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A randomized controlled trial of CDK7 inhibitor samuraciclib plus fulvestrant in advanced HR+/HER2− breast cancer

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Resistance to CDK4/6 inhibitors remains a major challenge in HR + /HER2− metastatic breast cancer. Samuraciclib is an oral selective CDK7 inhibitor that may overcome resistance to CDK4/6 inhibitors, targeting transcriptional programs sustaining tumor growth. This study presents a 3-arm randomized comparison of samuraciclib 360 mg plus fulvestrant, samuraciclib 240 mg plus fulvestrant and fulvestrant alone in females with advanced HR + /HER2− breast cancer previously treated with a CDK4/6 inhibitor (NCT05963984). 59 patients were randomized and stratified by *TP53* mutation and liver metastases status. 20, 19, and 20 patients were allocated to the samuraciclib 360 mg, 240 mg or fulvestrant arms respectively. For samuraciclib 360 mg plus fulvestrant and samuraciclib 240 mg plus fulvestrant compared with fulvestrant monotherapy, the primary endpoint of clinical benefit rate was 60.0%, 63.2% and 40.0%, respectively. Activity was enhanced in the selected secondary analysis populations of participants with no detectable *TP53* mutations (*TP53* wild-type), participants with no baseline liver metastases and participants with prior CDK4/6 inhibitor duration of ≥12 months. Adverse events were predominantly gastrointestinal toxicities, manageable with prophylaxis. These results support CDK7 inhibition with samuraciclib plus fulvestrant as a potential second line strategy in HR + /HER2- breast cancer and provide a rationale for a biomarker enriched (*TP53* wild-type tumors) clinical evaluation.

Hormone receptor-positive (HR +) breast cancer represents the most common subtype of breast cancer and accounts for most breast cancer-related deaths. CDK4/6 inhibitors (CDK4/6i)—palbociclib, ribociclib, and abemaciclib—have transformed the treatment for HR + , and human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer. However, clinical resistance remains a critical challenge, with ~10–20% of patients exhibiting de novo intrinsic resistance and the remainder inevitably developing acquired resistance[1–3]. A key challenge in treating metastatic disease after

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progression on endocrine therapy and a CDK4/6i is the existence of multiple mechanisms of resistance[4].

Cyclin-dependent kinase 7 (CDK7) is a compelling target in oncology since it has a critical role in the regulation of cell cycle and transcription[5–7]. CDK7 occupies a position distinct from the cell-cycle kinases targeted by CDK4/6 inhibitors. Through phosphorylation of the carboxy-terminal domain of RNA polymerase II, CDK7 governs transcriptional initiation and elongation, sustaining the expression of short-half-life oncogenic drivers, including *MYC* and cyclin-dependent transcriptional programs[8]. CDK7 also has a role in the activation of the *ER*α through phosphorylation of the receptor and the associated MED1 mediator protein[9,10]. Inhibition of CDK7 therefore both suppresses transcriptional dependencies and ligand-independent *ER* activation, which are not addressed by CDK4/6 blockade and are implicated in acquired resistance. In addition, in *TP53* wild-type tumors, it permits reactivation of p53-dependent apoptosis[11]. These factors provide the mechanistic rationale for activity following progression on a CDK4/6 inhibitor.

In HR+ breast cancer, preclinical studies indicate that CDK7 inhibition is more effective in *TP53* wild-type (*TP53*wt) tumors as it can activate the p53 pathway in *TP53*wt cancer cell lines, inducing apoptosis[11–13]. Samuraciclib (CT7001) is a selective, orally administered, competitive inhibitor of CDK7 given once daily. A Phase 1/2 clinical study, CT7001_001 (NCT03363893), demonstrated preliminary signs of anti-tumor efficacy and defined a recommended Phase 2 dose of 360 mg QD. In an expansion cohort, samuraciclib combined with fulvestrant demonstrated encouraging anti-tumor activity in patients with advanced HR+ breast cancer[14]. A retrospective analysis of this cohort indicated enhanced activity in patients with no pathogenic *TP53* mutation detected per baseline ctDNA. This finding was subsequently replicated in a Phase 1/2 clinical trial evaluating samuraciclib in combination with giredestrant[15], supporting the hypothesis that *TP53* status may influence sensitivity to CDK7 inhibition, in alignment with preclinical findings[11–13].

The SUMIT-BC study was designed to provide a randomized, controlled evaluation of these previous clinical findings through a comparison of samuraciclib plus fulvestrant compared to fulvestrant alone. Two dose levels of samuraciclib were studied to provide information on the overall benefit/risk, to inform future trial design, and the selected patient population to be enrolled. The study pre-specified an analysis based on *TP53* mutational status to explore its role as a predictive biomarker.

Here we report the results of this randomized phase II study, indicating that samuraciclib in combination with fulvestrant confers clinically meaningful benefits in patients with HR + , HER2- breast cancer who have progressed on prior CDK4/6i-based therapy.

Results

Patient demographics and baseline characteristics

A total of 60 participants with metastatic or locally advanced HR + , HER2- BC who had previously received treatment with an aromatase inhibitor and CDK4/6i were enrolled at 26 centers in 5 countries, including Hungary, Mexico, Spain, Turkey, and the United States. Participants were enrolled between November 2023 and August 2025. There was one screen-failure participant randomized in error (administrative) into the 240 mg arm; this participant was not dosed and is therefore not considered further. The remaining 59 participants were treated: 20 in the samuraciclib 360 mg + fulvestrant arm (SAM 360 mg + F), 19 in the samuraciclib 240 mg + fulvestrant arm (SAM 240 mg + F), and 20 in the fulvestrant arm (F). All participants were included in the full analysis set, the safety analysis set, and the pharmacokinetic (PK) analysis set.

All participants were female, most were postmenopausal (78.0%), the median age was 58.0 years (range: 29–76 years), and most of the participants (72.9%) were white.

In total, 30.5% of participants had *TP53* mutations detected in ctDNA analysis (referred to as being *TP53*mt; while those without detectable *TP53* mutations are termed *TP53*wt). Liver metastases were present in 22.0% of all participants, prior CDK4/6i use for at least 12 months was reported for 74.6% of participants (Table 1).

