San Antonio Breast Cancer Symposium®, December 7–10, 2021

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

R. Charles Coombes, MD, PhD, FMedSci,[1] Sacha Howell,[2] Matthew G. Krebs,[2] Simon Lord,[3] Laura Kenny,[1] Ash Bahl,[4] Glen Clack,[4] Edward Ainscow,[4] Paul A Dickinson,[5] Raluca Fostea,[6] Janine Mansi,[7] Carlo Palmieri,[8] Gianfilippo Bertelli,[9] Paul Richards,[10] Rinath Jeselsohn,[11] Zahi Mitri,[12] William Gradishar,[13] Sagar Sardesai,[14] Joyce O'Shaughnessy,[15] Patrick Ward,[16] Pavani Chalasani,[17] Manfred Lehnert,[4] Simak Ali[1] and Stuart McIntosh[4]

[1]Imperial College, London, UK; [2]The Christie NHS Foundation Trust, The University of Manchester, Manchester, UK; [3]Churchill Hospital, Oxford University Department of Oncology, Oxford, UK; [4]Carrick Therapeutics, Dublin, Ireland; [5]Seda Pharmaceutical Development Services, Macclesfield, UK; [6]The Wellington Hospital, London, UK; [7]Guy's and St Thomas' NHS Foundation Trust, London, UK; [8]The Clatterbridge Cancer Centre, Liverpool, UK; [9]Brighton & Sussex University Hospitals NHS Trust, Brighton, UK; [10]Blue Ridge Cancer Care, Salem, VA, USA; [11]Dana-Farber Cancer Institute, Boston, MA, USA; [12]Oregon Health Sciences University Knight Cancer Institute, Portland, OR, USA; [13]Northwestern University, Chicago, IL, USA; [14]The James Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [15]US Oncology Network, Dallas, TX, USA; [16]US Oncology Network, Cincinnati, OH, USA; [17]University of Arizona Cancer Center, Tucson, AZ, USA

Disclosures

- Professor Coombes holds a patent for samuraciclib, has shares and a travel grant from Carrick Therapeutics and is the recipient of a grant from AstraZeneca

Unmet need in advanced/metastatic HR+/HER2- breast cancer

No current agreed standard of care for treatment of women with advanced HR+ breast cancer who progress on CDK4/6 inhibition

- First-line standard of care: CDK4/6 inhibitor + aromatase inhibitor or CDK4/6 inhibitor + SERD[1,2]
- Key treatment options following progression (chemotherapy, mTOR inhibitor, PIK3CA inhibitor) are unsatisfactory in terms of efficacy and/or toxicity[1,3–5]
  - Toxicity includes myelosuppression, neuropathy, skin reactions, pneumonitis, hyperglycemia and alopecia
- Hormonal therapy is well tolerated, but efficacy is limited following prior CDK4/6 inhibitor therapy[6]

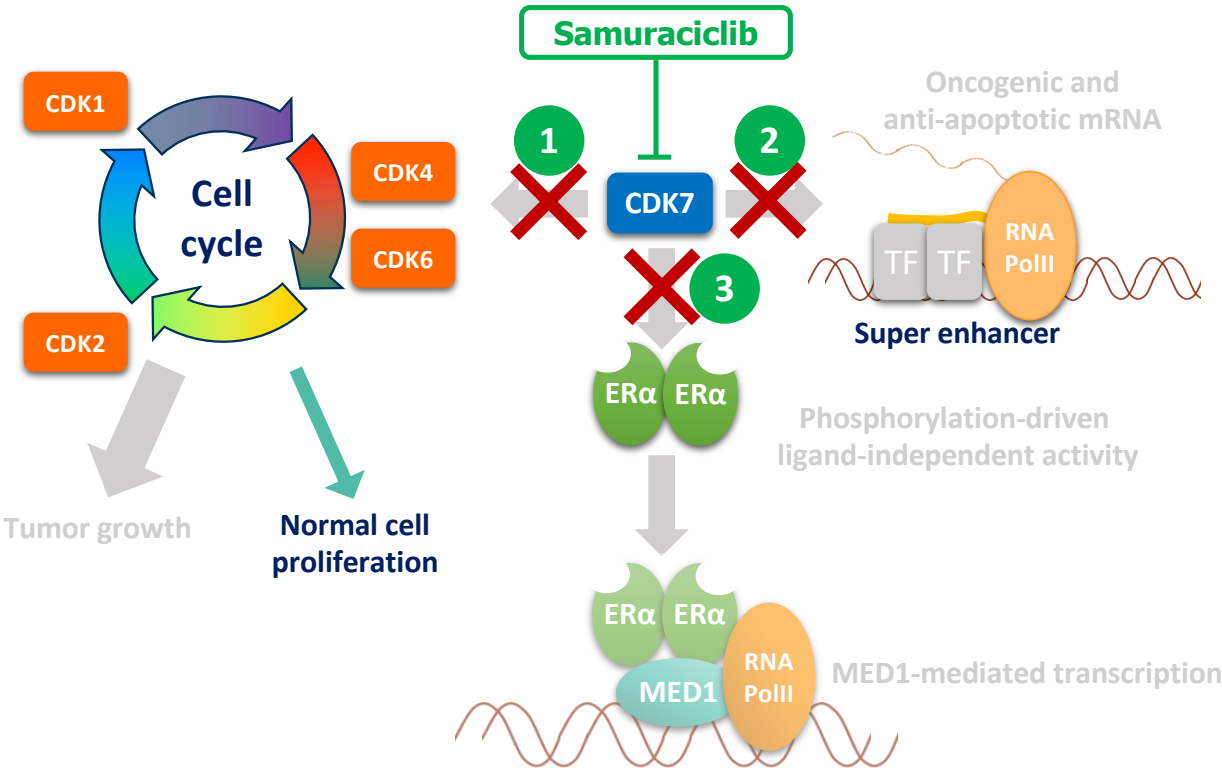
CDK, cyclin-dependent kinase; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mTOR, mammalian target of rapamycin; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; SERD, selective estrogen receptor degrader

