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Results of the phase 2 SUMIT-BC study, a randomized controlled phase II trial of the cyclin-dependent kinase 7 inhibitor (CDK7i) samuraciclib with fulvestrant in advanced hormone receptor positive (HR+)/HER2-negative breast cancer after a CDK4/6 inhibitor (CDK4/6i)

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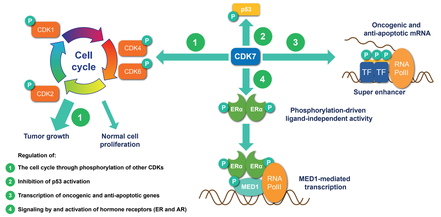
Summary

- **Once-daily samuraciclib combined with fulvestrant demonstrated promising efficacy in ER+/HER2− locally advanced or metastatic breast cancer previously treated with an aromatase inhibitor + CDK4/6 inhibitor**
- **Enhanced efficacy was observed for patients with no tumor *TP53* mutation detected in baseline ctDNA (ORR 55%, median PFS 14.5 months)**
- **This *TP53*-based selection prospectively replicates findings in other samuraciclib + SERD datasets[1]**
- **The tolerability profile of the new tablet formulation permitted long-term once-daily dosing, avoiding neutropenia, rash, stomatitis, and hyperglycemia**
- **These data indicate that a phase 3 trial of samuraciclib with fulvestrant in the 70% of post-CDK4/6 inhibitor patients with no *TP53* mutation is warranted**

Background

- CDK7 regulates cell division, transcription, and nuclear receptor function (**Figure 1**). Its inhibition is a novel anticancer strategy[2]
- 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[3]
- Clinical data indicate that samuraciclib combined with fulvestrant provides clinically meaningful anticancer activity with a favorable safety profile in patients with HR+/HER2− advanced breast cancer previously treated with CDK4/6 inhibitors[4]
- The international, multicenter, randomized, open-label, phase 2 SUMIT-BC (NCT05963984) study compared samuraciclib combined with fulvestrant with fulvestrant alone in metastatic or locally advanced HR+/HER2− breast cancer after prior aromatase inhibitor and CDK4/6 inhibitor therapy[5]

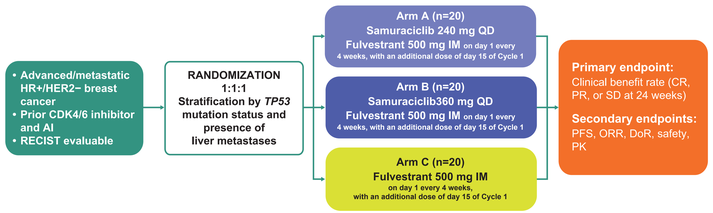
Figure 1. Role of CDK7 in cell cycle regulation and transcription



Trial design

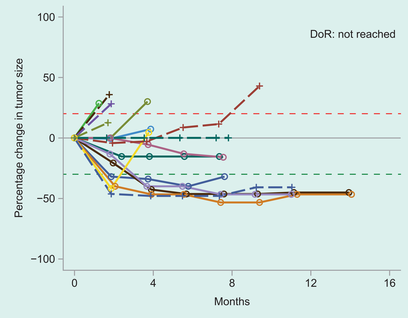
- Patients were randomized 1:1:1 to one of three arms as shown
  - Evaluation of two doses of samuraciclib is consistent with the principles of the FDA Oncology Center of Excellence Project OPTIMUS initiative[6]
- Baseline Guardant360 ctDNA evaluation of *TP53* mutational status was performed in all patients to permit prospective evaluation of its potential as a predictive biomarker
- Tumors were evaluated using RECIST v1.1 at baseline, every 8 weeks until week 48, then every 12 weeks
- Adverse events were monitored until ≥28 days after final study drug administration
- The pharmacokinetics of the novel single-dose tablet formulation of samuraciclib and fulvestrant were assessed