Primary efficacy analyses—full analysis set

The primary endpoint of the study was an evaluation of Clinical Benefit Rate (CBR) in the Full Analysis Set (FAS). In this population, the investigator-assessed CBR (complete response [CR], partial response [PR], or stable disease [SD] ≥24 weeks) was 60.0% in the SAM 360 mg + F arm, 63.2% in the SAM 240 mg + F arm and 40.0% in the F monotherapy arm (unstratified odds ratio: SAM 360 mg + F v F: 2.250; 90% CI: 0.652, 7.778, SAM 240 mg + F v F: 2.571; 90% CI: 0.724, 9.161, Table 2).

The objective response rate (ORR) in the FAS with measurable disease was 33.3% with SAM 360 mg + F, 21.4% with SAM 240 mg + F, and 14.3% with F alone. Responses were durable, as can be seen in the Spider Plots (Fig. 1).

In the FAS, median progression-free survival (mPFS) was 7.8 months in the SAM 360 mg + F arm and 8.5 months in the SAM 240 mg + F arm and 5.6 months in the F monotherapy arm (Table 2, Figs. 1 and 2).

Secondary efficacy analyses

Among participants with *TP53*wt status, the ORR, CBR, and median PFS were 54.5%, 69.2%, and 14.5 months in the SAM 360 mg+F arm, 25.0%, 64.7%, and 9.6 months in the SAM 240 mg + F arm, and 28.6%, 45.5%, and 6.8 months in the F monotherapy arm. All participants who achieved a best overall response of PR (regardless of treatment arm), had *TP53*wt tumors, whereas no PR were observed among participants with *TP53*mt disease (Table 3, Figs. 1 and 2).

When efficacy results were assessed according to baseline liver metastases, the ORR, CBR, and PFS in the samuraciclib + fulvestrant groups were higher for the participants without liver metastases (Table 3 and Supplementary Fig. 2).

When efficacy results were assessed according to the duration of prior CDK4/6i exposure, the ORR, CBR, and PFS in the samuraciclib + fulvestrant groups were higher in participants with ≥12 months of prior treatment than those who had <12 months (Table 3 and Supplementary Fig. 3).

Finally, in an exploratory analysis, the activity of samuraciclib in combination with fulvestrant appeared to be independent of *AKT* pathway abnormality (including *PIK3CA* mutations and *PTEN* loss) and *ESR1* mutational status per baseline ctDNA analysis (Supplementary Fig. 4).

Pharmacokinetics

Pharmacokinetic parameters showed a dose-related increase in C_{max} concentrations for samuraciclib, whilst fulvestrant trough concentrations were consistent across the treatment arms. On Cycle 2 Day 1, the geometric mean C_{max} and C_{trough} of samuraciclib 360 mg were 226.7 ng/mL and 71.24 ng/mL, respectively. On Cycle 2 Day 1, the geometric mean C_{max} and C_{trough} of samuraciclib 240 mg were 183.1 ng/mL and 67.83 ng/mL, respectively.

On Cycle 3 Day 1, the geometric mean C_{max} and C_{trough} of samuraciclib 360 mg were 279.6 ng/mL and 47.61 ng/mL, respectively. On Cycle 3 Day 1, the geometric mean C_{max} and C_{trough} of samuraciclib 240 mg were 141.0 ng/mL and 55.33 ng/mL, respectively.

Samuraciclib single-tablet exposure was consistent with that observed after dosing with the multiple capsules used in early development, which has been previously reported[14].

Geometric mean C_{trough} for fulvestrant on Cycle 2 Day 1 were 13.58 ng/mL for the samuraciclib 360 mg arm, 13.81 ng/mL for the samuraciclib 240 mg arm, and 12.13 ng/mL for the fulvestrant arm. On

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Table 1 | Key baseline demographic and baseline characteristics—full analysis set

	Samuraciclib 360 mg + Fulvestrant 500 (*N* = 20)	Samuraciclib 240 mg + Fulvestrant 500 (*N* = 19)	Fulvestrant 500 (*N* = 20)
Age (years)—median (range)	61.5 (29, 70)	56.0 (40, 72)	59.0 (36, 76)
Weight (kg)—median (range)	75.5 (52, 121)	70.0 (44, 93)	68.1 (49, 99)
ECOG Performance Status 0, *n* (%)	12 (60.0)	10 (52.6)	15 (75.0)
ECOG Performance Status 1, *n* (%)	8 (40.0)	9 (47.4)	5 (25.0)
Race, *n* (%)			
Black or African American	0	2 (10.5)	1 (5.0)
American Indian or Alaska Native	2 (10.0)	1 (5.3)	4 (20.0)
White	16 (80.0)	12 (63.2)	15 (75.0)
Not reported/unknown	2 (10.0)	4 (21.0)	0
Menopausal status, *n* (%)			
Postmenopausal	15 (75.0)	14 (73.7)	17 (85.0)
Pre/perimenopausal	5 (25.0)	5 (26.3)	3 (15.0)
***TP53* mutation status, *n* (%)**			
No	13 (65.0)	17 (89.5)	11 (55.0)
Yes	7 (35.0)	2 (10.5)	9 (45.0)
***AKT* (including *PIK3CA*), *n* (%)**			
No	11 (55.0)	8 (42.1)	15 (75.0)
Yes	9 (45.0)	11 (57.9)	5 (25.0)
***ESR1*, *n* (%)**			
No	12 (60.0)	10 (52.6)	11 (55.0)
Yes	8 (40.0)	9 (47.4)	9 (45.0)
Liver metastases, *n* (%)			
No	15 (75.0)	15 (78.9)	16 (80.0)
Yes	5 (25.0)	4 (21.1)	4 (20.0)
Duration of prior CDK4/6i			
≥12 Months	12 (60.0)	15 (78.9)	17 (85.0)
<12 Months	8 (40.0)	4 (21.1)	3 (15.0)
Prior adjuvant therapy, *n* (%)			
Yes	8 (40.0)	11 (57.9)	9 (45.0)
Prior advanced/metastatic therapy, *n* (%)			
Yes	20 (100.0)	17 (89.5)	19 (95.0)
Prior CDK4/6i as the immediate prior therapy, *n* (%)			
In adjuvant/neoadjuvant setting	0	2 (10.5)	1 (5.0)
In advanced/metastatic setting	20 (100)	17 (89.5)	19 (95.0)
Best response to prior CDK4/6i+AI therapy, *n* (%)			
CR	1 (5.0)	1 (5.3)	0
PR	8 (40.0)	5 (26.3)	7 (35.0)
SD	10 (50.0)	10 (52.6)	11 (55.0)
Unknown	1 (5.0)	3 (15.8)	2 (10.0)
Metastatic sites at baseline, *n* (%)			
Non-visceral bone-only	2 (10.0)	6 (31.6)	6 (30.0)
Visceral	6 (30.0)	8 (42.1)	5 (25.0)
Visceral and non-visceral	12 (60.0)	5 (26.3)	9 (45.0)
Progesterone receptor status, *n* (%)			
Negative	5 (25.0)	3 (15.8)	4 (20.0)
Positive	15 (75.0)	16 (84.2)	16 (80.0)