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, version 8.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (last accessed 13 October 2021); 2. Cardoso F, et al. Ann Oncol 2020;31:1623–49; 3. Cook MM, et al. Oncologist 2021;26:101–6; 4. Dhakal A, et al. Breast Cancer 2020;14:1–6; 5. Rugo HS, et al. Lancet Oncol 2021;22:489–98; 6. Lindeman GJ, et al. J Clin Oncol 2021;39(Suppl.):Abstract 1004

The CDK7 inhibitor samuraciclib (CT7001)

- Once-daily, oral, small molecule, ATP-competitive, selective inhibitor of CDK7
- Synergistic with hormonal therapy in HR+ breast cancer xenograft models
- Blocks CDK7-mediated oncogenic effects

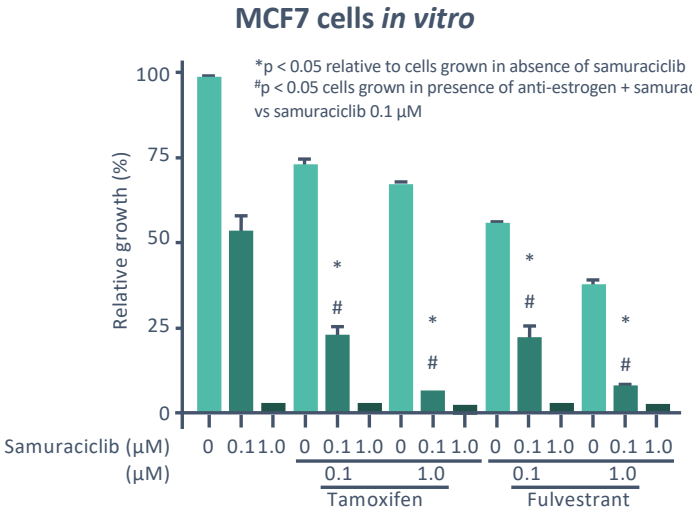
1. The cell cycle through phosphorylation of other CDKs
2. Transcription of oncogenic and anti-apoptotic genes
3. Signaling by and activation of hormone receptors (ER and AR)

