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Patient selection biomarkers for CDK7 inhibitor samuraciclib (SAM; CT7001) combined with selective estrogen receptor degrader (SERD) in hormone receptor-positive advanced breast cancer (HR+ ABC) post-CDK4/6 inhibitor (CDK4/6i)

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Key findings

- **The CDK7 inhibitor samuraciclib in combination with SERD therapy is being studied in HR+, HER2− advanced breast cancer**
- **Non-clinical data indicate that inhibition of CDK7 removes suppression of wild-type *TP53*[1–3]**
- **Two independent studies of samuraciclib in combination with the intramuscular SERD fulvestrant or the oral SERD giredestrant suggest that patients with no evidence of either *TP53* mutation or, separately, no liver metastases may preferentially benefit from this combination**
  - **The observed outcomes with samuraciclib in combination with a SERD appear greater than the anticipated prognostic impact of *TP53* mutation or liver metastases**
  - **Prior data for fulvestrant in a post-CDK4/6 inhibitor population indicate estimated median PFS for patients without *TP53* mutation of ≤4 months and ≤6 months for patients with no liver metastasis[4–7]**
- **This hypothesis is being evaluated in ongoing trials of samuraciclib combined with a variety of SERDs, including a trial in combination with the oral SERD elacestrant (SUMIT-ELA, NCT05963997) and a randomized controlled evaluation of the combination with fulvestrant (SUMIT-BC, NCT05963984)**

Introduction

- The combination of endocrine therapy with a CDK4/6 inhibitor is standard first-line therapy for HR+/HER2− metastatic breast cancer.[8–10] However, tumors in most patients develop resistance to such therapy, a challenge that can potentially be overcome by a new class of oral SERDs, which includes giredestrant and elacestrant[10–12]
- Mechanisms of resistance to CDK4/6 inhibition and SERDs 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 endocrine therapy in the metastatic setting[11]
- 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)[13]
  - These effects include removal of suppression of wild-type *TP53* in non-clinical models[1–3]
- Samuraciclib has demonstrated a favorable safety profile and clinical activity in combination with fulvestrant[14] or giredestrant[15] in patients with HR+/HER2− advanced breast cancer previously treated with a CDK4/6 inhibitor
- We have analyzed data from two independent studies of samuraciclib in combination with the SERD fulvestrant (CT7001_001 Module 2A; NCT03363893)[14] or giredestrant (MORPHEUS; NCT04802759)[15] to identify potential biomarkers for patient selection for treatment

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

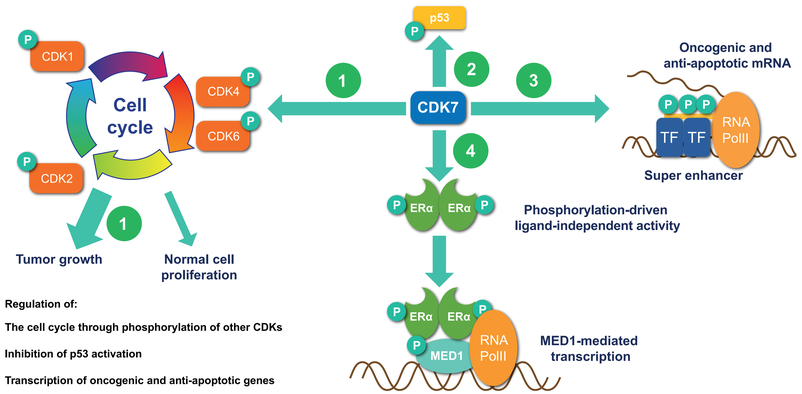
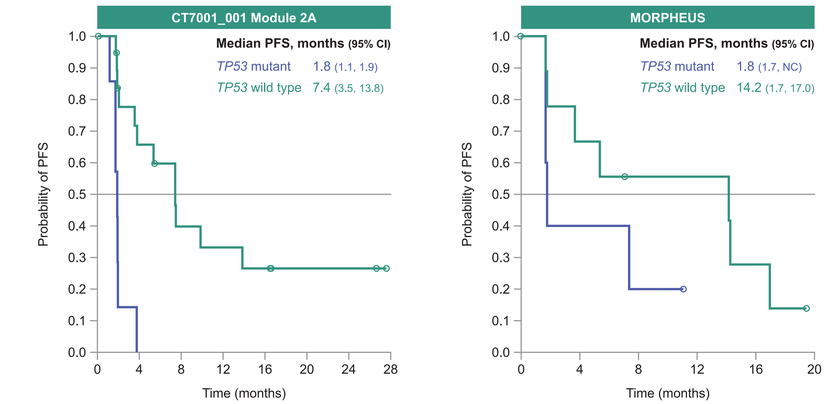


