A clinical study of samuraciclib (CT7001), a first-in-class, oral, selective inhibitor of CDK7, in patients with advanced triple negative breast cancer (TNBC)

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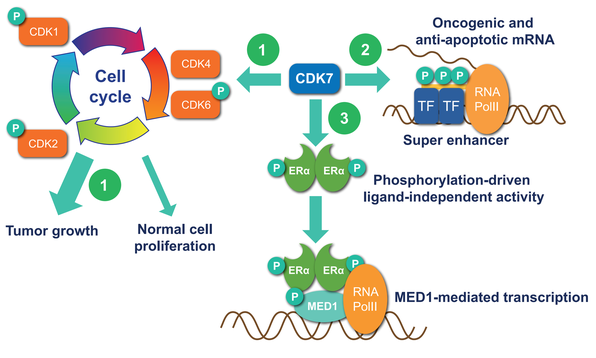
Summary

- **This poster reports the first dosing experience with the CDK7 inhibitor samuraciclib in patients with locally advanced/metastatic TNBC who had received one to three lines of prior chemotherapy**
- **Samuraciclib showed promising activity in this heavily pretreated population and acceptable safety and tolerability consistent with previous reports in other populations**
  - **Long-term administration was achieved in women with advanced TNBC: of five patients who received treatment for at least 24 weeks, three received treatment for >1 year**
  - **A patient with a confirmed partial response (61% RECIST reduction) remained on treatment for 72 weeks, with a disease control duration of 60 weeks**
  - **Treatment was generally well tolerated, with 22 of 23 patients staying on treatment until disease progression; adverse events were predominantly gastrointestinal and of low grade**
  - **A significant reduction in TK activity is seen with samuraciclib therapy, indicating target engagement**

Introduction

- TNBC is a heterogeneous form of breast cancer with a particularly poor prognosis: the incidence of distant metastasis, recurrence, and survival are worse for patients with TNBC than those with hormone receptor-positive and/or HER2-positive breast cancer[1–3]
- Chemotherapy remains the mainstay of treatment for TNBC, although PARP inhibitors and other targeted agents have a role in some patients.[4] However, effective new therapies are needed because median PFS is 1.7 months for patients with TNBC who are treated third line or later[5]
- CDK7 is a key kinase that regulates cell division, transcription, and nuclear receptor function (**Figure 1**)[6]

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



Regulation of:

1. **The cell cycle through phosphorylation of other CDKs**
2. **Transcription of oncogenic and anti-apoptotic genes**
3. **Signaling by and activation of hormone receptors (ER and AR)**

- CDK7 inhibition is a promising anticancer strategy, with preclinical data suggesting that TNBC cells show CDK7 dependence and undergo apoptosis if CDK7 is inhibited[7]
- Samuraciclib (CT7001) is a once-daily, oral, small molecule, ATP-competitive, selective inhibitor of CDK7 (**Figure 1**), with phase I data demonstrating activity in solid tumors, including hormone receptor-positive, HER2-negative breast cancer[8,9]
- We report data for an expansion cohort of patients with TNBC from a modular phase 1/2A trial of samuraciclib (**Figure 2**)

Study design and objectives

Figure 2. Design of the TNBC module of the phase 1/2A modular study of samuraciclib (NCT03363893[9])

Module 1B – TNBC

- Female, aged ≥18 years
- Histologically confirmed, metastatic or locally advanced breast cancer not expressing estrogen receptor, progesterone receptor, or HER2 receptor
- Measurable disease by RECIST version 1.1
- ECOG performance status 0 or 1
- One to three prior lines of cytotoxic therapy for metastatic or locally advanced disease
- No prior samuraciclib
- No advanced symptomatic visceral metastases or known symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease

→ **Samuraciclib 360 mg once daily (n=23)**

Objectives

- To further characterize the safety and tolerability of samuraciclib and determine the most appropriate dosing regimen for subsequent phase 2 testing (definitive RP2D)
- To evaluate the activity of samuraciclib as monotherapy in patients with metastatic or locally advanced TNBC