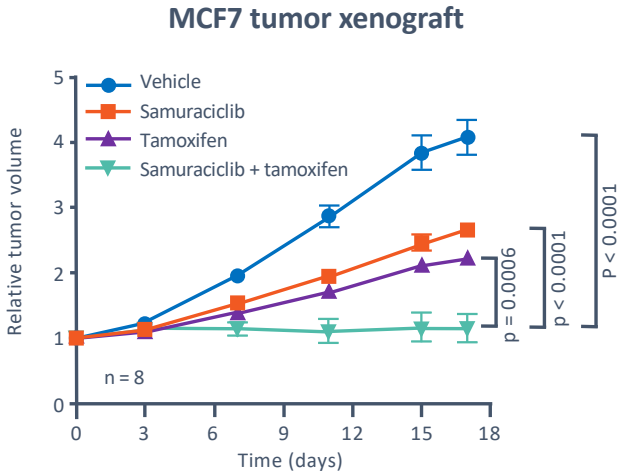


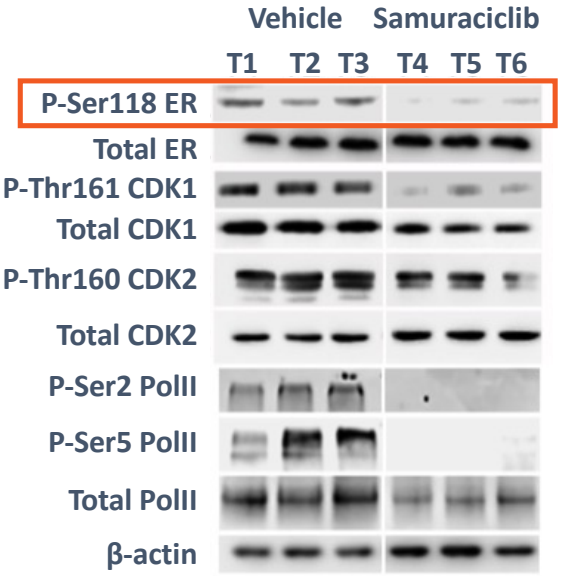
Patel H, et al. Mol Cancer Ther 2018;17:1156–66

Samuraciclib synergises with hormonal therapy

- Samuraciclib inhibition of ER+ breast cancer growth strongest in combination
- Active with tamoxifen and fulvestrant via direct inhibition of ER phosphorylation







Patel H, et al. Mol Cancer Ther 2018;17:1156–66

Study design and objectives (NCT03363893)

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 QD + fulvestrant 500 mg q4w (n=6)** → **Samuraciclib 360 mg QD + fulvestrant 500 mg q4w (n=25)**

Objectives

- To determine the dosing regimen(s) of samuraciclib and fulvestrant to be taken into a subsequent randomized, phase 2 trial
- 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 tumor assessment; used for ORR and CBR analyses

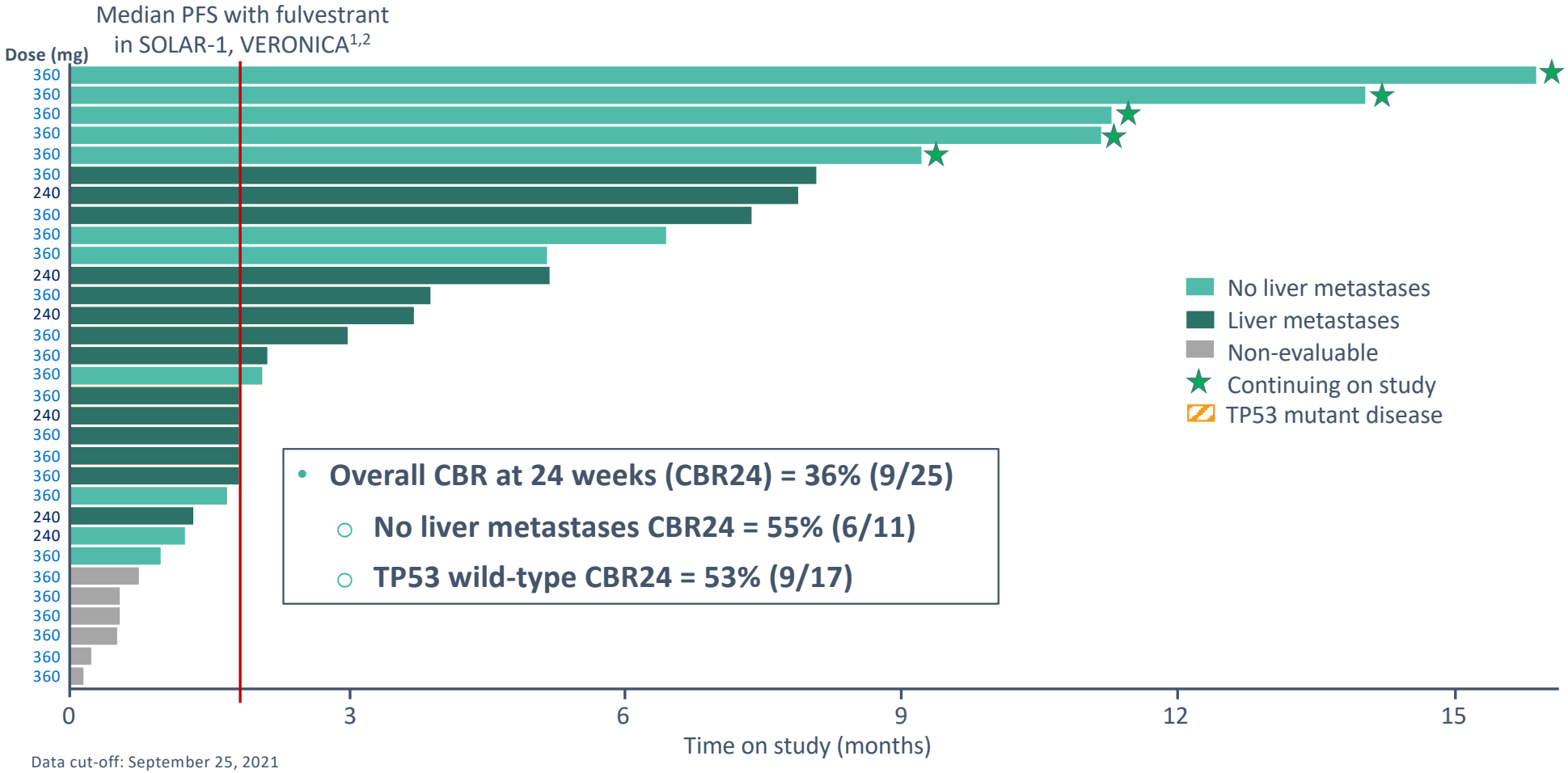
CBR, clinical benefit rate; ITT, intent to treat; ORR, objective response rate; PFS, progression-free survival; PGR, progesterone receptor; QD, once daily

