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Navigating through the re-design of a multi-arm, multi-stage (MAMS) trial in light of external data

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Introduction

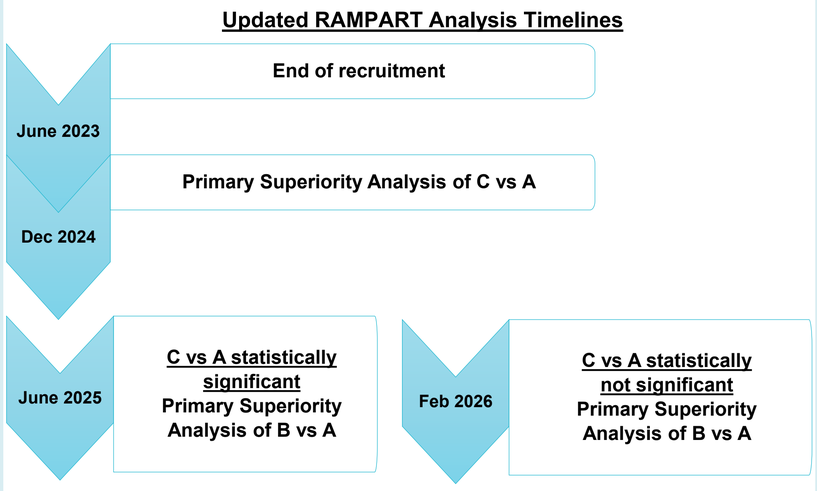
Immune checkpoint inhibitor (ICI) therapy has been shown to improve overall survival and has altered the treatment paradigm for patients with metastatic renal cell cancer (RCC). ICI therapies have been developed by multiple companies and evaluated in the adjuvant RCC setting, where there was no widely accepted standard of care.

Clinical trials to establish the efficacy of adjuvant therapy are lengthy and challenging, typically involving large samples of patients and extended follow-up.

- MAMS platform designs permit the evaluation of multiple treatments simultaneously, while offering the ability to adapt to a changing landscape as data on different agents emerges.
- RAMPART is an international academic-led trial designed to investigate two different ICI regimens compared with a common control arm of active monitoring.
- External evidence following slower than anticipated accrual due to the COVID-19 pandemic meant recruitment was no longer feasible.
- We present the challenges and solutions we employed to make the most of the contribution of our participants and the available randomised evidence.

Analysis Timelines

- The analysis timelines were obtained using the command **`artpep`**, within the ART Stata module.
- RAMPART's control arm data were used to inform the predictions (data from the two research arms were not made available); this led to the precise estimation of analysis timelines.



- The primary outcome will be analysed using flexible parametric models(FPMs). These allow for the inclusion of an interaction term of treatment with time which enables us to test the proportional hazards assumption. Under the assumption of proportional hazards, FPM mirrors the results of a Cox model.

Power and FWER

We set the revised overall power to 80% and maintained the family-wise error rate (FWER) at 2.5% (one-sided) as per the original design. To obtain the critical value for the two pairwise comparisons and control the FWER at 2.5%, we used Dunnett's correction. This enables us to account for the correlation between the two test statistics as both analyses use the same control arm patients. The resulting, Dunnett-corrected, one-sided alpha equals to 1.29%.

Discussion

- Confirmatory clinical trials in the adjuvant setting usually take many years to complete.
- There is a risk that external evidence can affect the ability to complete a trial as planned.
- We propose modifications, maintaining the integrity and power of the trial and using all available randomised evidence
- Timeline predictions in the time-to-event setting are complex and need to be periodically monitored in a blinded manner

If you need to predict the timelines of your analyses using time-to-event outcomes, scan the QR code to obtain the ART paper and get in touch for example code: e.frangou@ucl.ac.uk

Design Modifications

Parameter	Original	Updated
Recruitment duration	5.5 years	5 years
Accrual rate	30/month	10/month
Sample size	1750	790
Primary outcome	Disease-free survival (DFS), Overall survival (OS)	DFS
Interim analyses	3 (B vs. A), 1 (B vs. A)	0
Superiority analyses	B vs. A, C vs. A	B vs. A, C vs. A
Target hazard ratios (HRs)	$HR_{Cvs.A}$ = 0.7, $HR_{Bvs.A}$ = 0.75	$HR_{Cvs.A}$ = 0.55 , $HR_{Bvs.A}$ = 0.60
Target control arm events	276 (C vs. A), 416 (B vs. A)	91 (C vs. A), 102 (B vs. A and C vs. A not significant), 119 (B vs. A and C vs. A significant)
FWER+, one-sided	0.025	0.025
Overall power	0.90	0.80
Underlying survival distribution	SORCE trial (control arm)	RAMPART trial (accumulated data, control arm)

+ *family-wise error rate*

- KEYNOTE-564 was the first trial to report results for a checkpoint inhibitor in the adjuvant RCC setting; pembrolizumab improved DFS compared with placebo (HR = 0.63; 95% CI 0.50–0.80) and was approved for use in the UK and in some countries in Europe where RAMPART was recruiting.
- Recruiting the original target of participants would take an infeasibly long period of time and after discussion with our pharmaceutical partner (Astra Zeneca), recruitment ended earlier; in total, 790 participants were randomised.
- RAMPART's target HRs were modified in line with those observed in KEYNOTE-564. The HR for the monotherapy arm is slightly larger than what was observed in KEYNOTE-564; the HR for the combination arm reflects that a larger effect size would be expected when participants are treated with an additional agent.

Acknowledgments

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RAMPART Registration: ISRCTN53348826

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