 (33)
Vomiting	2 (17)	0	1 (8)	3 (25)
Fatigue	0	2 (17)	1 (8)	3 (25)
Blood creatinine increased	3 (25)	0	0	3 (25)
Glomerular filtration rate decreased	0	3 (25)	0	3 (25)
Neutrophil count decreased	2 (17)	1 (8)	0	3 (25)
Hypophosphataemia	1 (8)	2 (17)	0	3 (25)
Back pain	2 (17)	1 (8)	0	3 (25)
Headache	2 (17)	1 (8)	0	3 (25)

*One pt reported Grade 4 hypertension and hyponatraemia, and no pt reported Grade 5 TEAE.
Abbreviations: PT, preferred term; TEAE, treatment emergent adverse event.

Efficacy

- At the data cut-off (September 26, 2023), 6 pts received treatment > 24 weeks. Three (3) pts (1 in 150 mg QD and 2 in 150 mg BID cohorts) achieved partial responses (2 confirmed and 1 unconfirmed) and are still on treatment.

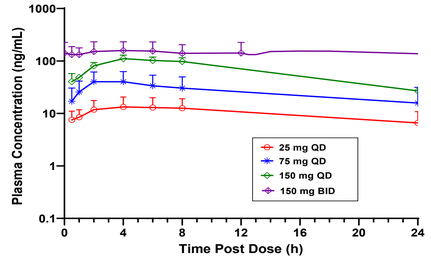


Abbreviations: BID, twice daily; CR, complete response; NE, not evaluable; QD, once daily; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 5. Time on treatment and response for all pts

Pharmacokinetics

- RGT-419B exposure increased in a dose proportional manner from 25 to 150 mg QD and to 150 mg BID at steady state.
- Six (6) pts in the 150 mg QD and 150 mg BID cohorts achieved coverage at least 1-fold above target coverage.
- Small peak to trough ratio further adds to favorable safety profile.
- Long half-life and large volume distribution.

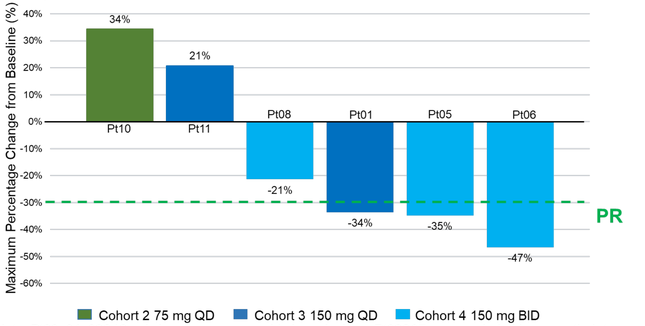


Abbreviations: BID, twice daily; QD, once daily; pRb, retinoblastoma protein; SD, standard deviation.

Figure 4. RGT-419B mean (±SD) plasma concentration time profile at Cycle-1 Day-14

Tumor Assessment

- Among 6* evaluable pts for efficacy analysis set below, 3 pts achieved partial response (PR), 1 pt achieved stable disease (SD), and 2 pts progression disease (PD). In the 150 mg BID cohort, all 3 pts had tumor size reduction.



*Note: Pt03, 04, 09&12 only have non-measurable bone lesions. Pt02&07 were excluded because their tumor assessments were measured by PET scan.
Abbreviations: BID, twice daily; CT, computed tomography; PET, positron emission tomography; QD, once daily.

Figure 6. Monotherapy efficacy in evaluable pts

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Disclosures
Dave Valacer is a former employee of Regor Pharmaceuticals, Inc. **Lili Yao, Jing Lin, Dawn Begley, Feifei Sun, Andie Zheng, Jing Han**, and **Julie Xie** report employment from Regor Therapeutics Group.