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SUMIT-BC: Phase 2 randomized study of fulvestrant with or without the cyclin-dependent kinase 7 inhibitor samuraciclib in advanced hormone receptor-positive breast cancer after CDK4/6 inhibitor

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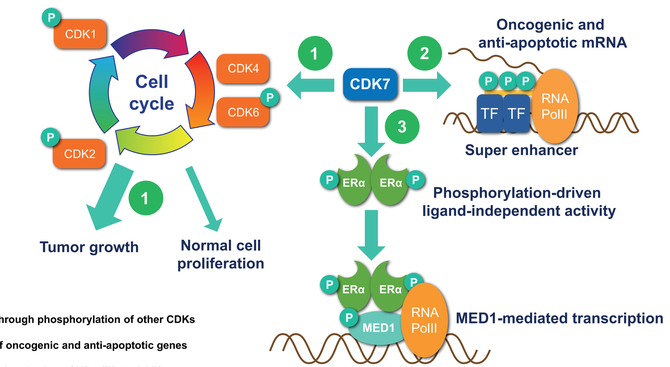
Summary

- **Samuraciclib is a CDK7 inhibitor that has demonstrated clinical activity when combined with fulvestrant in patients with HR+ advanced BC after a CDK4/6 inhibitor[1]**
- **The phase 2 SUMIT-BC trial (NCT05963984) is designed to compare the efficacy, safety, PK, and QoL of samuraciclib in combination with fulvestrant to that of fulvestrant**
- **The trial is currently recruiting. Sites in the USA, Hungary, Mexico, Spain, Turkey, and the UK will participate**

Introduction

- Inhibition of CDK7, a key kinase that regulates cell division, transcription, and nuclear receptor function, represents a novel anticancer strategy due to the critical roles that CDK7 plays in cancer (**Figure 1**)[2]

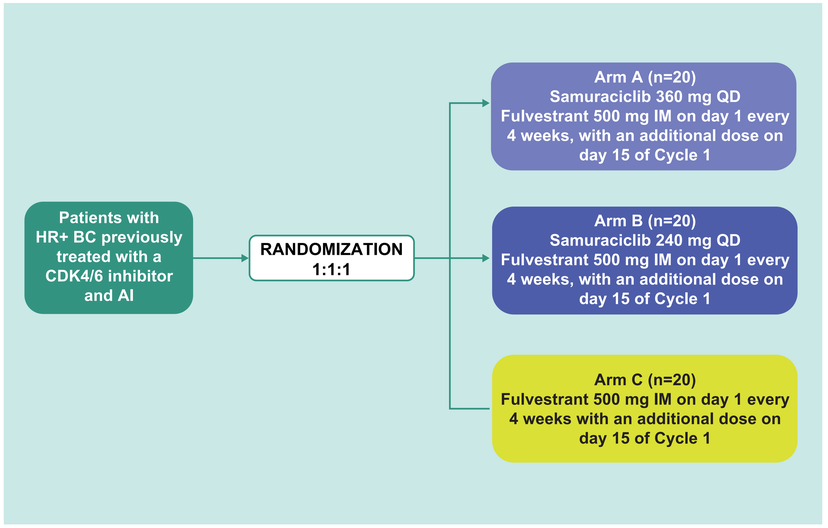
Figure 1. Role of CDK7 in cell cycle regulation and transcription and effects of CDK7 inhibition