Figure 2. PFS based on *TP53* status in A) CT7001_001 Module 2A and B) MORPHEUS



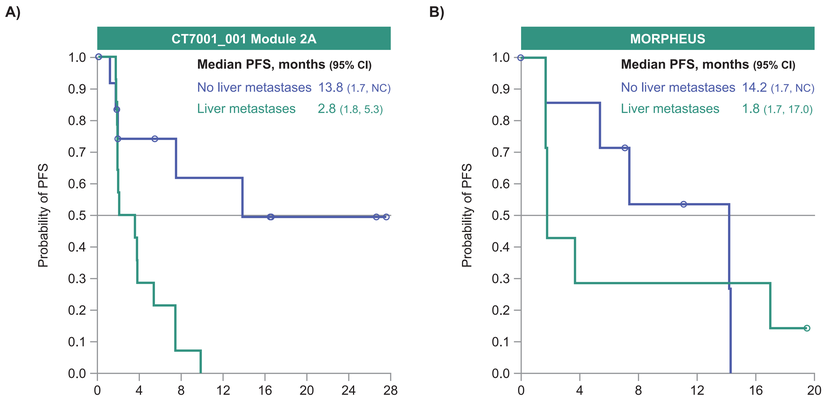
At risk (n)

TP53 mutant	7	0						
TP53 wild type	20	11	6	5	4	2	2	0

At risk (n)

TP53 mutant	5	2	1	0		
TP53 wild type	10	6	4	4	2	0

Figure 3. PFS in patients with and without liver metastases in A) CT7001_001 Module 2A and B) MORPHEUS



At risk (n)

No liver metastases	17	7	5	5	4	2	2	0
Liver metastases	14	4	1	0				

At risk (n)

No liver metastases	8	6	3	2	0	
Liver metastases	7	2	2	2	2	0

Methods

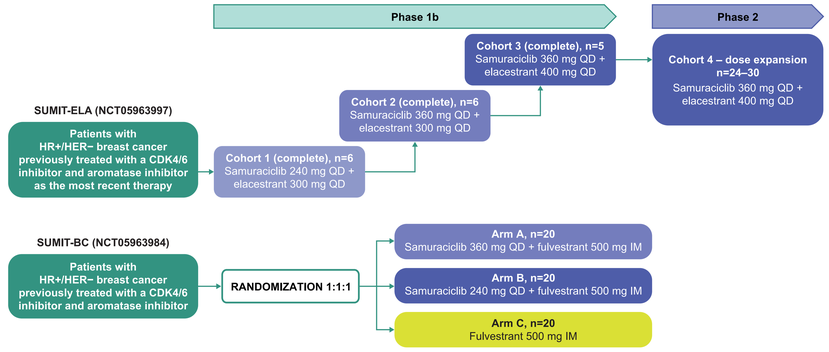
- Patients in both CT7001_001 Module 2A and MORPHEUS had RECIST-measurable HR+ advanced breast cancer and had received prior CDK4/6 inhibitor therapy
- Patients were treated as follows:
  - Samuraciclib 240 or 360 mg PO QD + fulvestrant 500 mg IM (CT7001_001 Module 2A)
  - Samuraciclib 360 mg PO QD + giredestrant 30 mg PO QD (MORPHEUS)
- *TP53* and *ESR1* mutations in circulating tumor DNA and the presence of liver metastases were assessed at screening. Exploratory analyses of PFS in subgroups defined based on these potential biomarkers are presented

Results

- In CT7001_001 Module 2A, six patients received samuraciclib 240 mg PO QD + fulvestrant 500 mg IM and 25 patients received samuraciclib 360 mg PO QD + fulvestrant 500 mg IM
- In MORPHEUS, 15 patients received samuraciclib 360 mg PO QD + giredestrant 30 mg QD
- Analysis of both studies suggested:
  - Improved PFS for patients with no baseline ctDNA *TP53* mutation vs those with mutations (Figure 2)
  - Improved PFS for patients with no baseline liver metastases vs those with metastases (Figure 3)

Ongoing studies

- Two ongoing studies will provide further insight into the predictive role of *TP53* mutation and liver metastases in patients treated with samuraciclib in combination with a SERD



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Abbreviations

AR, androgen receptor; **ATP**, adenosine triphosphate; **CDK**, cyclin-dependent kinase; **CI**, confidence interval; **ER**, estrogen receptor; **ESR1**, estrogen receptor alpha encoding gene; **HER2**, human epidermal growth factor receptor 2; **HR**, hormone receptor; **IM**, intramuscular; **NC**, not calculated; **PFS**, progression-free survival; **PO**, orally; **QD**, once daily; **RECIST**, Response Evaluation Criteria In Solid Tumors; **SERD**, selective estrogen receptor degrader

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Disclosures

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