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+, n (%)	31 (100)
Location of lesions, n (%)*	
Visceral disease	25 (81)
Bone	18 (58)
Liver	14 (45)
Lymph node	11 (36)
Other	6 (19)
Lines of prior endocrine therapy for metastatic disease, n (%)	
≥1	31 (100)
≥2	4 (13)
Prior CDK4/6 inhibitor-containing therapy, n (%)	31 (100)
Prior chemotherapy, n (%)	
Metastatic setting	7 (23)
Adjuvant setting	10 (32)
Neoadjuvant setting	3 (10)

*Patients may have had lesions in multiple sites
RECIST, Response Evaluation Criteria In Solid Tumors

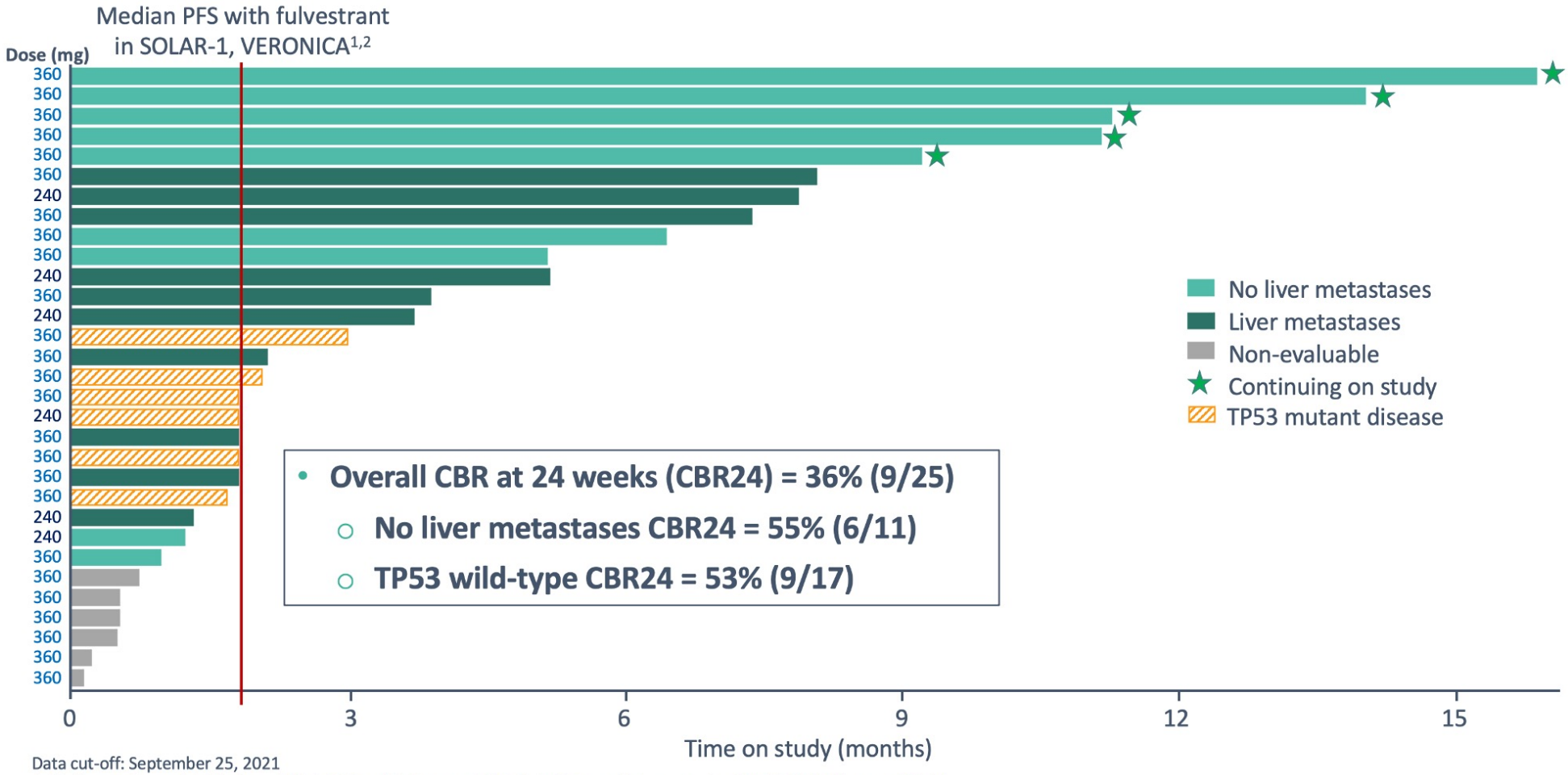
Samuraciclib-based therapy shows durable efficacy



