Study of samuraciclib (CT7001), a first-in-class, oral, selective inhibitor of CDK7, in combination with fulvestrant in patients with advanced hormone receptor positive HER2 negative breast cancer (HR+ BC)

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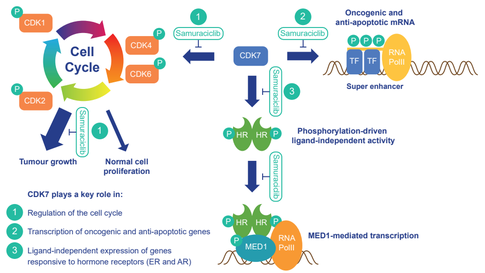
Summary

- **This poster reports the first dosing experience with the CDK7 inhibitor samuraciclib in combination with fulvestrant in patients with HR-positive breast cancer who have progressed on a CDK4/6 inhibitor**
- **The activity and tolerability in this study support further clinical development of samuraciclib in combination with fulvestrant and novel oral SERDs for HR-positive breast cancer**
- **The samuraciclib dose currently recommended for further study is 360 mg OD:**
  - **Long-term administration was achieved in women with breast cancer whose disease had progressed on an aromatase inhibitor + CDK4/6 inhibitor therapy**
  - **Evidence of antitumour activity was demonstrated by a CBR of 39%, including a cPR in a patient who remains in remission after 14 months of therapy**
  - **Adverse events were predominantly GI, of lower grade and manageable with standard supportive medication and/or dose reduction**
  - **The PK profiles of samuraciclib and fulvestrant are unaffected by co-administration**
- **Exploratory ctDNA analysis indicates that tumour TP53 mutation status has biomarker potential**
- **The duration of benefit appears to be enhanced in patients without baseline liver metastases and in patients with TP53 wild-type tumours**

Introduction

- CDK7 has multiple mechanisms of action (**Figure 1**)[1]

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



- Samuraciclib (CT7001) is a once-daily, oral, small molecule, ATP-competitive, selective inhibitor of CDK7 (**Figure 1**) that is active in xenograft models, including HR-positive breast cancer, alone and with hormonal therapy[2]
- Patients with advanced/metastatic HR-positive/HER2-negative breast cancer typically receive first-line therapy with the combination of a CDK4/6 inhibitor with an aromatase inhibitor[3,4]
- Treatment options following progression on a CDK4/6 inhibitor are compromised in terms of efficacy and/or have challenges with toxicity such as myelosuppression, neuropathy, skin reactions, pneumonitis, hyperglycaemia and alopecia[5]
- Hormonal therapy has a favourable tolerability profile, but the efficacy of fulvestrant following prior CDK4/6 inhibitor therapy is limited (median PFS ≈8 weeks) and outcomes are further compromised in patients with liver metastases[6–8]

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Abbreviations

AR, androgen receptor; AST, aspartate aminotransferase; ATP, adenosine triphosphate; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; cPR, confirmed partial response; CR, complete response; CT, computed tomography; ctDNA, circulating tumour DNA; ER, oestrogen receptor; GI, gastrointestinal; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ITT, intention to treat; MRI, magnetic resonance imaging; mt, mutant; OD, once daily; ORR, objective response rate; PFS, progression-free survival; PGR, progesterone receptor; PK, pharmacokinetics; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; SERD, selective ER degrader; uPR, unconfirmed partial response; wt, wild type

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Study design and objectives

Figure 2. Design of Module 2A of a phase 1/2 modular study evaluating samuraciclib (NCT03363893[9])

Module 2A
- Female, aged ≥18 years
- Histologically confirmed, metastatic or locally advanced, ER+ and/or PGR+, HER2– breast cancer
- Measurable disease
- Prior CDK4/6 inhibitor therapy
- No prior fulvestrant
- ≤1 line of chemotherapy or ≤2 lines of endocrine therapy for advanced breast cancer

→ **Samuraciclib 240 mg OD + fulvestrant 500 mg (n=6)**

→ **Samuraciclib 360 mg OD + fulvestrant 500 mg (n=25)**

Objectives
- To determine the recommended phase 2 dose of samuraciclib given in combination with fulvestrant 500 mg
- To investigate preliminary signs of activity and potential biomarkers