CDK4/6i cyclin-dependent kinase 4/6 inhibitor, *CR* complete response, *ECOG* Eastern Cooperative Oncology Group, *PR* partial response, *SD* stable disease, *ESR1* estrogen receptor 1.

Cycle 3 Day 1, the geometric mean C_{trough} of fulvestrant was 12.65 ng/mL in the samuraciclib 360 mg arm, 12.24 ng/mL in the samuraciclib 240 mg arm, and 9.96 ng/mL in the fulvestrant arm. This is consistent with reported fulvestrant steady-state trough levels of 12.2 ng/mL after multiple doses[16].

Safety and tolerability

The most common treatment-related adverse events (TRAEs) in the samuraciclib arms were gastrointestinal, including diarrhea, nausea, and vomiting (Table 4). Diarrhea occurred in 80.0%, 52.6%, and 0% of participants in the SAM 360 mg + F, SAM 240 mg + F and F alone arms respectively, nausea in 75.0%, 42.1%, and 15.0%, and vomiting in 65.0%, 31.6%, and 5.0%. These events were managed by specific prophylaxis, with an anti-HT3 antagonist and loperamide when required. Only one participant discontinued from the study due to an adverse event; a participant in the SAM 240 mg + F arm because of constipation and decreased appetite (Table 5, supplied Excel data file "Supplementary Data 1").

Grade 3 TRAE reported in >1 participant were diarrhea (2 participants [10.0%] in the SAM 360 mg + F arm and 2 participants [10.5%] in the SAM 240 mg + F arm), nausea (3 participants [15.0%] in the SAM 360 mg + F arm), and hyperglycemia (2 participants [10.5%] in the SAM 240 mg + F arm). There were no Grade 4 or 5 TRAEs in any treatment arm (Table 5).

A total of 4 deaths were reported in the study, 2 in the SAM 360 mg + F arm and 2 in the SAM 240 mg + F arm; all 4 were reported as due to disease progression and not related to the study treatment (see supplementary information). At the time of death, one of these participants was experiencing hepatic failure, which the treating investigator attributed to disease progression—it should be noted that alkaline phosphatase was raised at a baseline, and transaminase increases were subsequently reported during samuraciclib treatment. Further details can be found in Supplementary Note 1.

Overall, no new safety signals were identified for either samuraciclib or fulvestrant (Table 5).

Discussion

In the SUMIT-BC study, improved clinical outcomes were observed for participants with HR + /HER2- breast cancer treated with SAM 360 mg + F or SAM 240 mg + F compared to F alone. The confidence in this differential activity is supported by participants in the SAM 360 mg + F arm having a lower proportion with indolent non-visceral bone-only disease (10.0 versus 30.0%), and correspondingly greater visceral involvement, alongside prior CDK4/6i < 12 months (40.0% versus 15.0%) and ECOG performance status of 1 (40.0% versus 25.0%, Table 1). Bone-only disease is recognized as more indolent with a comparatively favorable prognosis, consistent with the inferior outcomes observed in participants with liver metastases. Safety was consistent with that seen in previous studies, with the majority of

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Table 2 | Clinical benefit rate, overall response rate and median progression-free survival

Assessment	Samuraciclib 360 mg + fulvestrant	Samuraciclib 240 mg + fulvestrant	Fulvestrant
Clinical benefit rate	***N*** **= 20**	***N*** **= 19**	***N*** **= 20**
n (%)	12 (60.0)	12 (63.2)	8 (40.0)
90% CI	41.9, 75.8	44.4, 78.6	24.2, 58.1
Complete response	0	0	0
Partial response	6 (30.0)	3 (15.8)	2 (10.0)
SD/non-CR/non-PD ≥ 24 weeks	6 (30.0)	9 (47.4)	6 (30.0)
SD/non-CR/non-PD < 24 weeks	3 (15.0)	1 (5.3)	6 (30.0)
Progressive disease	4 (20.00)	4 (21.1)	6 (30.0)
Not evaluable	1 (5.0)	2 (10.5)	0
ORR	***N*** **= 18**	***N*** **= 14**	***N*** **= 14**
n (%)	6 (33.3)	3 (21.4)	2 (14.3)
90% CI	18.3, 52.7	8.9, 43.2	4.8, 35.3
PFS	*N* = 20	*N* = 19	*N* = 20
Median (90% CI)	7.8 (3.7, 9.4)	8.5 (3.5, 11.2)	5.6 (2.1, 9.1)

ORR overall response rate, *PFS* progression-free survival, *SD* stable disease, *PD* progressive disease, *CI* confidence interval.
Summary of response rates.
Clinical benefit rate defined as the percentage of patients with CR or PR or stabilization of disease for at least 24 weeks between randomization and disease progression or death due to any cause. Response was assessed with RECIST v1.1. Statistical analyses were performed on the Full Analysis Set. ORR defined as the percentage of patients with a best overall response of CR or PR between randomization until disease progression or death due to any cause. The number of evaluable participants (*N*) for ORR are lower than for CBR and PFS as only participants with measurable disease at baseline were included.

adverse events being from the GI system. Long durations of administration were achieved with a very low rate of discontinuation.

Baseline testing for *TP53* mutations in ctDNA permitted the identification of a subgroup of participants with no detectable *TP53* mutations—*TP53*wt. In the pre-specified analysis of efficacy outcomes by *TP53* mutational status, enhanced benefit was observed from the addition of samuraciclib to fulvestrant in the subgroup of *TP53*wt participants, in terms of ORR, CBR, and mPFS compared to participants receiving fulvestrant alone. This was consistent with the samuraciclib non-clinical mechanism of action studies, with the less notable changes in outcome in the fulvestrant arm, indicating this was a CDK7i-driven effect rather than a prognostic impact from *TP53* status. These results are consistent with previously reported clinical studies[14].