- Preclinical data indicate that CDK7 inhibitors are effective in HR+ BC, even after resistance to CDK4/6 inhibitors develops[3]
  - A CDK4/6 inhibitor combined with an AI or the SERD fulvestrant is a standard treatment for patients with HR+ metastatic BC[4,5]
  - Patients with HR+ metastatic BC whose disease progresses after CDK4/6 inhibitor therapy have limited treatment options[6]
- Samuraciclib (CT7001) is a small molecule, ATP competitive, selective oral inhibitor of CDK7 that potently inhibits key biological effects of CDK7 in cancer cells.[2] Samuraciclib selectively targets transcription to limit synthesis of mRNAs involved in tumor growth without inhibiting transcription of housekeeping genes.[7]
- Previous clinical data suggested that the combination of samuraciclib with fulvestrant provides clinically meaningful anticancer activity with a favorable safety profile in patients with HR+/HER2− advanced BC previously treated with CDK4/6 inhibitors[1]
  - Enhanced benefit was observed in patients with tumors with no detectable *TP53* mutations (≈70% of patients; PFS: 7.4 vs 1.8 months with *TP53* mutation, p<0.001; CBR 47.4% vs 0) and without liver metastases at baseline (PFS: 13.8 vs 2.8 months with liver metastases, p<0.003; CBR 54.5% vs 21.4%)
  - Samuraciclib was associated with mainly low-grade GI AEs such as nausea, vomiting, and diarrhea, which can be managed with prophylaxis and patient counseling
- In preparation for larger-scale phase 3 trials, a switch to a scalable tablet formulation from manual-fill instant release capsules is now occurring
- We describe the design of the international, multicenter, randomized, open-label, phase 2 SUMIT-BC (NCT05963984) study of samuraciclib combined with fulvestrant in patients with metastatic or locally advanced HR+ and HER2− BC after prior AI and CDK4/6 inhibitor therapy[8]

Trial design

Figure 2. Study schema



- A total of 60 patients will be randomized in a 1:1:1 ratio to receive fulvestrant alone, fulvestrant + samuraciclib 240 mg QD, or fulvestrant + samuraciclib 360 mg QD (**Figure 2**)
  - An instant release capsule formulation was used in the initial clinical evaluation of samuraciclib, requiring patients to take multiple capsules that release material high in the GI tract; in SUMIT-BC, a novel single tablet formulation will be administered, which may enhance GI tolerability[9]
  - Evaluation of two doses of samuraciclib is consistent with the principles of the FDA Oncology Center of Excellence Project OPTIMUS initiative[10]
- All patients will undergo baseline Guardant360 ctDNA evaluation of *TP53* mutation status to permit a prospective evaluation of its potential as a predictive biomarker
- Patients will be stratified by the presence of *TP53* mutations and/or liver metastases
  - If at any time during the study the number of patients with tumor *TP53* mutations exceeds approximately 30%, no additional patients with *TP53* mutations will be enrolled
  - As patients with liver metastases tend to have poorer prognosis than those without, enrollment may be capped to no more than 40% of participants with liver metastases
- Patients will undergo RECIST v1.1 evaluation of tumors at baseline, every 8 weeks until week 48, then every 12 weeks
- Active collection of AEs will start when informed consent is provided until at least 28 days after final study drug administration
- The PK of samuraciclib and fulvestrant will be studied during the first 6 months of the study
- To evaluate QoL, the FACT-B questionnaire will be completed at screening and on day 1 of all cycles of treatment received
- The end of the study is defined as 48 weeks after the last participant has been enrolled

Eligibility

Table 1. Key eligibility criteria

Key inclusion criteria	Key exclusion criteria
Histologically confirmed BC with evidence of metastatic or locally advanced disease not amenable to resection or radiation therapy with curative intent	Prior treatment with: • A SERD or similar agent in the advanced/metastatic setting • >1 line of endocrine treatment for locally advanced or metastatic disease • Chemotherapy for locally advanced or metastatic disease
Documentation of ER positivity ± PgR positivity and HER2 negativity	Other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix
Known *TP53* mutation status	Inflammatory BC
RECIST version 1.1 measurable disease or bone-only disease, which can be measurable or non-measurable	Any current or prior central nervous system metastases, carcinomatous meningitis, or leptomeningeal disease
Documented objective disease progression while on or ≤6 months after the end of prior AI combined with a CDK4/6 inhibitor	Unresolved toxicity (except alopecia, peripheral neuropathy, arthralgia, or other toxicities not considered a safety risk for the participant per the investigator's judgment) from prior therapy of Grade ≥2 according to NCI CTCAE version 5.0
Received prior AI combined with a CDK4/6 inhibitor: • Locally advanced or metastatic disease: ≥6 months of clinical benefit or <6 months of CDK4/6 inhibitor due to tolerability issues but ≥6 months of AI • Adjuvant: disease-free interval before first-line treatment of locally advanced or metastatic disease of >24 months	Patients with known HBV, HCV, and/or HIV+ infections are allowed as long as they have undetectable viral load
ECOG performance status ≤1	Inadequate hepatic, renal, or bone marrow function
Pre/peri-menopausal participants must have commenced treatment with a LHRH agonist ≥4 weeks prior to first dose of study drug	Clinically significant cardiovascular disease
	Pregnant or breastfeeding