Analysis populations
- ITT: all enrolled patients with designated study drug assignment; used for baseline demographics and PFS analyses
- Response Evaluable: all patients who received ≥1 dose of samuraciclib and had a post-baseline tumour assessment; used for ORR and CBR analyses

Results

Patient and disease characteristics

- Thirty-one patients were enrolled into Module 2A, with 24 evaluable for response. Baseline characteristics are shown in **Table 1**

Table 1. Baseline patient and disease characteristics

Characteristic	N=31
Median age, years (range)	60 (41–81)
Female, n (%)	31 (100)
RECIST v1.1 measurable disease, n (%)	31 (100)
ER/PGR positive, n (%)	31 (100)
Location of lesions, n (%)*	
Visceral disease	25 (80.6)
Bone	18 (58.1)
Liver	14 (45.2)
Lymph node	11 (35.5)
Other	6 (19.4)
Prior CDK4/6 inhibitor-containing therapy, n (%)	31 (100)
Prior chemotherapy, n (%)	
Metastatic setting	7 (22.6)
Adjuvant setting	10 (32.3)
Neoadjuvant setting	3 (9.7)

*Patients may have had lesions in multiple sites.

Pharmacokinetics

- Preliminary PK analyses indicated that the PK profiles of samuraciclib and fulvestrant are unaffected by co-administration

Safety

- The initial samuraciclib dose was 240 mg (n=6) and then escalated to 360 mg (n=25) OD
- Adverse events were predominantly low-grade GI events that were reversible and manageable using standard medication, with long-term administration achieved (**Table 2**)
  - Six patients (19%) discontinued treatment due to treatment-related GI adverse events
  - One patient (3%) treated with samuraciclib 240 mg had a samuraciclib-related serious adverse event of diarrhoea (grade 2); one dose-limiting toxicity of nausea, vomiting and neck pain was observed at samuraciclib 240 mg
  - Eleven patients had samuraciclib dose reductions, of whom nine continued treatment; median relative dose intensity (dose received/intended) was 100% (30–124%)
- The neutropenia and significant myelosuppression associated with inhibitors of other CDKs were not observed

Table 2. Samuraciclib-related adverse events occurring in >10% of patients

Adverse event	All grades, n (%)	Grade ≥3, n (%)
Any samuraciclib-related adverse event	30 (96.8)	13 (41.9)
Diarrhoea	28 (90.3)	6 (19.4)
Nausea	25 (80.6)	3 (9.7)
Vomiting	23 (74.2)	1 (3.2)
Fatigue	11 (35.5)	1 (3.2)
Decreased appetite	9 (29.0)	0
Abdominal pain	7 (22.6)	0
AST increased	4 (12.9)	0
Upper abdominal pain	4 (12.9)	0
Dysgeusia	4 (12.9)	0
Headache	4 (12.9)	0

Efficacy

- Of 24 patients evaluable for response, 17 (71%) had tumour shrinkage, with a best RECIST response of PR in two (8%) patients and SD in 13 (54%) patients (**Figure 3**)
  - One patient with a confirmed PR has received samuraciclib and fulvestrant for 14 months (see **Figure 7**)
  - One patient with liver metastases achieved an unconfirmed PR
  - A further patient, also with liver metastases, showed a 24% size reduction on CT imaging follow up. Due to contrast allergy, MRI was performed in parallel and showed evidence of CR

Figure 3. Best RECIST response

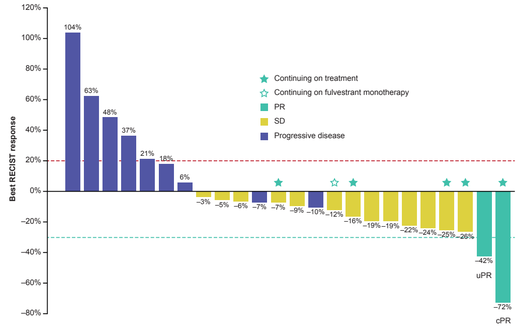


Figure 4. Time on study showing patients with clinical benefit at 24 weeks (vertical green line)

