Abstract citation ID: oyaf276.011

10

Investigating the mechanisms of neoadjuvant olaparib and cediranib in renal cancer: results of arms 1 to 3 of the WIndow of opportunity in REnal cancer (WIRE) clinical trial

James Jones[1], Rebecca Wray[1], Ines Horvat Menih[2], Martin Thomas[3], Sulekha Said[3], Helen Mossop[4], Maria Aquino[3], James Arimtage[3], Harriet Baker[2], Carley Batley[5], James Blackmur[6], Sarah Burge[1], Anita Chhabra[3], Farhana Easita[5], Tim Eisen[5], Kate Fife[3], Angela Godoy[5], Richard Goodwin[7], Will Ince[3], Rose John[3], Alexander Laird[6], Natalia Lukashchuk[7], Athena Matakidou[3], Thomas Mitchell[8], Andrew Priest[2], Andrew Protheroe[9], Sreenidhi Ranjit[3], Anthony Riddick[3], Jamal Sipple[3], Amy Strong[3], Helen Su[5],

Mark Sullivan[9], Silvia Tarantino[3], Gemma Tsang-Pells[5], Stephan Ursprung[10], Lauren Wallis[5], Anne Warren[3], James Wason[4], Sarah Welsh[11], Younghwa Kim[7], John Stone[7], Mireia Crispin-Ortuzar[1], Ferdia Gallagher[2], on behalf of the WIRE Trial Group

[1]Department of Oncology, University of Cambridge, [2]Department of Radiology, University of Cambridge, [3]Cambridge University Hospitals NHS Foundation Trust, [4]University of Newcastle, [5]University of Cambridge, [6]Western General Hospital, Edinburgh, [7]AstraZeneca, [8]Department of Surgery, University of Cambridge, [9]Oxford University Hospitals NHS Foundation Trust, [10]Beatson West of Scotland Cancer Centre, [11]Royal Devon University Healthcare NHS Foundation Trust

Background: New treatments are required for patients with resistance to current renal cell cancer (RCC) therapies. In contrast to the success of immunotherapy and VEGF directed therapies, few treatments have successfully targeted the RCC cell directly. Pre-clinical data suggests that PARP inhibitors have activity against RCC, and PARP inhibitors have been investigated in advanced RCC either alone or combined with VEGF directed therapy. Neoadjuvant window of opportunity studies allow us to understand drug mechanism by comparing the tumour before and after treatment. WIRE (WIndow of opportunity in REnal Cancer) is a phase II, multi-centre, multi-arm, non-randomised, neoadjuvant clinical trial platform (NCT03741426) investigating novel RCC treatments. Here we report updated outcome data for arms 1-3 and ongoing translational analysis.

Methods: WIRE enrols patients with clear cell RCC, planned to have surgery, stage cT1b+, cN0/1, cM0/1, with no contraindication to IMP. A Bayesian adaptive design with pre-defined stop/go criteria efficiently assigns patients to each arm. Arms 1-3 comprised: 1. cediranib (a VEGF inhibitor), 2. cediranib + olaparib (a PARP inhibitor), 3. olaparib. Patients received 14-28 days of IMP before surgery. The primary endpoint is a ≥30% reduction in dynamic contrast enhanced (DCE) MRI assessed vascular permeability (median Ktrans) post-treatment compared to baseline. Secondary endpoints include a ≥30% increase in IHC-assessed tumour CD8+ T cell density post-treatment compared to baseline, and percentage change in MRI assessed tumour volume. Extensive tissue and blood samples are taken during the trial for mechanistic analysis.

Results: 29 patients were recruited (arm 1 = 6, arm 2 = 16, arm 3 = 7), 28/29 were male, median age 61 years (range 48-75 years). 8 patients had M1 disease. Treatment was well tolerated, and importantly all patients had surgery within the planned window. 3 patients were not evaluable for the primary endpoint due to inadequate dose of IMP (<70% compliance rate in total doses of IMP within 7 days prior to presurgical imaging).

