Cyclin-dependent kinase 7 (CDK7) inhibitor samuraciclib combined with selective estrogen receptor degrader (SERD) elacestrant in advanced HR+ breast cancer after CDK4/6i: dose escalation data from the Phase 1b/2 SUMIT-ELA study

Francois-Clement Bidard,[1] Maxime Brunet,[2] Amita Patnaik,[3] Cécile Vicier,[4] Raquel Gomez,[5] Sacha Howell,[6] Luisa Sanchez,[7] Erin Roesch,[8] Mario Campone,[9] Agostina Stradella,[10] Simon Lord,[11] Carlos Garay,[12] Paolo Mazzei,[13] Glen Clack,[14] Stuart McIntosh,[14] William Gradishar[15]

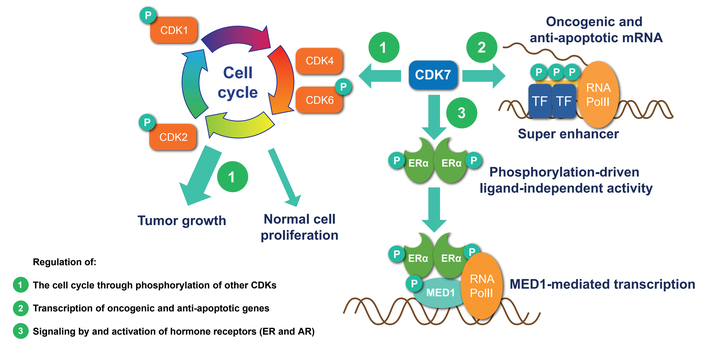
1. Institut Curie, Paris & Saint Cloud, France; 2. Institut Bergonié, Bordeaux, France; 3. START San Antonio, San Antonio, TX, USA; 4. Institut Paoli-Calmettes, Marseille, France; 5. Hospital Clínic de Barcelona Institute of Cancer and Blood Diseases, Barcelona, Spain; 6. The Christie NHS Foundation Trust, Manchester, UK; 7. Clínica Universidad de Navarra, Madrid, Spain; 8. Cleveland Clinic, Cleveland, OH, USA; 9. Institut de Cancérologie de l'Ouest (ICO) – René Gauducheau, Saint Herblain, France; 10. Institut Catala d'Oncologia Hospitalet, Barcelona, Spain; 11. University of Oxford, Churchill Hospital, Oxford, UK; 12. Menarini Group, New York, NY, USA; 13. Menarini Group, Florence, Italy; 14. Carrick Therapeutics, Dublin, Ireland; 15. Department of Medicine, Division of Hematology and Oncology, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA

Key findings

- **The CDK7 inhibitor samuraciclib 360 mg QD combined with the SERD elacestrant 400 mg QD was declared to be the Recommended Phase 2 Dose based on data from Phase 1b dose-escalation**
- **The safety profile of the combination of samuraciclib and elacestrant was manageable, with the most frequent treatment-related AEs being similar to the known safety profiles of samuraciclib and elacestrant from previous studies**
- **Co-dosing of samuraciclib and elacestrant had no significant impact on the PK profile of either agent**
- **The combination produced preliminary signs of antitumor activity**
- **The Phase 2 dose expansion cohort is currently ongoing**

Introduction

Figure 1. Role of CDK7 in cell cycle regulation and transcription and effects of CDK7 inhibition

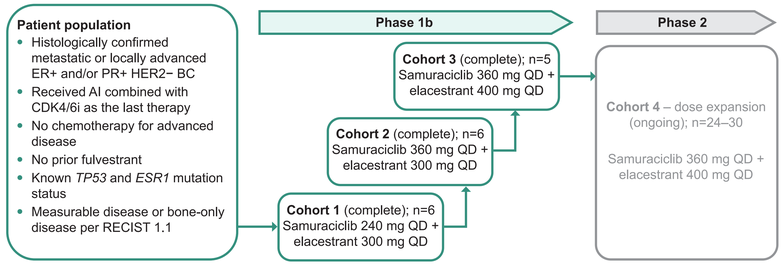


- ET + CDK4/6i is the mainstay of first-line therapy for the management of ER+/HER2− mBC.[1–3] However, most patients with mBC develop resistance to ET + CDK4/6i, a challenge that can potentially be overcome by a new class of oral SERDs[3]
- Due to the heterogeneous nature of the disease, resistance mechanisms include intrinsic alterations, e.g. in the PI3K/AKT/mTOR or cell cycle pathways, and acquired alterations such as *ESR1* mutations, which emerge in 30–40% of patients after initial ET in the metastatic setting[3]
- In the Phase 3 EMERALD trial, single-agent elacestrant significantly prolonged median PFS with a manageable safety profile vs SOC ET in women with ER+/HER2− advanced BC previously treated with a CDK4/6i, particularly those with *ESR1*-mutant tumors[4]
  - Patients with *ESR1*-mutated tumors had a 45% reduction in risk of progression or death with elacestrant vs SOC ET (HR=0.55; 95% CI: 0.39–0.77; p=0.0005)[4]
  - Among these patients, those who had received ≥12 months of prior ET + CDK4/6i had median PFS with elacestrant of 8.6 vs 1.9 months with SOC (HR=0.41; 95% CI: 0.26–0.63)[5]
- Samuraciclib (CT7001) is a small molecule, ATP-competitive, selective oral inhibitor of CDK7 that potently inhibits all key biological effects of CDK7 in cancer cells (**Figure 1**),[6] and has demonstrated a favorable safety profile and clinical activity in combination with fulvestrant in patients with HR+/HER2− advanced BC previously treated with a CDK4/6i[7]
  - Benefit appeared to be greater in patients without *TP53* mutations detectable in ctDNA at baseline
- The rationale for combining elacestrant with samuraciclib is to overcome different resistance mechanisms
- The open-label Phase 1b dose-escalation and Phase 2 dose-expansion SUMIT-ELA trial (NCT05963997) is evaluating the safety, PK, and antitumor activity of samuraciclib combined with elacestrant in patients with advanced HR+/HER2− BC. Here, we report dose-escalation results from Phase 1b

