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SUMIT-ELA: Phase 1b/2 combination of cyclin-dependent kinase 7 inhibitor samuraciclib and selective estrogen receptor degrader elacestrant in advanced hormone receptor positive breast cancer after CDK4/6 inhibitor

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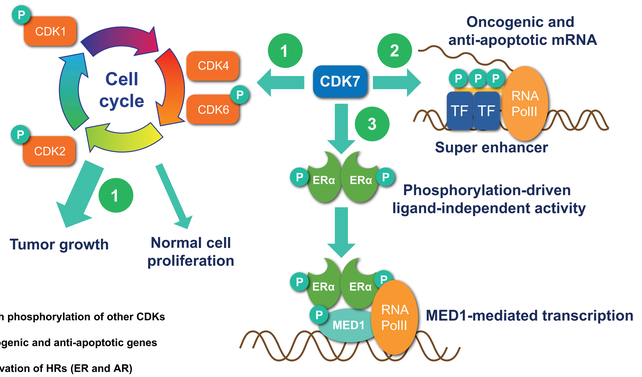
Summary

- **The phase 1b/2 SUMIT-ELA trial (NCT05963997) is designed to characterize the safety, tolerability, and PK, to determine the RP2D, and to assess the antitumor activity of samuraciclib in combination with elacestrant in patients with advanced HR+/HER2− BC who have received prior CDK4/6 inhibitor therapy**
- **Samuraciclib is a CDK7 inhibitor that has demonstrated clinical activity combined with the SERD fulvestrant in patients with HR+ advanced BC after a CDK4/6 inhibitor[1]**
- **Elacestrant demonstrated clinical efficacy in patients with ER+, HER2− advanced or metastatic BC previously exposed to CDK4/6 inhibitors,[2] leading to FDA/EMA approval in patients with ER+, HER2−, *ESR1*-mutant advanced or metastatic BC previously exposed to CDK4/6 inhibitors**
- **SUMIT-ELA is currently recruiting. Sites in the USA, France, Spain, and UK will participate**

Introduction

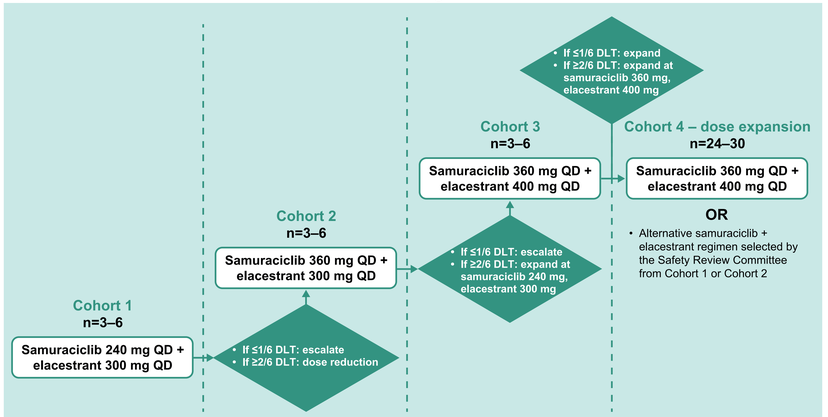
Figure 1. Role of CDK7 in cell cycle regulation and transcription and effects of CDK7 inhibition