Data cut-off: September 25, 2021

1. Lindeman GJ, et al. J Clin Oncol 2021;39(Suppl.):Abstract 1004; 2. Juric D, et al. Presented at SABCS 2018:Abstract GS3-08

Samuraciclib-based therapy shows durable efficacy

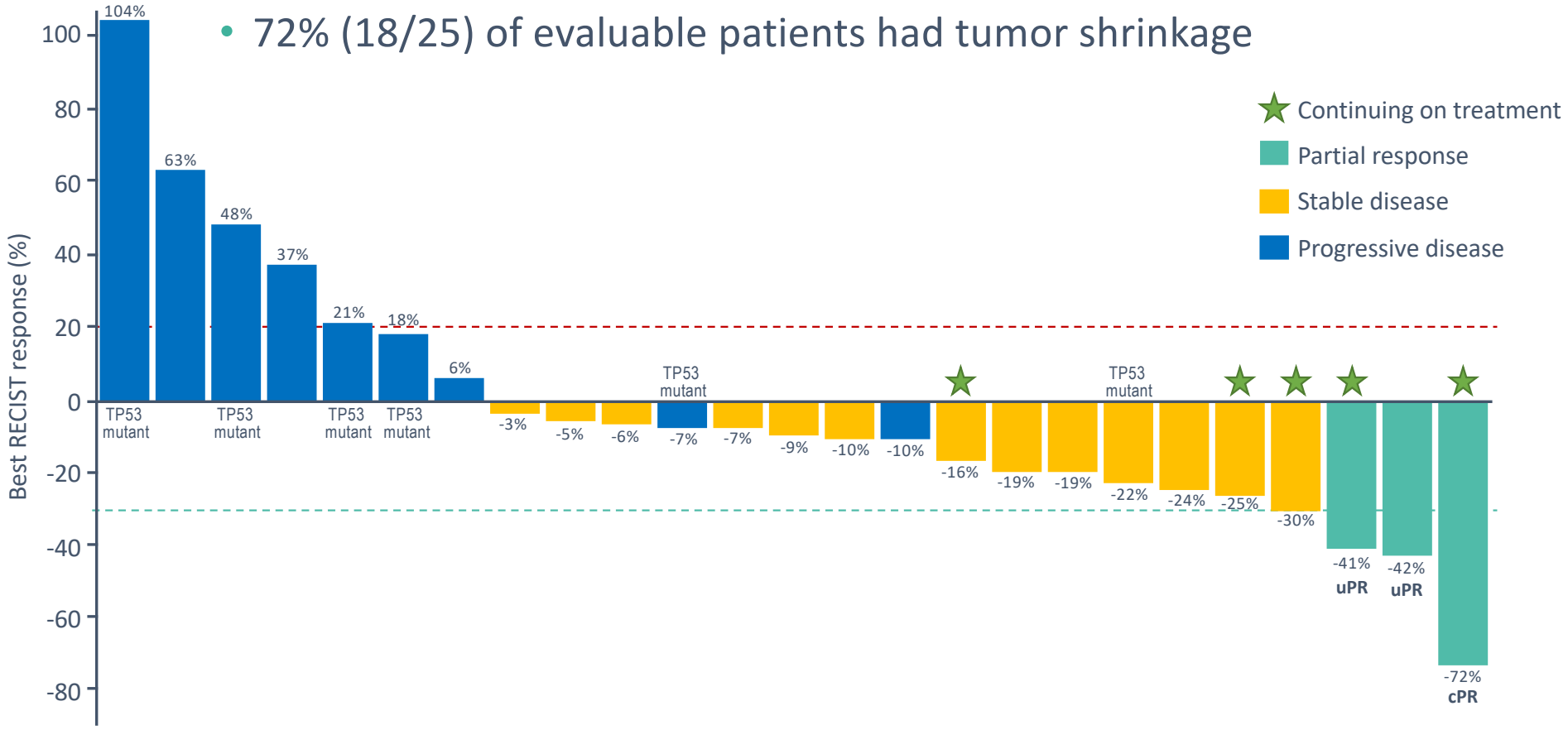