Overall outcomes also favored participants treated without liver metastases and those with prior CDK4/6i treatment ≥12 months. These findings are potentially prognostic, and it is not proposed that they be used to determine eligibility for samuraciclib treatment, but they should clearly be considered as stratification factors in future clinical trials.

In an exploratory analysis, mPFS was similar regardless of *AKT* and *ESR1* mutation status, suggesting that samuraciclib activity is independent of the mutation status for these pathways. This is consistent with the preclinical data, as CDK7 inhibitors, and in particular samuraciclib, may be more effective in tumors with highly active growth signaling. These include cancers with mutations in *ESR1* and/or the PI3K/Akt/mTOR signaling pathway[17,18]. Indeed, Wilson et al. demonstrate that the growth inhibitory activity of samuraciclib can be reduced by inhibiting the PI3K/Akt/mTOR pathway in cancer cells[18].

The pharmacokinetic profile of the tablet was consistent with that of the previously used capsules and supports once daily dosing[14]. It is intended to use this scalable tablet formulation in Phase 3 development.

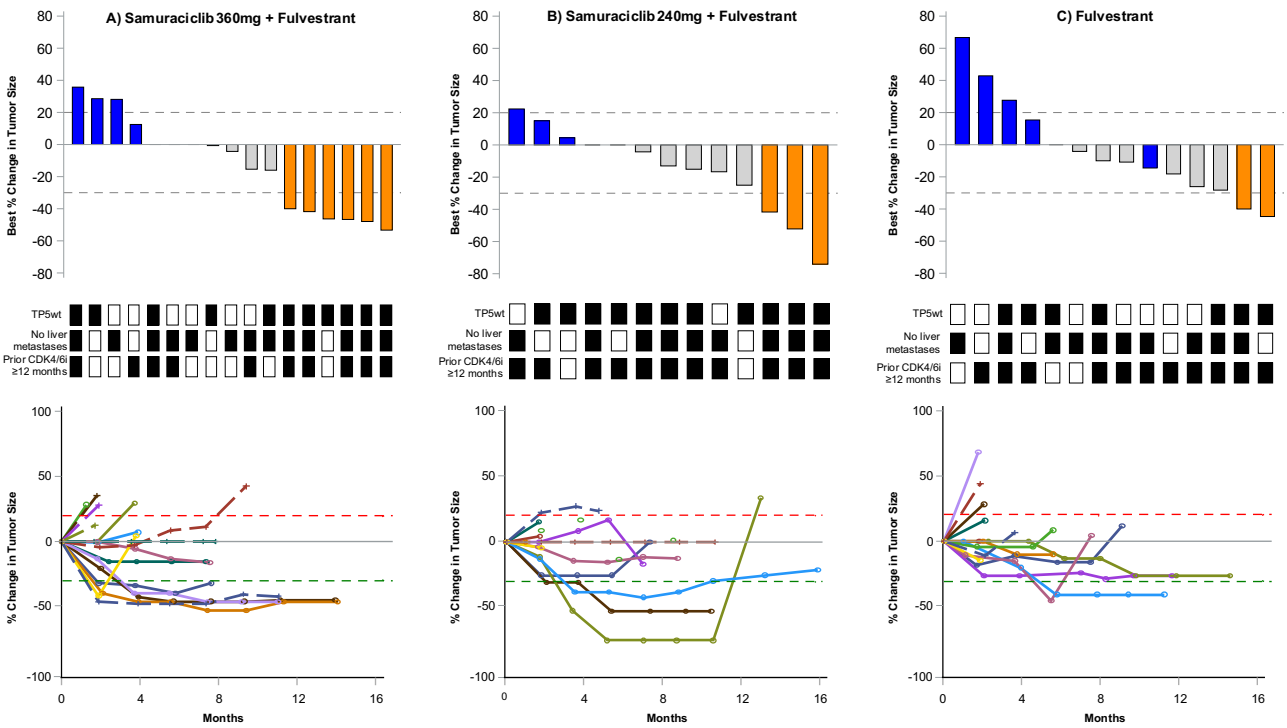


Fig. 1 | Response by subgroup. Tumor response by *TP53* status, prior CDK4/6i use, and presence of liver metastases. **A** Samuraciclib 360 mg + Fulvestrant. **B** Samuraciclib 240 mg + Fulvestrant. **C** Fulvestrant. Waterfall plots show the best percent change in tumor size with Best Overall Response (orange = partial response, gray = stable disease, blue = progressive disease). Spider graphs show the percent change in tumor size with different colors denoting individual patients. CDK4/6i = cyclin-dependent kinase 4/6 inhibitor. Black rectangle = *TP53*wt, prior CDK4/6i ≥ 12 months, no liver metastases. White rectangle = *TP53*mt, prior CDK4/6i < 12 months, liver metastases. Source data is available in the source data file.