Figure 2. Study design



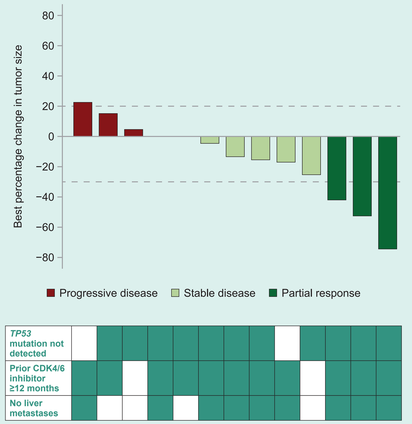
Key findings

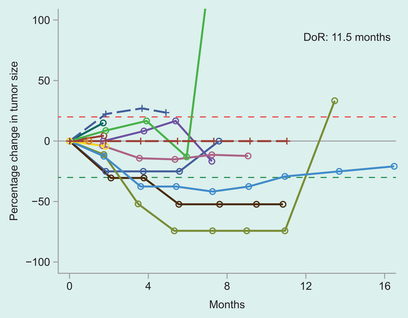
Samuraciclib 360 mg + fulvestrant



	ORR, % (n/N)	CBR, % (n/N)	Median PFS (months)
TP53 mutation not detected	55 (6/11)	69 (9/13)	14.5
TP53 mutation not detected and prior CDK4/6 inhibitor ≥12 months	71 (5/7)	78 (7/9)	14.5
Prior CDK4/6 inhibitor ≥12 months	50 (5/10)	67 (8/12)	8.9
No liver metastases	39 (5/13)	73 (11/15)	8.9
Unselected	33 (6/18)	60 (12/20)	7.8

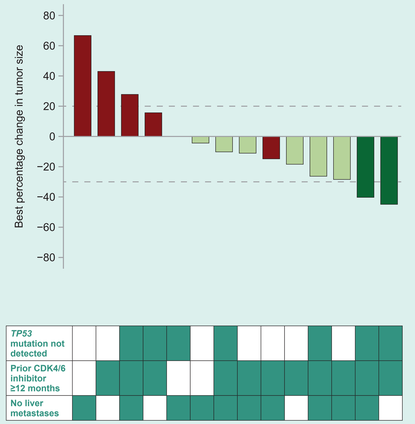
Samuraciclib 240 mg + fulvestrant

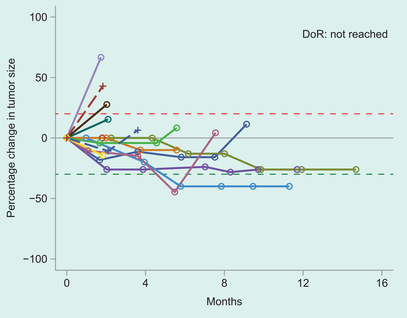




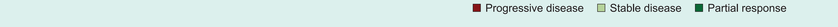
	ORR, % (n/N)	CBR, % (n/N)	Median PFS (months)
TP53 mutation not detected	25 (3/12)	65 (11/17)	9.6
TP53 mutation not detected and prior CDK4/6 inhibitor ≥12 months	33 (3/9)	69 (9/13)	11.7
Prior CDK4/6 inhibitor ≥12 months	27 (3/11)	67 (10/15)	9.6
No liver metastases	30 (3/10)	67 (10/15)	9.6
Unselected	21 (3/14)	63 (12/19)	8.5

Control: fulvestrant





	ORR, % (n/N)	CBR, % (n/N)	Median PFS (months)
TP53 mutation not detected	29 (2/7)	46 (5/11)	6.8
TP53 mutation not detected and prior CDK4/6 inhibitor ≥12 months	33 (2/6)	50 (5/10)	6.8
Prior CDK4/6 inhibitor ≥12 months	18 (2/11)	47 (8/17)	6.0
No liver metastases	10 (1/10)	38 (6/16)	5.6
Unselected	14 (2/14)	40 (8/20)	5.6



Subgroups shown are those including meaningful numbers of patients. **ORR**: overall response rate in RECIST v1.1 measurable disease population; **CBR**: clinical benefit rate RECISTv1.1 (CR, PR or SD ≥ 24 weeks in intent to treat population); **PFS**: progression-free survival in intent to treat population.