Study design and methods

- Patients with histologically confirmed metastatic or locally advanced ER+ and/or PR+, HER2− BC not amenable to resection or radiation therapy with curative intent who have received an AI combined with a CDK4/6i as the last therapy are eligible[8]
  - Tumor *ESR1* and *TP53* status are determined before enrollment utilizing the Guardant360 ctDNA profile
- The Phase 1b part follows a rolling 6-dose escalation design (**Figure 2**).[8] The Phase 2 part is a dose-expansion study
- Protocol-defined DLTs are evaluated during the first cycle (28 days) of treatment
- Tumors are evaluated at baseline, every 8 weeks until week 48, and every 12 weeks thereafter; response is evaluated using RECIST v1.1

Figure 2. Phase 1b/2 dose escalation and expansion trial design



Primary objective (Phase 1b): RP2D of samuraciclib + elacestrant
Secondary objectives (Phase 1b):
- Safety and tolerability of samuraciclib + elacestrant
- PK of samuraciclib + elacestrant and explore any potential drug–drug interactions
- Antitumor activity of samuraciclib + elacestrant
- Correlations between tumor *ESR1* and *TP53* mutations and efficacy/safety findings

Dose escalation results

Patient and disease characteristics

- From October 9, 2023 to April 29, 2024, 17 women with advanced HR+, HER2− BC were recruited and treated with samuraciclib + elacestrant
- Baseline patient and disease characteristics are shown in **Table 1**

Table 1. Baseline patient and disease characteristics

Characteristic	Samuraciclib 240 mg QD + elacestrant 300 mg QD (n=6)	Samuraciclib 360 mg QD + elacestrant 300 mg QD (n=6)	Samuraciclib 360 mg QD + elacestrant 400 mg QD (n=5)	Total (n=17)
Median age, years (range)	52 (43–75)	60 (41–66)	54 (44–59)	55 (41–75)
Female, n (%)	6 (100)	6 (100)	5 (100)	17 (100)
ECOG PS 0/1, n (%)	5 (83)/1 (17)	4 (67)/2 (33)	3 (60)/2 (40)	12 (71)/5 (29)
HR status, n (%)				
ER+	6 (100)	6 (100)	5 (100)	17 (100)
PR+	4 (67)	6 (100)	3 (60)	13 (76)
Location of metastases, n (%)*				
Lung	1 (17)	1 (17)	1 (20)	3 (18)
Liver	2 (33)	3 (50)	2 (40)	7 (41)
Bone only	1 (17)	1 (17)	0	2 (12)
Prior CDK4/6i therapy for mBC, n (%)	6 (100)	6 (100)	5 (100)	17 (100)
Duration of prior ET + CDK4/6i, n (%)				
≤12 months	2 (33)	1 (17)	1 (20)	4 (24)
>12 months	4 (67)	5 (83)	4 (80)	13 (77)
Best response to prior ET + CDK4/6, n (%)				
CR	1 (17)	2 (33)	0	3 (18)
PR	0	2 (33)	2 (40)	4 (24)
SD	3 (50)	1 (17)	3 (60)	7 (41)
PD/NE	2 (33)	1 (17)	0	3 (18)
TP53 mutation detected, n (%)	3 (50)	2 (33)	1 (20)	6 (35)
PIK3CA mutation detected, n (%)	2 (33)	3 (50)	3 (60)	8 (47)
ESR1 mutation detected, n (%)	2 (33)	2 (33)	2 (40)	6 (35)

*Only those sites of metastasis most associated with patient prognosis are included; no patients had brain metastases at baseline.