Data cut-off: September 25, 2021

1. Lindeman GJ, et al. J Clin Oncol 2021;39(Suppl.):Abstract 1004; 2. Juric D, et al. Presented at SABCS 2018:Abstract GS3-08

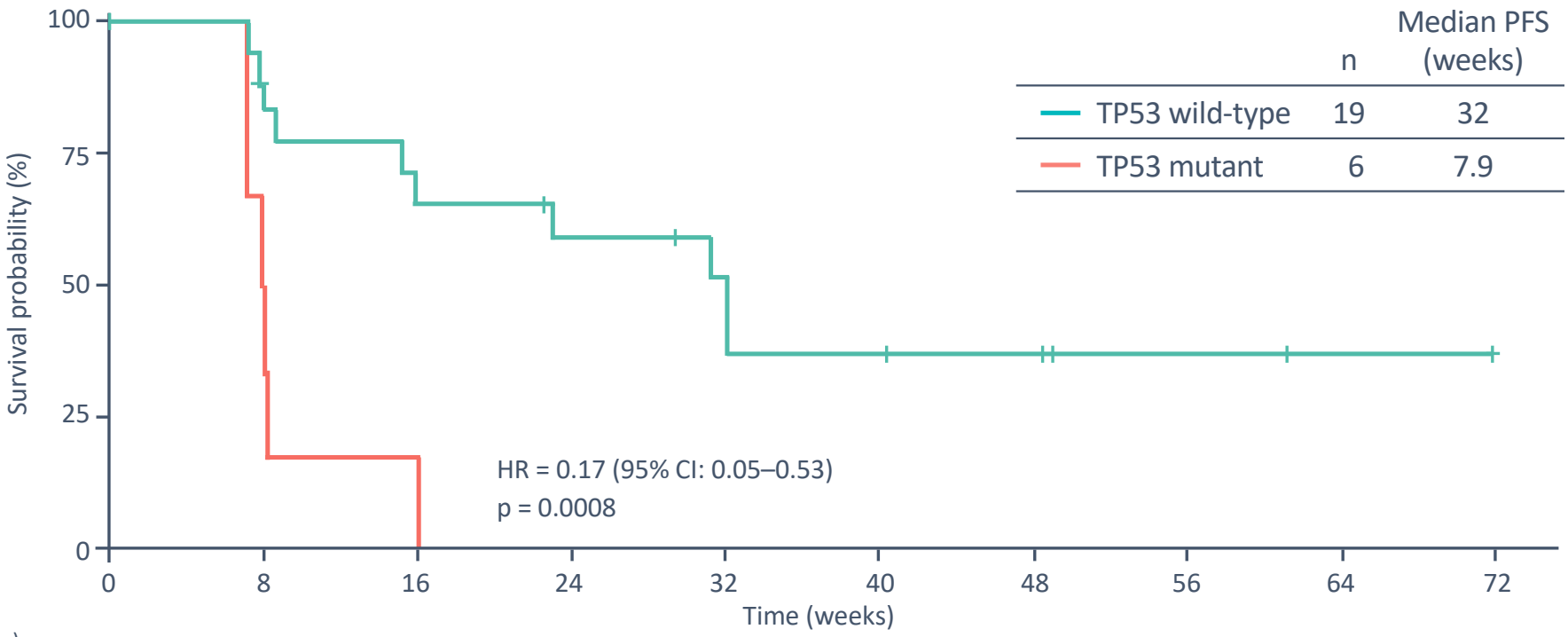
Best RECIST response confirms that samuraciclib-based therapy is active