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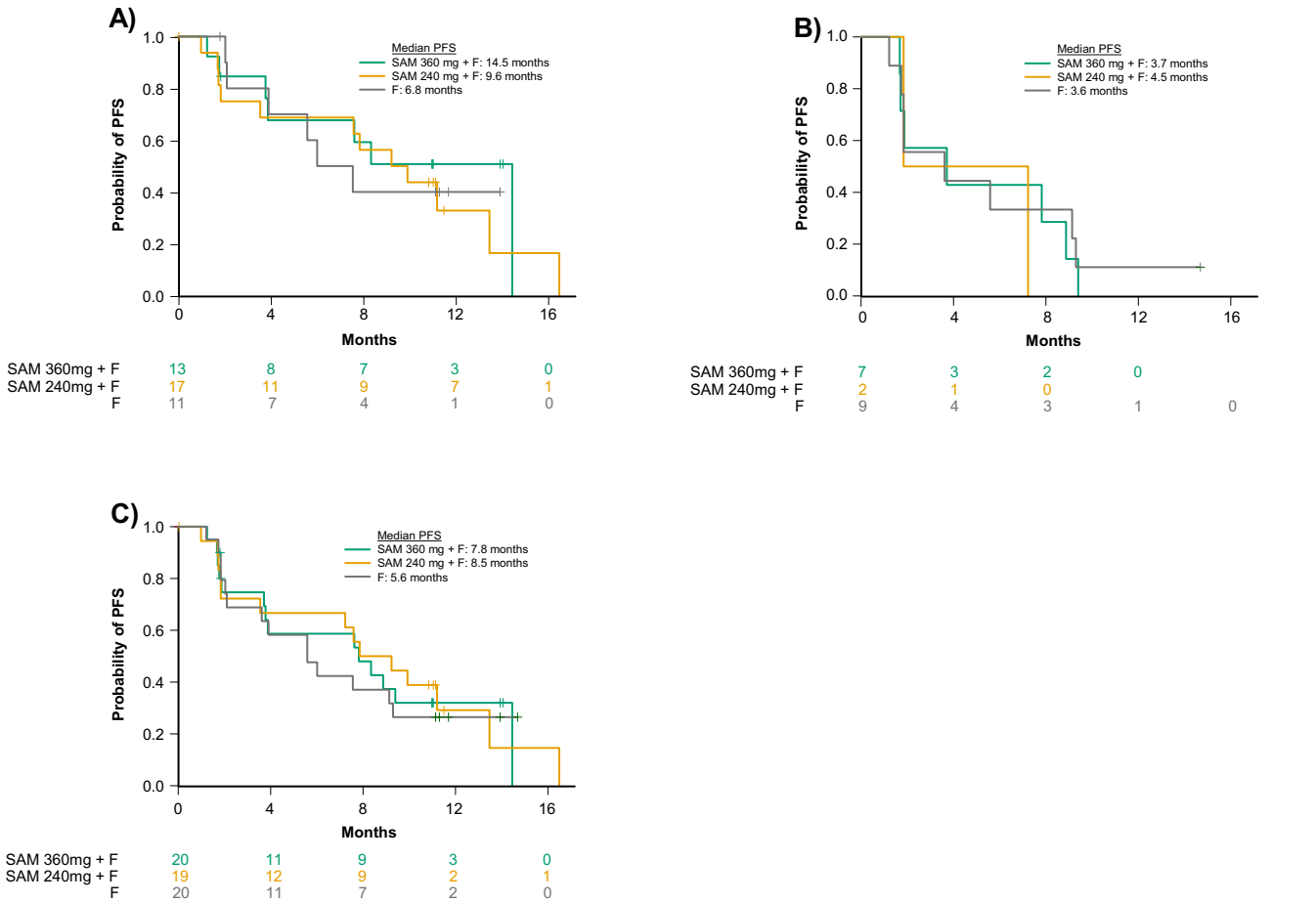


Fig. 2 | Progression-free survival by *TP53* status and in the full analysis set. Kaplan–Meier plots of progression-free survival. Survival as derived investigator assessment, RECIST Version 1.1. **A** *TP53*wt participant. **B** *TP53*mt participants. **C** FAS population. Small vertical dashes denote censored patients. FULV fulvestrant, PFS progression-free survival, SAM samuraciclib. Source data is available in the Source Data File.

All participants received prophylactic antiemetic medication prior to dosing, and antidiarrheal medication was readily available. The most common TRAEs in the combined therapy arms were related to the GI system, with the highest frequencies observed in the SAM 360 mg + F arm. These events were predominantly mild to moderate (Grades 1–2) in severity and were manageable with symptomatic treatment or with dose reductions (42–45% of participants with dose reductions), allowing for continued treatment with the combination therapy. Only 1/39 (2.6%) participant discontinued treatment due to an adverse event in the combined therapy arms. This discontinuation rate due to adverse events is lower than in our initial clinical study of samuraciclib in combination with fulvestrant, in which 7/31 (22.6%) of patients discontinued due to adverse events[14]. This is likely due to the effective implementation of GI prophylaxis, the specifics of which will be refined for future trials, and the effectiveness in mitigating symptoms will be intensely studied.

There is no current consensus regarding the standard of care for the treatment of patients with advanced HR + /HER2- breast cancer whose disease progresses after endocrine therapy plus CDK4/6i. Treatment options are limited by restrictive eligibility, limited efficacy, and tolerability issues. Clinical practice guidelines recommend tumor genomic profiling (e.g., next-generation sequencing) to help guide subsequent therapy selection. It is important that efficacy and tolerability are balanced in order to bring the greatest benefit to patients.

While some patients are switched to cytotoxic agents such as paclitaxel or capecitabine, or even to newer antibody–drug conjugates, most patients remain candidates for endocrine therapy (ET) based strategies. If combination ET is continued, currently approved options include: ET plus everolimus, ET plus the PI3K inhibitor alpelisib for patients with *PIK3CA* mutations; ET plus the AKT inhibitor capivasertib for cases with PTEN/AKT/mTOR pathway alterations; new oral ER antagonists for patients with *ESR1* mutations; or a second CDK4/6i in the absence of actionable molecular alterations. Additionally, PARP inhibitors must be considered in the small group of patients harboring germinal BRCA1/2 and PALB2 mutations.

The potential benefit of combined fulvestrant and samuraciclib is therefore important as an opportunity to expand the treatment options for patients with disease progression following aromatase inhibitor and CDK4/6i. The greatest efficacy was seen in *TP53*wt participants, and the use of a blood-based companion diagnostic was able to reliably identify these participants in the study. Samuraciclib in combination with fulvestrant was well tolerated, with only 1 participant discontinuing treatment due to an adverse event. Further adaptation of the GI prophylaxis regimen may further improve the tolerability of the treatment.

The limitations of this study are a sample size that cannot be formally tested for statistical significance, the open-label design, no blinded independent central review (BICR) of the investigator-assessed RECIST evaluations, and no independent Data Monitoring Committee.

