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First in human, modular study of samuraciclib (CT7001), a first-in-class, oral, selective inhibitor of CDK7, in patients with advanced solid malignancies

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Background

CDK7 inhibition is a promising therapeutic strategy in cancer. CDK7 is a key kinase, regulating cell division, transcription and nuclear receptor function, particularly the oestrogen receptor.

Methods

Tolerability, pharmacokinetics and efficacy of samuraciclib were assessed; including evaluation of ascending doses (M1A), paired tumour biopsy (PB) samples (M1A), effect of food on bioavailability (M4) and a triple-negative breast cancer (TNBC) expansion cohort (M1B).

Results

M1A recruited 33 patients in 5 cohorts: 120, 240, 360mg and 480 mg once daily (OD), and 180 mg twice daily (BID). 11 further patients were dosed in PB cohorts for pharmacodynamic assessment. M4 recruited 15 patients. M1B recruited 23 patients. At 120 mg, 240 mg and 360mg, most common adverse drug reactions (AE) were: G1-2 nausea, vomiting and diarrhoea. At 480 mg, 3/6 patients experienced a DLT (G3 diarrhoea, G3 oral mucositis, G3 vomiting). At 180mg BD, 1/7 patients experienced a DLT (G4 thrombocytopaenia). 240mg OD and 360 mg OD were determined clinically relevant doses, with 360mg OD as the preliminary recommended phase 2 dose. In fasted patients, median T_{max} = 1.5 - 4 hrs and geomean $T_{1/2}$ ⊠ 75 hrs. Steady-state was achieved within 8 - 15 days. Plasma exposure increased dose proportionally; pharmacologically active exposures were achieved throughout the entire dosing period. Food had no clinically significant effect on exposure. 57% (25/44) of RECIST evaluable patients had evidence of disease control at first post baseline scan (FPBS) observed across the ‘all comer’ cohorts in M1A and M4, including a partial response (PR) in a patient with HR+ breast cancer; PSA reductions were observed in the 4 castrate-resistant prostate cancer patients recruited. Preliminary tumour biopsy data supports tumour target engagement. 20 patients with TNBC were evaluable for RECIST assessment: 12/20 had stable disease at FPBS; 3 have been on treatment > 1 year.

Conclusions

Samuraciclib has demonstrated an acceptable safety profile with evidence of anti-tumour activity.

Clinical trial identification

2017-002026-20.

Legal entity responsible for the study

Carrick Therapeutics.

Funding

Carrick Therapeutics.

Disclosure

M.G. Krebs: Financial Interests, Personal, Advisory Board: Roche; Financial Interests, Personal, Advisory Board: Janssen; Financial Interests, Personal, Advisory Board: Bayer; Financial Interests, Personal, Advisory Board: Seattle Ger; Financial Interests, Personal, Advisory Board: Om Pharma; Financial Interests, Personal, Invited Speaker: Roche; Financial Interests, Personal, Speaker's Bureau: Janssen; Financial Interests, Personal, Other, travel expenses: BerGenBio; Financial Interests, Personal, Other, travel expenses: Immutep; Financial Interests, Institutional, Research Grant: Roche; Financial Interests, Institutional, Research Grant: Bergenbio; Financial Interests, Personal, Advisory Board: Achilles Therapeutics; Financial Interests, Institutional, Principal Investigator: Carrick; Financial Interests, Institutional, Principal Investigator: Turning Point; Financial Interests, Institutional, Principal Investigator: Janssen; Financial Interests, Institutional, Principal Investigator: Roche; Financial Interests, Institutional, Principal Investigator: AstraZeneca; Financial Interests, Institutional, Principal Investigator: Blueprint; Financial Interests, Institutional, Principal Investigator: bergenbio; Financial Interests, Institutional, Principal Investigator: Immutep; Financial Interests, Institutional, Principal Investigator: Astellas; Financial Interests, Institutional, Principal Investigator: Seattle Ger. S. Lord: Financial Interests, Personal, Other: Eisai; Financial Interests, Personal, Other: Prosigna; Financial Interests, Personal, Other: Roche; Non-Financial Interests, Personal, Advisory Board: Shionogi; Non-Financial Interests, Personal, Advisory Board: Sanofi; Financial Interests, Institutional, Research Grant: CRUK; Financial Interests, Institutional, Research Grant: Against Breast Cancer; Financial Interests, Institutional, Research Grant: Pathios Therapeutics; Financial Interests, Personal, Funding: Pfizer; Financial Interests, Personal, Funding: Roche; Financial Interests, Personal, Funding: Synthon; Financial Interests, Personal, Funding: Piqur Therapeutics; Financial Interests, Personal, Stocks/Shares: Mitox Therapeutics; Financial Interests, Personal, Full or part-time Employment: Pfizer. A. Bahl: Financial Interests, Personal, Stocks/Shares: Carrick Therapeutics; Financial Interests, Personal, Full or part-time Employment: Carrick Therapeutics. G. Clack: Financial Interests, Personal, Stocks/Shares, Employee: Carrick Therapeutics; Financial Interests, Personal, Stocks/Shares: Athenex Inc. E. Ainscow: Financial Interests, Personal, Full or part-time Employment: Carrick Therapeutics; Financial Interests, Personal, Stocks/Shares: Carrick Therapeutics; Financial Interests, Personal, Stocks/Shares: Astrazeneca. A.G. Barrett: Financial Interests, Institutional, Full or part-time Employment: Imperial College. P. Dickinson: Financial Interests, Institutional, Full or part-time Employment: Seda Pharma Development Services Ltd . M.J. Fuchter: Financial Interests, Personal, Full or part-time Employment: NK:IO Ltd; Non-Financial Interests, Personal and Institutional, Full or part-time Employment: IMperial College Hospital. M. Lehnert: Financial Interests, Personal, Full or part-time Employment: Carrick Therapeutics; Financial Interests, Personal, Stocks/Shares: Carrick Therapeutics.S. Ali: Financial Interests, Personal, Stocks/Shares: Carrick Therapeutics. S. Mcintosh: Financial Interests, Personal, Stocks/Shares: Carrick Therapeutics; Financial Interests, Personal, Full or part-time Employment: Carrick Therapeutics. R.C. Coombes: Financial Interests, Personal, Stocks/Shares: Carrick Therapeutics; Financial Interests, Personal, Funding: AstraZeneca. All other authors have declared no conflicts of interest.