The numbers of evaluable patients which met the primary endpoint for Ktrans reduction were arm 1 (cediranib): 4/6 (67%), arm 2 (cediranib + olaparib): 4/14 (29%), arm 3 (olaparib): 0/6 (0%). For the secondary endpoint of increase in tumour CD8+ T cell density, the numbers were arm 1: 3/6 (50%), arm 2: 9/14 (64%), arm 3: 1/6 (17%). There were reductions in MRI-assessed tumour volume in arms 1 and 2 compared to arm 3 (median change & [range], arm 1: -9.01% [-43.78% to -4.78%]; arm 2: -11.47% [-37.47% to 10.53%]; arm 3: 8.29% [-5.43% to 13.28%]).

In exploratory analysis, there was significant induction of VEGF-A and Placental Growth Factor (PlGF) in plasma prior to surgery compared to baseline in the combination arm 2 (VEGF-A $P = .0330$, PlGF $P = .00071$). There were no correlations between degree of angiogenic cytokine induction and MRI assessed change in Ktrans or tumour volume.

Conclusions: Responses as measured by Ktrans were observed particularly in the cediranib only arm, less so in the combination arm and not at all in the olaparib arm. Within a short duration of therapy, consistent tumour volume reductions occurred in both cediranib containing arms. Greater induction of PlGF and VEGF-A in the combination arm indicates possible synergy between cediranib and olaparib.

Ongoing translational work is investigating the relationship between other DCE-MRI metrics assessed during the trial. Transcriptomics and digital pathology will be performed comparing baseline biopsies with multiple regions sampled at nephrectomy. These methods will define tumour environments associated with response or non-response. Machine learning approaches will be used to integrate the multiple data modalities (Figure 1). Arm 4, using volrustomig—a PD-1/CTLA-4 bispecific antibody is actively recruiting.

Keywords: neoadjuvant; window of opportunity; angiogenesis; PARP; AI

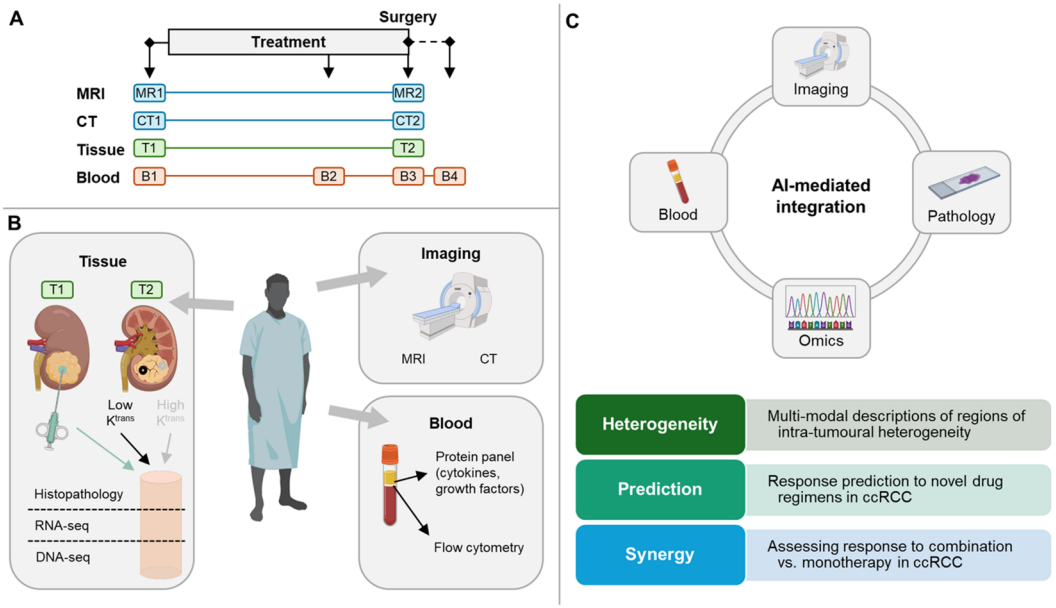

Figure 1. Multimodal data integration in the WIRE Trial

A. Trial schematic showing imaging, tissue and blood collection events. B. Key translational analysis performed on the trial. Biopsies and multi-region tissue samples from nephrectomy will be assessed by histopathology and transcriptomics. Serial blood samples are analysed for cytokine and immune cell profiles. Results will be compared to tumour response as measured by DCE-MRI and CT scanning. C. AI approaches will be used to integrate multiple data modalities to understand tumour response to therapy.