- HR+/HER2− BC is the most common BC subtype, with an age-adjusted annual incidence rate of 87.2 new cases per 100,000 women and representing approximately 70% of all female BCs[3]
- A CDK4/6 inhibitor combined with an AI or the SERD fulvestrant is a standard option for patients with HR+ metastatic BC[4]
- Patients with HR+ metastatic BC progressing after combined CDK4/6 inhibitor and endocrine therapy have limited further endocrine therapy options, and cytotoxic chemotherapy is frequently required to obtain disease control[6]
- CDK7 is a key kinase that regulates cell division, transcription, and nuclear receptor function; its inhibition is therefore a promising novel anticancer therapeutic strategy (**Figure 1**)[7]
- 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[7]
- Samuraciclib demonstrated a favorable safety profile and clinical activity in combination with fulvestrant in patients with HR+/HER2− advanced BC previously treated with a CDK4/6 inhibitor[1]
  - Benefit appeared to be greater in patients without *TP53* mutations detectable in ctDNA at baseline
- Limitations to the PK properties and administration route of fulvestrant (intramuscular only) mean that examining oral alternatives in combination with samuraciclib is warranted[8]
- The oral SERD elacestrant demonstrated a significant PFS benefit over standard-of-care endocrine treatment in women with ER+/HER2− advanced BC previously treated with a CDK4/6 inhibitor, particularly those with *ESR1*-mutant tumors[2]
  - Non-clinical data indicate that the underlying biology driving the activity of samuraciclib in combination with endocrine therapy translates from fulvestrant to elacestrant[9]
- Therefore, this open-label phase 1b dose escalation and phase 2 dose expansion trial (SUMIT-ELA; NCT05963997) is evaluating the safety, antitumor activity, and PK of samuraciclib combined with elacestrant in participants with advanced HR+/HER2− BC

Study design and methods

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



- Prior to enrollment, tumor *ESR1* and *TP53* status will be determined utilizing the Guardant360 ctDNA profile
- The phase 1b part follows a rolling 6 dose escalation design (**Figure 2**).[10] The phase 2 part will be a dose-expansion study
- 24-hour intensive blood sampling for PK analysis will be conducted at cycles 1 and 2, days 1 and 2. ctDNA samples will be taken pre-dose on day 1 of cycles 1, 2, and 3
- AEs will be classified using the MedDRA classification system and their severity will be graded using NCI CTCAE v5.0
- Protocol-defined DLTs will be evaluated during the first cycle (28 days) of treatment
- Tumors will be evaluated at baseline, every 8 weeks until week 48, and every 12 weeks thereafter; response will be evaluated using RECIST v1.1

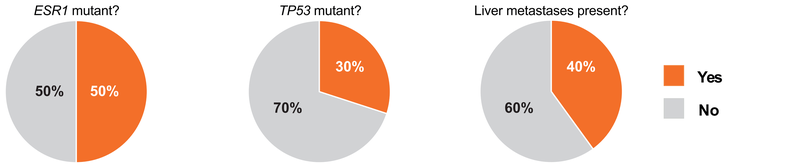
Eligibility

Table 1. Key eligibility criteria

Key inclusion criteria	
≥18 years of age	RECIST version 1.1 evaluable disease (measurable disease or bone-only disease with evaluable lesions)
Histologically confirmed carcinoma of the breast with evidence of metastatic or locally advanced disease, not amenable to resection or radiation therapy with curative intent	Documented objective disease progression while on or within 6 months after the end of the most recent therapy
Documentation of ER-positivity ± PgR-positivity (defined as ≥10% positive cells) and HER2 negativity (IHC 0/1+, FISH/CISH/SISH HER2/CEP17 ratio <2 or HER2 copy number <4) based on local testing	Must have received an AI in combination with a CDK4/6 inhibitor with ≥6 months of clinical benefit in the metastatic setting, or with >24 months disease-free interval in the adjuvant setting
ECOG performance status of 0 or 1 with no deterioration over previous 2 weeks	ECOG performance status ≤1
Key exclusion criteria	
Prior therapy with a SERD or other investigational SERDs or alike agents in the advanced/metastatic setting	Non-biological anticancer medicines within 28 days or ≤5 half-lives, or biological anticancer medicines within 42 days before the first study dose
>1 line of endocrine treatment or prior treatment with cytotoxic chemotherapy for locally advanced or metastatic disease	Inadequate hepatic, renal, bone marrow, or cardiac function, uncontrolled diabetes, or organ transplant
Prior treatment with an mTOR inhibitor	Known CNS metastases, carcinomatous meningitis, or leptomeningeal disease
Prior treatment with cytotoxic chemotherapy for locally advanced or metastatic BC	Active infection requiring systemic antibiotic, antifungal, or antiviral medication within 14 days prior to allocation
Unresolved toxicity (except alopecia) from prior therapy of Grade ≥2 according to NCI CTCAE version 5.0	Concomitant medication, herbal supplement, or food that is a strong or moderate inhibitor or inducer of CYP3A4, CYP2C19, or CYP2D6, or a strong inhibitor of P-glycoprotein activity within 21 days before the first study dose or within 5 half-lives
Inflammatory breast cancer	Major surgery within 28 days before the first study dose