Objectives and endpoints

Table 2. Objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of 2 doses of samuraciclib in combination with fulvestrant	Clinical benefit response (complete response, partial response, or stable disease [≥24 weeks after randomization])
Secondary	
To further characterize the efficacy of samuraciclib in combination with fulvestrant (includes *TP53* correlation)	Progression-free survival; objective response rate; duration of response
To characterize the safety and tolerability of samuraciclib in combination with fulvestrant	AEs and laboratory abnormalities as graded by NCI CTCAE v5.0
To evaluate the PK of samuraciclib and fulvestrant	Samuraciclib: C_{max} and C_{trough}; fulvestrant: C_{trough}
Exploratory	
To compare PROs between treatment arms	FACT-B
To evaluate correlations between samuraciclib and fulvestrant exposures and efficacy/safety	Correlations between samuraciclib and fulvestrant exposures and efficacy/safety findings
To evaluate the impact of patient characteristics (including but not limited to race, ethnicity, and age) on steady-state PK	Effect of participant characteristics on trough concentrations of samuraciclib and fulvestrant
To further explore mutations in and expression of genes, proteins, and RNAs relevant to the cell cycle, drug target engagement, and tumor sensitivity and/or resistance in tumor-derived materials including ctDNA and tumor tissue, and their potential impact on efficacy	Biomarkers in ctDNA and tumor tissue, including but not limited to DNA, RNA expression, and proteins (eg, c-Myc, MCL-1, phosphorylated CDK1 and Rb proteins, TP53, ESR1, CDK7, ER, AR, PIK3CA)

Statistical analysis

- All efficacy analyses will be performed using the full analysis set of all patients who are enrolled and randomized
- All safety analyses will be performed using all patients who are randomized and receive at least one dose of study treatment
- The primary analysis will be performed by 24 weeks after randomization, and final analyses will be performed 48 weeks after randomization

References

1. Coombes RC, et al. Nat Commun 2023;14:4444
2. Patel H, et al. Mol Cancer Ther 2018;17:1156–1166
3. Guarducci C, et al. Cancer Res 2019;79:PD7-12
4. Rugo HS, et al. J Clin Oncol 2016;34:3069–3103
5. Cardoso F, et al. Ann Oncol 2018;29:1634–1657
6. Mittal A, et al. Cancers 2023;15:2015
7. Diab S, et al. J Med Chem 2020;63:7458–7474
8. Clinicaltrials.gov. https://clinicaltrials.gov/study/NCT05963984. Accessed September 13, 2023.
9. Bardia A, et al. J Clin Oncol 2021;39:1360–1370.
10. FDA. https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus. Accessed September 14, 2023

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Abbreviations

AE, adverse event; AI, aromatase inhibitor; AR, androgen receptor; BC, breast cancer; CDK, cyclin-dependent kinase; CDKi, cyclin-dependent kinase inhibitor; CTCAE, Common Terminology Criteria for Adverse Events; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; FACT-B, Functional Assessment of Cancer Therapy-Breast questionnaire; GI, gastrointestinal; HBV, hepatitis virus B; HCV, hepatitis virus C; HER2, human epidermal growth factor receptor 2; HIV, human immunodeficiency virus; HR, hormone receptor; IM, intramuscular; LHRH, luteinizing hormone releasing hormone; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PK, pharmacokinetics; PgR, progesterone receptor; PRO, patient-reported outcome; QD, once daily; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; SERD, selective estrogen receptor degrader

Disclosures

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Further information: hello@carricktherapeutics.com; https://clinicaltrials.gov/study/NCT05963984