There is a rationale for further dose optimization of samuraciclib in combination with fulvestrant. The greatest activity in terms of RECIST response and PFS was observed for patients receiving SAM 360 mg + F over SAM 240 mg + F, but this was associated with a higher

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Table 3 | Clinical benefit rate, overall response rate, and median progression-free survival—subgroup analyses

	Samuraciclib 360+Fulvestrant	Samuraciclib 240+Fulvestrant	Fulvestrant
Clinical benefit rate, *n*/*N* (%)			
*TP53*wt	9/13 (69.2)	11/17 (64.7)	5/11 (45.5)
*TP53*mt	3/7 (42.9)	1/2 (50.0)	3/9 (33.3)
Liver metastases—no	11/15 (73.3)	10/15 (66.7)	6/16 (37.5)
Liver metastases—yes	1/5 (20.0)	2/4 (50.0)	2/4 (50.0)
Prior CDK4/6i ≥12 months	8/12 (66.7)	10/15 (66.7)	8/17 (47.1)
Prior CDK4/6i <12 months	4/8 (50.0)	2/4 (50.0)	0/3
Overall response rate, *n*/*N* (%)			
*TP53*wt	6/11 (54.5)	3/12 (25.0)	2/7 (28.6)
*TP53*mt	0/7 (0)	0/2 (0)	0/7 (0)
Liver metastases—no	5/13 (38.5)	3/10 (30.0)	1/10 (10.0)
Liver metastases—yes	1/5 (20.0)	0/4	1/4 (25.0)
Prior CDK4/6i ≥12 months	5/10 (50.0)	3/11 (27.3)	2/11 (18.2)
Prior CDK4/6i <12 months	1/8 (12.5)	0/3	0/3
Progression-free survival, median months			
*TP53*wt	14.5	9.6	6.8
*TP53*mt	3.7	4.5	3.6
Liver metastases—no	8.9	9.6	5.6
Liver metastases—yes	1.7	4.7	4.8
Prior CDK4/6i ≥12 months	8.9	9.6	6.0
Prior CDK4/6i <12 months	5.8	4.7	5.6

CDK4/6i cyclin-dependent kinase 4/6 inhibitor, *TP53*mt = *TP53* mutation detected in circulating tumor DNA, *TP53*wt no *TP53* mutation detected in circulating tumor DNA.
Clinical benefit rate defined as the percentage of patients with complete response or partial response or stabilization of disease for at least 24 weeks between randomization and disease progression or death due to any cause. Response was assessed with RECIST v1.1.
Overall response rate defined as the percentage of patients with a best overall response of complete response or partial response. The number of evaluable participants (N) for ORR are lower than for CBR and PFS as only participants with measurable disease at baseline were included.
Subgroups are not mutually exclusive.

Table 4 | Treatment-related adverse events in >2 participants in any treatment arm

	Samuraciclib 360 mg + fulvestrant *N* = 20, *n* (%)		Samuraciclib 240 mg + fulvestrant *N* = 19, *n* (%)		Fulvestrant *N* = 20, *n* (%)	
	Total	Grade 3	Total	Grade 3	Total	Grade 3
With at least 1 event	20 (100.0)	7 (35.0)	16 (84.2)	6 (31.6)	12 (60.0)	0
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
Neutropenia	4 (20.0)	0	0	0	0	0
Abdominal Pain	3 (15.0)	0	3 (15.8)	0	0	0
Asthenia	3 (15.0)	0	5 (26.3)	0	0	0
Fatigue	3 (15.0)	1 (5.0)	3 (15.8)	0	0	0
Lymphopenia	3 (15.0)	0	2 (10.5)	0	0	0
Decreased appetite	2 (10.0)	0	4 (21.1)	0	0	0

Treatment-related means data related to any study intervention, including data up to 28 days after the last dose of the study drug. Participants with more than 1 treatment-related adverse event within a preferred term (PT) are counted only once in that PT. None of these events were CTCAE Grade 4 or 5.

tolerability burden. All of these factors will be important design considerations for future studies, in particular, the formation of an independent DMC and the use of BICR in Phase 3 development.

In summary, treatment with samuraciclib plus fulvestrant improved outcomes in participants with HR + /HER2 breast cancer previously treated with CDK4/6i, with greater benefit observed in patients with *TP53*wt tumors. These findings suggest that CDK7 inhibition represents a promising strategy to address the significant medical need in patients whose disease has progressed following aromatase inhibitor + CDK4/6i therapy. Further clinical evaluation is warranted, particularly in biomarker-selected *TP53* wild-type populations.

Table 5 | Safety Summary

	Samuraciclib 360 mg + fulvestrant *N* = 20, *n* (%)	Samuraciclib 240 mg + fulvestrant *N* = 19, *n* (%)	Fulvestrant *N* = 20, *n* (%)
Adverse events (AEs)	20 (100)	17 (89.5)	19 (95.0)
Treatment-related AE (TRAE)	20 (100)	16 (84.2)	12 (60.0)
Maximum Grade 3 TRAEs	7 (35.0)	6 (31.6)	0
Maximum Grade 4 or 5 TREAEs	0	0	0
TRAEs leading to permanent discontinuations from the study intervention, samuraciclib	0	1 (5.3)	0
TRAEs leading to dose reductions of the study intervention, samuraciclib	9 (45.0)	8 (42.1)	0

Includes data up to 28 days after the last dose of the study drug.

Methods

Study design

SUMIT-BC was a multi-center, randomized, open-label, active-controlled Phase 2 trial that was approved by the relevant ethics committees (see Supplementary Table 1) and was conducted in accordance with ICH-GCP guidelines, the Declaration of Helsinki, and all legal, regulatory, and data protection requirements. The trial was prospectively registered on 30 June 2023 prior to the start of participant enrollment (NCT05963984). The trial did not involve a data monitoring committee. All participants provided written informed consent and were not compensated.

The study enrolled participants with metastatic or locally advanced HR+ and HER2- breast cancer who met the following criteria:

Inclusion criteria

1. Age 18 years or older.
2. Histologically confirmed carcinoma of the breast with evidence of metastatic or locally advanced disease, not amenable to resection or radiation therapy with curative intent:
   a) ER+ with or without PgR-positive (ER+ defined as ≥1% positive stained cells regardless of PgR result).
   b) HER2- based on local testing on most recent tumor biopsy (HER2- defined as ICH score 0/1+ or negative by FISH/CISH/SISH, with HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number of <4).
3. Known *TP53* mutation status.
   For participants without a known *TP53* status at screening, blood samples must be sent to the central laboratory with results confirmed prior to randomization. The proportion of *TP53* mutation-positive participants was not to exceed ~30%.
4. One of the following, as defined by RECIST v1.1:
   a) Measurable disease.
   b) Bone-only disease, which can be measurable or non-measurable.
5. Documented objective disease progression while on or within 6 months after the end of the most recent therapy (ie, AI in combination with a CDK4/6i).