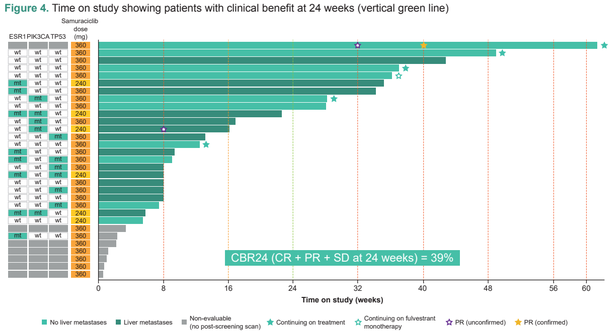
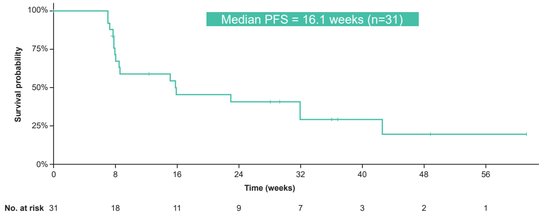


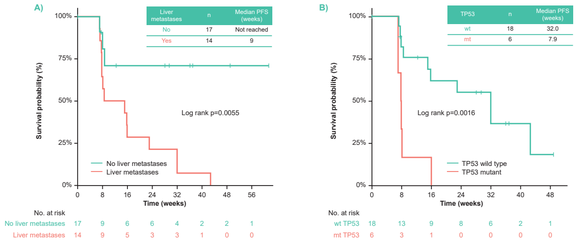
Figure 5. Kaplan–Meier plot showing PFS in the ITT population



Subgroup analyses

- Although prolonged disease control was observed for some patients with liver metastases at baseline, in patients without liver involvement, the median PFS has not yet been reached (**Figure 6A**)
- Biomarker potential for TP53 status was shown by median PFS of 32 weeks in TP53 wild-type tumours per ctDNA analysis (CBR at 24 weeks 50%) (**Figure 6B**). No association was apparent for PIK3CA or ESR1 mutational status (data not shown)

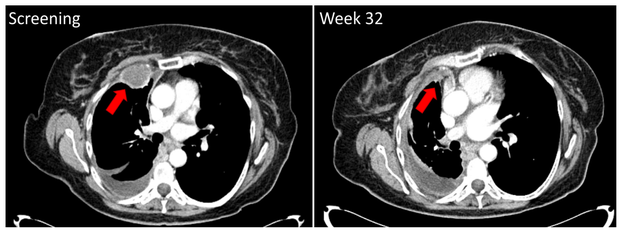
Figure 6. Kaplan–Meier plots showing PFS in **A**) patients with and without liver metastases and **B**) patients with and without tumour TP53 mutations (TP53 status was assessed in 24 patients [23 evaluable, one non-evaluable])



Evidence of tumour regression and patient benefit

- One patient has been receiving samuraciclib 360 mg OD + fulvestrant for 14 months and remains on treatment:
  - A 58-year-old woman with lung and lymph node metastases who previously progressed after 7 months of therapy with an aromatase inhibitor + palbociclib
  - PR at 32 weeks of treatment with samuraciclib + fulvestrant, with complete resolution in three of four non-target lesions; currently remains in remission (**Figure 7**)

Figure 7. Clear size reduction of pleural lesion in patient with cPR



Future directions

- **The activity and tolerability demonstrated support further clinical development of samuraciclib in combination with fulvestrant and novel oral SERDs**
- **A randomised, controlled study of the PFS benefit of samuraciclib and fulvestrant is planned; to reflect the overall HR+ breast cancer population, patients with RECIST v1.1 non-measurable disease will be eligible**
  - **It is hypothesised that the treatment effect in patients with RECIST v1.1 non-measurable disease will be at least similar to that observed in patients without liver metastases in the reported dataset**
- **Patients will be stratified based on the presence of liver metastases and TP53 status**
- **Initial combination dosing experience with the oral SERD giredestrant will be obtained via collaboration with the Roche/Genentech MORPHEUS – Breast Cancer program**

Disclosures

Sacha Howell has received speaker fees from Eisai and Pfizer and has participated in advisory boards for AstraZeneca and Pfizer

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