Patient and disease characteristics

		SAM 360+F (N=20)		SAM 240+F (N=19)		F (N=20)	
Age, median (range)		61.5	(29–70)	56.0	(40–72)	59.0	(36–76)
Age ≥65 years, n (%)		5	(25.0)	4	(21.1)	7	(35.0)
Weight, median (range)		75.5	(52–121)	70.0	(44–93)	68.1	(47–99)
ECOG performance status 1, n (%)		8	(40.0)	9	(47.4)	5	(25.0)
TP53 mutation not detected, n (%)		13	(65.0)	17	(89.5)	11	(55.0)
No liver metastases, n (%)		15	(75.0)	15	(78.9)	16	(80.0)
Measurable disease at baseline, n (%)		18	(90.0)	14	(73.7)	14	(70.0)
Post menopausal, n (%)		15	(75.0)	14	(73.7)	17	(85.0)
Duration of prior CDK4/6 inhibitor ≥12 months, n (%)		12	(60.0)	15	(78.9)	17	(85.0)
Type of prior CDK4/6 inhibitor for advanced disease, n (%)	Abemaciclib	1	(5.0)	1	(5.3)	3	(15.0)
	Palbociclib	9	(45.0)	10	(52.6)	8	(40.0)
	Ribociclib	11	(55.0)	8	(42.1)	12	(60.0)

*One participant who failed screening was mistakenly randomized to samuraciclib 240 mg + fulvestrant. The error was recognized immediately and the patient withdrawn having never been dosed. This patient was therefore not considered eligible for analysis.

Safety

Participants, n (%)	SAM 360+F (N=20)		SAM 240+F (N=19)		F (N=20)	
Treatment-related AEs occurring in ≥20% of patients in any arm	All grades	Grade 3	All grades	Grade 3	All grades	Grade 3
Diarrhea	16 (80.0)	2 (10.0)	10 (52.6)	2 (10.5)	0	0
Nausea	15 (75.0)	3 (15.0)	8 (42.1)	0	3 (15.0)	0
Vomiting	13 (65.0)	1 (5.0)	6 (31.6)	0	1 (5.0)	0
Anemia	5 (25.0)	0	2 (10.5)	1 (5.3)	3 (15.0)	0
Aspartate aminotransferase increased	5 (25.0)	1 (5.0)	1 (5.3)	0	0	0
Alanine aminotransferase increased	4 (20.0)	1 (5.0)	1 (5.3)	0	0	0
Leukopenia	4 (20.0)	0	1 (5.3)	0	0	0
Neutopenia	4 (20.0)	0	0	0	0	0
Asthenia	3 (15.0)	0	5 (26.3)	0	1 (5.0)	0
Decreased appetite	2 (10.0)	0	4 (21.1)	0	1 (5.0)	0
Discontinuations due to AEs	0	0	1 (5.3)	0	0	0

- The most common were dose-related GI AEs managed with standard prophylaxis
- Only 1 of 39 patients treated with samuraciclib discontinued treatment due to AEs

Pharmacokinetics

- Samuraciclib single-tablet exposure was consistent with that observed after dosing with the multiple capsules used in early development
- The low rate of samuraciclib discontinuation supports the use of the tablet formulation in phase 3 trials

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Abbreviations

AE, adverse event; **AR**, androgen receptor; **ATP**, adenosine triphosphate; **CDK**, cyclin-dependent kinase; **CDK4/6i**, CDK4/6 inhibitor; **CR**, complete response; **ctDNA**, circulating tumor DNA; **DoR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **ER**, estrogen receptor; **ERS1**, estrogen receptor alpha encoding gene; **GI**, gastrointestinal; **HER2**, human epidermal growth factor receptor 2; **HR**, hormone receptor; **IM**, intramuscular; **mRNA**, messenger ribonucleic acid; **ORR**, overall response rate; **PFS**, progression-free survival; **PK**, pharmacokinetic; **PR**, partial response; **QD**, once daily; **RECIST**, Response Evaluation Criteria in Solid Tumors; **SD**, stable disease; **SERD**, selective estrogen receptor degrader.

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Disclosures

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Further information

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