Intervention

Participants were randomized 1:1:1 to SAM 360 mg + F, SAM 240 mg + F, or F monotherapy. Participants were stratified by the presence or absence of *TP53* mutation and/or liver metastases. Participants were to receive treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, withdrawal of consent, pregnancy, loss to follow-up, investigator decision to discontinue the participant, or sponsor decision to stop the study, whichever occurred first. The end of the study was defined as 48 weeks after the last participant had been enrolled. Dose reductions for fulvestrant were not permitted. In the event of fulvestrant-related toxicity, the dose could be skipped or delayed by up to 7 days. In the event of samuraciclib toxicity, dose modifications could occur within a cycle (dosing interrupted until adequate recovery and/or dose reduction), between cycles (delay next cycle administration), or in the next cycle (dose reduction may be required, depending on the toxicity experienced in the previous cycle).

At initiation of dosing, all participants were to receive prophylactic antiemetic and antidiarrheal therapy in accordance with local guidelines and standard of care. The choice of treatment and the duration were at the discretion of the investigator, with sponsor approval, assuming there is no known or expected drug-drug interaction.

Imaging tumor response assessments

During screening, a CT scan with IV contrast of the chest, abdomen, and pelvis was preferred, although if there was concern about radiation exposure, an MRI could be used instead of a CT. In addition, if a radionuclide bone scan had not been done within 12 weeks prior to randomization, any bone lesions detected were subsequently confirmed as evaluable for follow-up using CT, MRI, or X-ray. Every effort was made to assess each lesion that was identified at screening by the same method throughout the study so that the comparison was consistent.

During treatment, chest, abdomen, and pelvis CT (or MRI) scans were performed. Bone lesions identified at Screening were continued to be imaged at subsequent scheduled visits using localized CT, MRI, or X-ray (using the same method used at baseline for all visits for any given lesion). Additional imaging evaluations could be performed at any time if there was symptomatic evidence suggesting the possibility of disease progression based on clinical symptoms or physical examination.

All CT scans were performed with IV contrast. If a participant was known to have a medical contraindication to the contrast agent, or developed a contraindication during the study, a CT scan without IV contrast of the chest and MRI with IV contrast, if possible, of the abdomen and pelvis could be performed.

Chest X-ray or ultrasound was not used for tumor response assessments in this study.

Any lesions that had been subjected to prior loco-regional therapies (e.g., radiotherapy, ablation, etc.) were considered non-measurable, unless they had clearly progressed since the therapy. Previously treated lesions that had not progressed were considered non-measurable and therefore assessed as non-target lesions.

While FDG-PET scans were not required for this study, sites could perform combined PET/CT scans as per their local standard of care, provided the CT was of similar diagnostic quality as CT performed without PET, including the use of oral and IV contrast media. If

acquired according to local standard of care, FDG-PET could be relied upon to document PD in accordance with RECIST version 1.1.

Anti-tumor activity was assessed through radiological tumor assessments performed locally that were conducted at screening and during treatment. Assessment of response was made using RECIST version 1.1.

Pharmacokinetics

PK samples were taken during Cycle 1 (pre-dose on Days 1, 8, and 15), Cycles 2 and 3 (pre-dose, 2 h, and 4 h post-dose on Day 1), Cycles 4, 5, and 6 (pre-dose on Day 1), and at the end of treatment. Samples collected for measurement of plasma concentrations of samuraciclib and fulvestrant were analyzed using validated analytical methods (one for each analyte).

Safety assessments

Standard safety assessments were performed throughout the study, including physical examination, vital signs, blood pressure, pulse rate, temperature, respiratory rate, ECOG performance status, ECGs, biochemistry, hematology, and urinalysis.

Biomarkers

Screening blood samples were collected from all participants, prior to randomization, for central laboratory confirmation of *TP53* mutation status by ctDNA analysis with the Guardant360 assay. *AKT*/*PIK3CA*/*PTEN* and *ESR1* status were determined from the same baseline Guardant360 ctDNA analysis.

Trial endpoints

The primary endpoint was CBR (CR, PR, or SD [≥24 weeks after randomization]). Secondary endpoints were AEs and laboratory abnormalities as graded by NCI CTCAE v5.0, PFS, ORR, DOR, and samuraciclib and fulvestrant PK parameters. Tertiary/exploratory endpoints included exposure/response analyses, subgroup analyses for PK, and biomarker analyses. Lesions underwent investigator assessment per RECIST v1.1. As this was a randomized study, confirmation of response was not required, the CBR and ORR include confirmed and unconfirmed responses.

Statistics and reproducibility

The study is not designed to perform a formal hypothesis test but rather to evaluate two dosages of samuraciclib in combination with fulvestrant with the presence of fulvestrant monotherapy to establish an optimal dosage based on the totality of anti-tumor activity in the overall and biomarker-selected populations, along with safety and tolerability data observed from this study.

The primary efficacy analysis population was the full analysis set (All enrolled participants who were randomized [ITT]. Participants were analyzed according to the treatment they were randomized to receive. CBR was defined as the number and percentage of patients with CR or PR at any time or stabilization of disease/Non-CR/Non-PD (for participants with non-measurable disease) for at least 24 weeks, along with the corresponding 2-sided 90% confidence interval calculated using the Wilson score method. The odds ratio and the corresponding 2-sided 90% confidence interval were calculated.

Statistical analyses of PFS using the Kaplan–Meier method were performed on the FAS. AEs were summarized for the Safety Population (defined as all patients who received at least 1 dose of study intervention) using the MedDRA system organ class (SOC), preferred term (PT), and graded according to CTCAE V5.0 (Supplementary Information).