- Samuraciclib and elacestrant may have greater activity in patients with tumors that are *TP53* wild-type and/or harbor *ESR1* mutations, respectively. Furthermore, the PFS of patients with liver metastases of BC has been reported to be significantly lower than that of patients without liver involvement when treated with fulvestrant[11]
- To balance the study population, enrollment of patients with *ESR1* mutant and *TP53* mutant disease and with liver metastases may be limited to the approximate proportions shown in **Figure 3**

Figure 3. Limits to enrollment based on predefined tumor characteristics



Objectives and endpoints

Table 2. Objectives and endpoints

Objectives	Endpoints
Primary	
Phase 1b: to determine the RP2D of samuraciclib and elacestrant in combination	DLTs and type, incidence, severity (as graded by CTCAE v5.0), seriousness, and relationship to study medications of AEs and laboratory abnormalities
Phase 2: to assess the efficacy of samuraciclib and elacestrant in combination	PFS, defined as the time from enrollment until disease progression or death
Secondary	
To characterize the safety and tolerability of samuraciclib and elacestrant in combination	Type, incidence, severity (as graded by CTCAE v5.0), seriousness, and relationship to study medications of AEs and laboratory abnormalities
To evaluate the PK of samuraciclib and elacestrant in combination and explore any potential drug-drug interactions	Plasma concentrations and PK parameters of samuraciclib and elacestrant
To further assess the biological and antitumor activity of samuraciclib and elacestrant in combination	CBR, ORR, DOR, and best percentage change in tumor size
To evaluate correlations between tumor *ESR1* and *TP53* mutations and efficacy/safety findings in this participant population	Correlations between tumor *ESR1* and *TP53* mutations and efficacy/safety findings
Exploratory	
To evaluate correlations between samuraciclib and elacestrant exposures and efficacy/safety findings	Correlations between samuraciclib and elacestrant exposures and efficacy/safety findings. Type, incidence, severity (as graded by CTCAE v5.0), seriousness, and relationship to study medications of gastrointestinal events
To evaluate correlations between the presence of liver metastases and efficacy/safety findings	Correlations between presence or absence of liver metastases and efficacy/safety findings
To further evaluate the impact of participant demographics on the steady-state PK profile of samuraciclib and elacestrant	Effect of participant demographics on trough concentrations of samuraciclib and elacestrant
To provide data for subsequent population PK analysis	
To explore mutations in and expression of genes, proteins, and RNAs relevant to the cell cycle, drug target engagement, and tumor sensitivity and/or resistance, and their potential impact on efficacy	Biomarkers in ctDNA and tumor tissue, including genes, RNA expression, and proteins

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Abbreviations

AE, adverse event; AI, aromatase inhibitor; AR, androgen receptor; ATP, adenosine triphosphate; BC, breast cancer; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; CISH, chromogenic in situ hybridization; CNS, central nervous system; ctDNA, circulating tumor DNA; DLT, dose-limiting toxicity; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, overall response rate; PK, pharmacokinetics; PFS, progression-free survival; PgR, progesterone receptor; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors; RP2D, recommended phase 2 dose; SERD, selective estrogen receptor degrader; SISH, silver-enhanced in situ hybridization; TF, transcription factor

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Disclosures

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Further information: hello@carricktherapeutics.com; info.fortrea.com/General-Inquiry; https://clinicaltrials.gov/study/NCT05963997

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