Analysis populations

- Safety analysis population: all patients who received at least one dose of study treatment
- Response Evaluable population: all patients who received at least one dose of samuraciclib and at least one post-baseline assessment

Results

Patient and disease characteristics

- From January 29, 2019, to April 12, 2021, 23 women with advanced TNBC were recruited and treated with samuraciclib 360 mg QD (**Table 1**)

Table 1. Baseline patient and disease characteristics

Characteristic	N=23
Median age, years (range)	54 (32–75)
Female, n (%)	23 (100)
Location of lesions, n (%)*	
Lymph node	15 (65)
Lung	11 (48)
Chest wall	4 (17)
Liver	4 (17)
Other	4 (17)
Median lines of prior chemotherapy in advanced/metastatic setting, n (range)	2 (1–3)
Setting of prior chemotherapy, n (%)†	
Locally advanced/metastatic setting	23 (100)
Adjuvant	10 (43.5)
Neo-adjuvant	10 (43.5)
Other prior therapies, n (%)	
Surgery	23 (100)
Radiotherapy	21 (91.3)
Biological/immunological/other therapy	8 (34.8)
Hormonal therapy‡	7 (30.4)

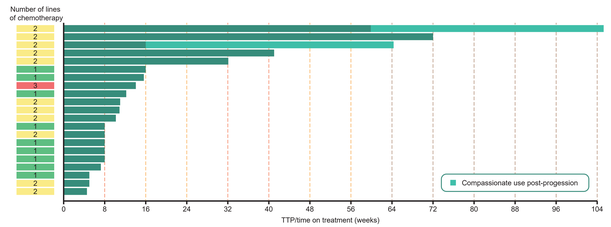
*Patients may have had lesions in multiple locations; †Patients may have had chemotherapy in multiple settings; ‡All patients had confirmed TNBC status prior to study entry.

Safety

- Samuraciclib was generally well tolerated, with 22 of 23 patients remaining on treatment until disease progression
  - One patient discontinued samuraciclib therapy due to treatment-related grade 1 nausea and diarrhea
- The most common adverse events were gastrointestinal and of grade 1/2 severity (**Table 2**)
  - Samuraciclib dose reductions to 300 mg occurred in five patients, primarily due to grade 2 gastrointestinal events
- In addition to the grade ≥3 events shown in **Table 2**, one patient had grade 3 anemia and another had grade 4 thrombocytopenia

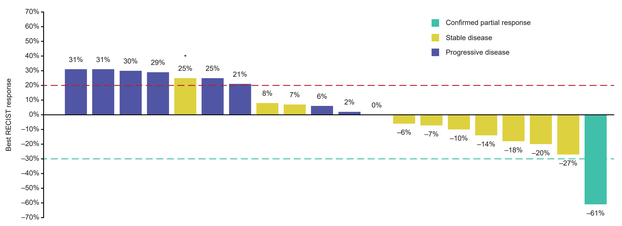
Efficacy

Figure 3. Time on study*



*Graph shows TTP for patients who have confirmed RECIST progression or time to last confirmed samuraciclib dose.

Figure 4. Best RECIST response



*Increase in lesion size from 12 to 15 mm was below the threshold for classification as progressive disease (minimum increase of 5 mm).

- Twenty-one patients were evaluable for efficacy at the data cut-off date of July 8, 2021
- Five patients received treatment for ≥24 weeks, of whom three received treatment for >1 year (**Figure 3**)
- One patient had a best RECIST response of partial response and 11 had stable disease (**Figure 4**)
  - Eight patients had a best RECIST response of progressive disease
  - One patient was found to have developed new brain metastases at assessment after 3 weeks of treatment; no target lesion measurements were available
- Two patients continued samuraciclib therapy post-progression based on compassionate use:
  - One developed a new lesion (lung) at week 60 scan, while target lesions (axilla and lung) remained controlled. Treatment was stopped at week 105 due to a new brain lesion and progression of target lesions
  - The other had a new lesion (lung) at week 16 scan, which subsequently resolved on therapy by week 42. Treatment was stopped at week 64 due to significant progression of target (axilla) lesions