- 72% (18/25) of evaluable patients had tumor shrinkage



cPR, confirmed partial response; uPR, unconfirmed partial response, based on RECIST criteria
Data cut-off: September 25, 2021

Median PFS by TP53 status

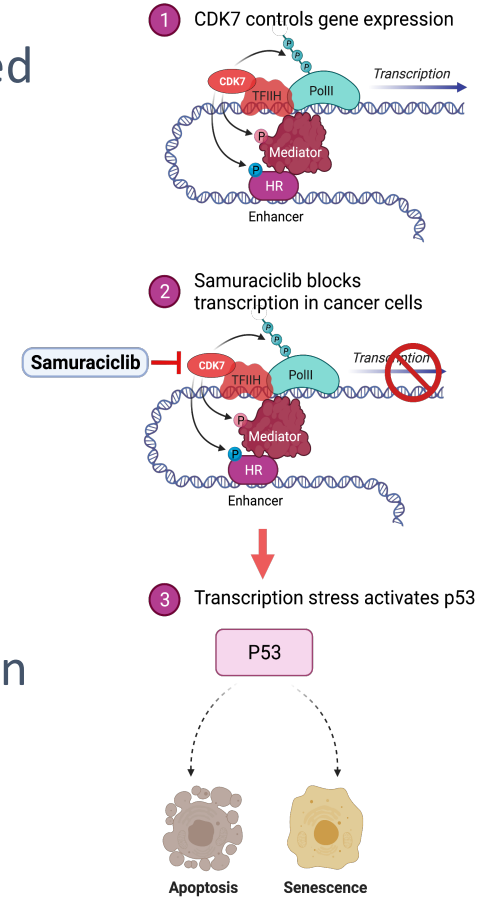


At risk (n)									
TP53 wild-type	19	14	11	9	7	5	4	2	1	0
TP53 mutant	6	3	1	0	0	0	0	0	0	0

HR, hazard ratio
Data cut-off: September 25, 2021

Tumour TP53 status appears to predict outcome of samuraciclib therapy

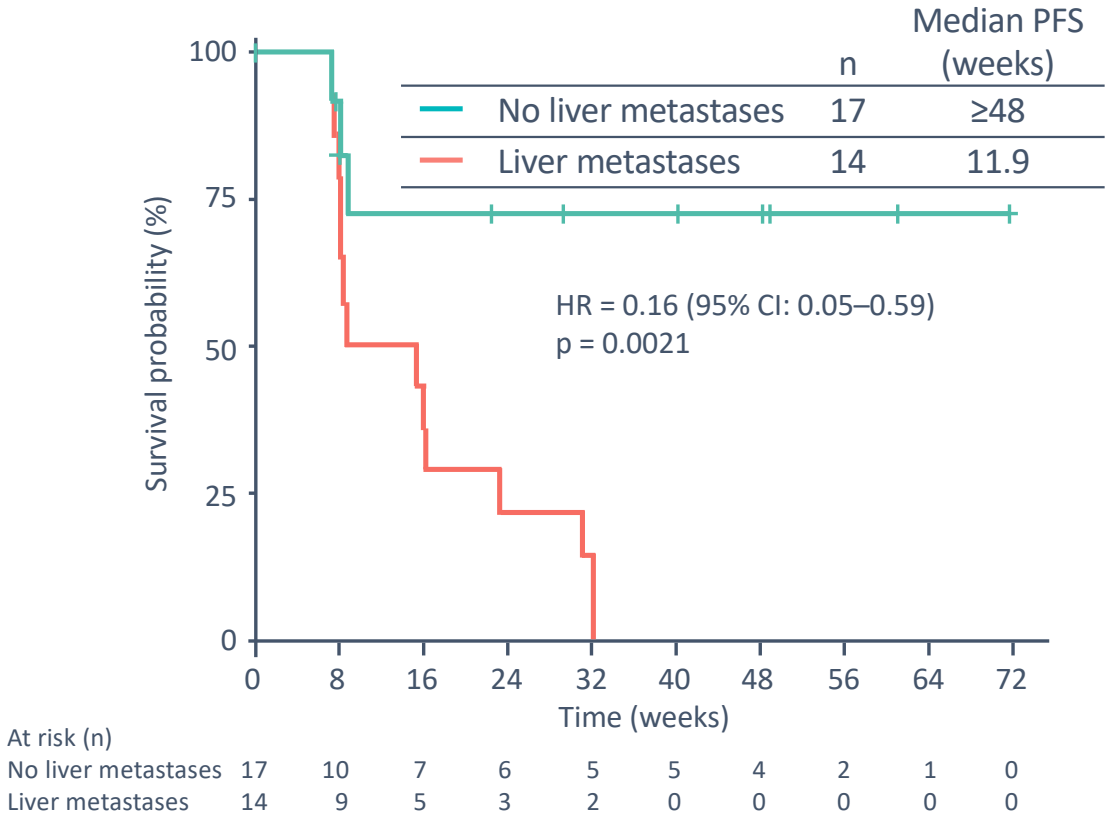
- Impact of TP53 mutation in this study is greater than that reported for a range of other therapies
- Preclinical data indicate that CDK7 inhibition activates the p53 pathway in TP53 wild-type, HR+ breast cancer cells, inducing apoptosis[1–3]
- p53 pathway activation by samuraciclib appears to work in combination with the other effects of CDK7 inhibition to control cancer growth
- Patients with TP53 wild-type tumors represent ≈70% of patients in this setting,[4–6] meaning that samuraciclib has the potential to benefit the majority of patients