Safety

- 12 patients remained on treatment until PD
- The most frequent all-grade treatment-related AEs were diarrhea, nausea, vomiting, asthenia, and dysgeusia (**Table 2**)
  - Grade 3 treatment-related AEs were infrequent: one grade 3 diarrhea (leading to treatment discontinuation) and one grade 3 nausea. No grade 4 treatment-related AEs were reported
- One DLT was observed: diarrhea (n=1, samuraciclib 360 mg QD + elacestrant 300 mg QD)

Table 2. Treatment-related AEs occurring in at least two patients overall

AE, n (%)	Samuraciclib 240 mg QD + elacestrant 300 mg QD (n=6) Grade 1/2	Grade 3	Samuraciclib 360 mg QD + elacestrant 300 mg QD (n=6) Grade 1/2	Grade 3	Samuraciclib 360 mg QD + elacestrant 400 mg QD (n=5) Grade 1/2	Grade 3	Total (n=17) Grade 1/2	Grade 3
Diarrhea	5 (83)	0	5 (83)	1 (17)	5 (100)	0	**15 (88)**	**1 (6)**
Nausea	4 (67)	0	3 (50)	0	4 (80)	1 (20)	**11 (65)**	**1 (6)**
Vomiting	2 (33)	0	3 (50)	0	4 (80)	0	**9 (53)**	**0**
Asthenia	1 (17)	0	1 (17)	0	3 (60)	0	**5 (29)**	**0**
Dysgeusia	2 (33)	0	1 (17)	0	2 (40)	0	**5 (29)**	**0**
Abdominal pain	2 (33)	0	0	0	2 (40)	0	**4 (24)**	**0**
Decreased appetite	0	0	2 (33)	0	2 (40)	0	**4 (24)**	**0**
Epistaxis	1 (17)	0	1 (17)	0	1 (20)	0	**3 (18)**	**0**
Thrombocytopenia	0	0	1 (17)	0	2 (40)	0	**3 (18)**	**0**
Alopecia	1 (17)	0	0	0	1 (20)	0	**2 (12)**	**0**
Anemia	0	0	1 (17)	0	1 (20)	0	**2 (12)**	**0**
Dehydration	1 (17)	0	1 (17)	0	0	0	**2 (12)**	**0**
Dry skin	2 (33)	0	0	0	0	0	**2 (12)**	**0**
Dyspepsia	2 (33)	0	0	0	0	0	**2 (12)**	**0**
Stomatitis	0	0	1 (17)	0	1 (20)	0	**2 (12)**	**0**
Weight decreased	0	0	1 (17)	0	1 (20)	0	**2 (12)**	**0**

Efficacy

- A 53-year-old woman with *TP53*wt, *ESR1*wt mBC with liver metastases who received samuraciclib 240 mg QD + elacestrant 300 mg QD experienced a confirmed PR, with a 37% reduction in the size of target lesions (**Figure 3**)
- Longer-term efficacy data, including data for the expansion cohort, will be presented at a future meeting

Pharmacokinetics

- Samuraciclib exposure appeared more variable than observed previously for monotherapy; therefore, average exposure was similar, but the range of individual exposures was greater (**Figure 4A**)
- After single and repeated doses, elacestrant observed concentrations and PK parameters when co-dosed with samuraciclib are within the range of the population PK model-predicted concentrations for elacestrant administered as a single agent (**Figure 4B**)
- Elacestrant is a sensitive substrate of CYP3A4 (>5-fold increase with itraconazole); therefore, the data indicate that samuraciclib is not a clinical inhibitor of CYP3A4 at the RP2D

Figure 3. Imaging results for a woman with *TP53*wt, *ESR1*wt mBC with liver metastasis who had a confirmed PR

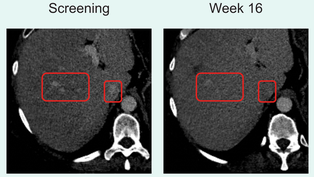
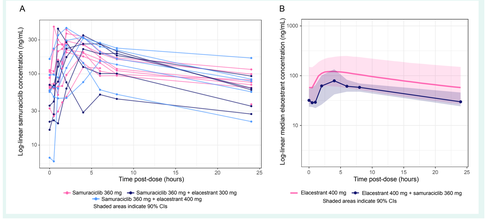


Figure 4. Plasma concentrations of A) samuraciclib and B) elacestrant at cycle 2, day 1 when administered in combination and compared with historical monotherapy data



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Abbreviations

AE, adverse event; **AI**, aromatase inhibitor; **AR**, androgen receptor; **ATP**, adenosine triphosphate; **BC**, breast cancer; **CDK**, cyclin-dependent kinase; **CDK4/6i**, CDK4/6 inhibitor; **CI**, confidence interval; **CR**, complete response; **ctDNA**, circulating tumor DNA; **DLT**, dose-limiting toxicity; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ER**, estrogen receptor; **ERS1**, estrogen receptor alpha encoding gene; **ET**, endocrine therapy; **HER2**, human epidermal growth factor receptor 2; **HR**, hormone receptor *or* hazard ratio; **mBC**, metastatic breast cancer; **NE**, not evaluable; **PD**, disease progression; **PK**, pharmacokinetics; **PFS**, progression-free survival; **PR**, progesterone receptor *or* partial response; **QD**, once daily; **RECIST**, Response Evaluation Criteria In Solid Tumors; **RP2D**, Recommended Phase 2 Dose; **SD**, stable disease; **SERD**, selective estrogen receptor degrader; **SOC**, standard of care; **wt**, wild type

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Disclosures

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Further information: hello@carricktherapeutics.com; https://clinicaltrials.gov/study/NCT05963997