Data collection was performed using the Inform clinical data management system. All non-standard Clinical Data Analysis and Reporting System (CDARS) code was generated using SAS version 9.4 in the LINUX production environment.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The individual participant data from this study cannot be made publicly available due to the sponsor's, Carrick Therapeutics, contractual obligations. Data may be requested after the product and indication have been approved by major health authorities and/or 24 months after completion of all the clinical study reports for the reported arms of the NCT05963984 trial (anticipated to be completed by the end of 2027). Researchers should submit a proposal to the corresponding author (spernas@iconcologia.net) outlining the reasons for requiring the data. Applications should specifically outline the data the parties are interested in receiving and how the data will be used; the use of the data must also comply with the country- or region-specific regulations and will be supplied as de-identified data so individual participants cannot be identified. The corresponding author and sponsor will endeavor to respond to requests within 6 weeks of receipt. A signed data access agreement with the sponsor is required before accessing the shared data, and access will be limited to a defined period (to be agreed with the requester). The study protocol is included in the Supplementary Information file (Supplementary Note 2). The remaining data are available within the article and its Supplementary Information. Source data are provided with this paper.

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Author contributions

These authors jointly supervised this work (recruiting investigators, being involved in study design and data interpretation): S.P., C.K., C.G-N., S.A., M.B.E., N.K., O.Y., M.A-K., B.B.d.l.H., M.G.C., M.G., C.H., R.L.M., E.dlM.J., C.Z.F.d.V., C.A., S.K., M.M.G., D.M-K., J.P., T.P., G.S., and R.C.C. The following authors are Carrick employees and were involved in the study design and data interpretation: G.C., A.B., S.M.

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Competing interests

S.P. has received an institutional grant from Roche, consulting fees from AstraZeneca-Daiichi-Sankyo, Ely-Lilly, Novartis, Pfizer, MSD-Merck, Gebro Pharma, Reveal, and Jiangsu Hengrui Pharma, payments or honoraria from AstraZeneca-Daiichi-Sankyo, Gilead, Lilly, Pfizer, Novartis, and Roche, support for attending meetings from Gilead, Pfizer, Menarini, Novartis, and Roche, and is a member of SOLTI's Executive Board and Scientific Committee. C.K. has received consulting fees and payments or honoraria from AbbVie, Gilead, Novartis, Pfizer, and Roche, support for attending meetings from Pfizer, and Novartis, and participation on a data safety monitoring board or advisory board from Gilead, Novartis, Pfizer, and Roche. M.B.E. has received consulting fees from Pfizer, Novartis, Lilly, Roche, AstraZeneca, Stemline-Menarini, and Merck Sharpe & Dohme, has received payments or honoraria from Pfizer, Novartis, Lilly, Roche, AstraZeneca, Stemline-Menarini, and Merck Sharpe & Dohme, has received support for attending meetings from Pfizer, Novartis, Roche, and Stemline-Menarini, and has participated on a data safety monitoring board or advisory board for Pfizer, Novartis, Lilly, Roche, AstraZeneca, Stemline-Menarini, and Merck Sharpe & Dohme. O.Y. has received consulting fees from Roche, Novartis, Pfizer, Astellas, and Bristol Myers Squibb, payments or honoraria from Roche, Merck, Bristol Myers Squibb, Novartis, Pfizer, Astellas, and Merck Sharpe & Dohme, and support for attending meetings from Roche, Bristol Myers Squibb, AstraZeneca, Novartis, Pfizer, and Astellas. M.A-K. has received grants from Pfizer, Lilly, and Genentech. B.B.dlH. has received consulting fees from Pfizer, Novartis, Menarini, and Gilead, payments or honoraria from AstraZeneca, Daiichi-Sankyo, and Pfizer, payments for expert testimony from Roche, and Merck Sharpe & Dohme, and support for attending meetings from Roche, Pfizer, and Gilead. M.G. has received consulting fees from Roche, Pfizer, AstraZeneca, and Amgen, payment of honoraria from Bayer, Roche, Astellas, Pfizer, and Amgen, and support for attending meetings from Roche. C.H. has received payments for presentations from Novartis, Lilly, Pfizer, and Daiichi-Sankyo, and support for attending meetings from Gilead. R.L.M. has received payments or honoraria from Advanced Accelerator Applications, Johnson & Johnson, Astellas, Roche, Bayer, Sanofi, IPSEN, AstraZeneca, and Pfizer, payment for expert testimony from Johnson & Johnson, Merck, Pfizer, Orion Pharma, and Advanced Accelerator Applications, support for attending meetings from Roche, Astellas, Sanofi, Johnson & Johnson, Merck Sharpe & Dohme, Bristol Myers Squibb, and Merck. C.A. has received payments or honoraria from Bristol Myers Squibb, Johnson & Johnson, Teva, Amgen, Bayer, Roche, Novartis, Merck, AstraZeneca, Astellas, Delcath, and Merck Sharpe & Dohme, and support for attending meetings from Bristol Myers Squibb, Johnson & Johnson, Teva, Amgen, Bayer, Roche, Novartis, Merck, AstraZeneca, Astellas, Delcath, Merck Sharpe & Dohme, and Pfizer. M.M.G. has received payments or honoraria from Novocure, support for attending meetings from Roche, Pfizer, Gilead Sciences, Daiichi-Sankyo, AstraZeneca, Boehringer Ingelheim, and Beone, and participation on a data safety monitoring board or advisory board for Boehringer Ingelheim, Pfizer, Gilead Sciences, and Novocure. J.P. has received an institutional grant from AstraZeneca, payments or honoraria from AstraZeneca, Lilly, Novartis, Pfizer, and Roche, support for attending meetings from AstraZeneca, Gilead, Novartis, Pfizer, and Roche, and participation on a data safety monitoring board or advisory board for AstraZeneca, Guardant Health, Menarini-Stemline, Merck Sharpe & Dohme, and Roche. T.P. has received an institutional grant from Pfizer, BioNTech, Daiichi, AstraZeneca, Gilead, BridgeBio, Merck, Celcuity, Jazz Pharma, Arvinas, Scorpion/Lilly, Sermonix, BMS, Daiichi, BioNTech, Iambic, BridgeBio, and Pfizer, consulting fees from Pfizer, Natera, SAGA diagnostics, and Lilly, and payment for speaking from Gilead, Pfizer, Stemline, and AstraZeneca. G.C., A.B., and S.M. are employees and shareholders of Carrick Therapeutics. R.C.C. has had a travel grant from, is on the advisory board of, and is a shareholder of Carrick Therapeutics, and owns a patent on samuraciclib (patent number WO/2015/124941). The remaining authors declare no competing interests.

Additional information

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