TFIIH, transcription factor IIH

1. Wang Y, et al. Mol Biosci 2021 (https://doi.org/10.3389/fmolb.2021.697457); 2. Ali S, et al. Cancer Res 2009;69:6208–15; 3. Ali S, et al. unpublished data;
4. Razavi P, et al. J Clin Oncol 2019;37(Suppl):Abstract 1009; 5. Jhaveri K, et al. Presented at ESMO Breast Cancer 2020:Abstract LBA1; 6. Andre F, et al. J Clin Oncol 2021;39(Suppl):Abstract 1015

Median PFS by baseline liver metastasis status



- Median PFS not yet reached in patients without baseline liver metastases
- Presence of liver metastases is a known risk factor for poor prognosis in patients with HR+ breast cancer
- The strength of the effect observed suggests that liver metastases have predictive potential for clinical benefit from samuraciclib-based therapy
- This will be evaluated in future studies

Data cut-off: September 25, 2021

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

Adverse event	All grades, n (%)	Grade ≥3, n (%)
Diarrhea	28 (90)	6 (19)
Nausea	25 (81)	3 (10)
Vomiting	23 (74)	1 (3)
Fatigue	11 (36)	1 (3)
Decreased appetite	9 (29)	0
Abdominal pain	7 (23)	0
AST increased	4 (13)	0
Dysgeusia	4 (13)	0
Headache	4 (13)	0
Upper abdominal pain	4 (13)	0

- Reversible, low-grade GI events were most common
- Of 11 patients who had dose reductions, 9 continued treatment
- No neutropenia or significant myelosuppression observed
- Long-term samuraciclib administration achieved in many patients
  - 6 patients discontinued due to GI events
- Ondansetron prophylaxis is now routine for patients receiving samuraciclib

GI, gastrointestinal
Data cut-off: July 8, 2021

Conclusions and future directions

- Samuraciclib + fulvestrant is active in CDK4/6 inhibitor-pretreated HR+ breast cancer
- Baseline tumor TP53 wild-type status (per ctDNA) may predict extended benefit from samuraciclib-based therapy in these patients
- Samuraciclib will be co-administered with oral SERDs in future clinical studies to extend the limited PFS benefit of single-agent endocrine therapy
- Samuraciclib has been granted fast-track status by the US FDA

ctDNA, circulating tumour DNA; FDA, Food and Drug Administration

Acknowledgements

The authors would like to thank:

- The patients who participated in this trial and their families
- The physicians and nurses who recruited and treated patients and all those involved in the conduct of the trial
- Trial funded by Carrick Therapeutics
- Cancer Research UK Manchester (Dominic Rothwell, Daniel White and Alexander Jordan) for performing the ctDNA analyses
- Cancer Research UK for supporting the discovery of samuraciclib