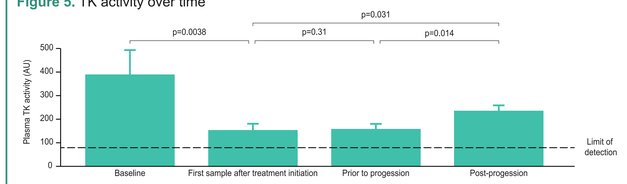
Table 2. Samuraciclib-related adverse events occurring in at least two patients

Adverse event	All grades, n (%)	Grade ≥3, n (%)
Nausea	22 (96)	0 (0)
Diarrhea	21 (91)	2 (9)
Vomiting	12 (52)	1 (4)
Fatigue	9 (39)	1 (4)
Abdominal pain	4 (18)	0 (0)
Stomatitis	2 (9)	1 (4)
Abdominal pain upper	2 (9)	0 (0)
Alopecia	2 (9)	0 (0)
Constipation	2 (9)	0 (0)
Decreased appetite	2 (9)	0 (0)
Flushing	2 (9)	0 (0)
Mucosal inflammation	2 (9)	0 (0)
Platelet count decreased	2 (9)	0 (0)

Effect of samuraciclib on TK activity over time

- A significant reduction in TK activity, as measured by the DiviTum® TK activity assay, is seen with samuraciclib therapy, indicating inhibition of cell cycle progression[10] (**Figure 5**)

Figure 5. TK activity over time

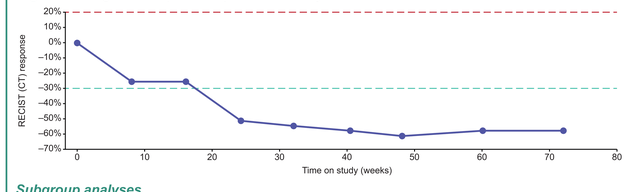


Values are mean ± SEM for n=9 patients; p values are Wilcoxon signed rank. Progression defined by RECIST version 1.1. Post-progression samples were taken an average of 6 days (range 1–15) after progression was observed, with six of nine patients on treatment with samuraciclib at blood draw of post-progression sample.

Evidence of long-term patient response and tolerability

- A 49-year-old woman, with two target axillary lymph node lesions and one non-target lateral lymph node lesion, who had received prior chemotherapy in the neo-adjuvant (paclitaxel + carboplatin), locally advanced (capecitabine), and metastatic (gemcitabine + carboplatin) settings was on study for 72 weeks (**Figure 6**)
  - Disease control duration was 60 weeks
  - Best response was a confirmed partial response: 61% reduction by RECIST
  - No samuraciclib dose reductions or delays were required
    - The maximum gastrointestinal toxicity experienced was CTCAE grade 2 nausea
    - Gastrointestinal adverse events were managed using metoclopromide (day 1), ondansetron (days 2–5), and a single dose of loperamide (day 6)
  - The patient discontinued samuraciclib due to disease progression, with development of a new lesion on the chest wall

Figure 6. Long-term response in patient on study for 72 weeks: RECIST evaluations



Subgroup analyses

- No statistically significant association was observed between tumor TP53 mutational status and best RECIST response or TTP

Future directions

- **The samuraciclib monotherapy dose currently recommended for further study is 360 mg QD**
- **Exploration of the activity and tolerability of samuraciclib in combination with chemotherapy in earlier lines of treatment for locally advanced/metastatic TNBC is planned**
- **Approaches to further understand potential biomarkers of response to samuraciclib are being explored**

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Abbreviations

AR, androgen receptor; AU, arbitrary unit; CDK, cyclin-dependent kinase; CNS, central nervous system; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; mRNA, messenger ribonucleic acid; PARP, poly-adenosine diphosphate ribose polymerase; PFS, progression-free survival; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors; RNA, ribonucleic acid; RP2D, recommended phase 2 dose; SEM, standard error of the mean; TF, transcription factor; TK, thymidine kinase; TNBC, triple-negative breast cancer; TTP, time to progression

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