Fulvestrant plus capivasertib for metastatic breast cancer

Authors' reply

We thank Tim Johannes Adrianus Dekker for his comments on the molecular analysis done in the FAKTION trial, but disagree that it was "muddled".

The eligibility criteria for the FAKTION trial included patients with non-measurable and bone-only disease. Taking the biopsy success rates from the SAFIR01 study,[1] the maximum achievable biopsy success in FAKTION would have been 60%. We believe that this relatively low success rate, together with data showing genetic heterogeneity between metastases in the same patient, including for PIK3CA[2] and PTEN,[3] indicates that single metastasis biopsy is not necessarily the optimal approach. Additionally, mandating biopsies would exclude many patients and would slow down recruitment.

Of note, in the SOLAR-1 phase 3 trial,[4] which showed improved progression-free survival with the addition of alpelisib to fulvestrant in patients with *PIK3CA*-mutant tumours, the progression-free survival analysis based on circulating tumour DNA was similar to that based on archival tissue analysis, 76% of which was done on primary tumour tissue. Analysis of progression-free survival in the 22 (16%) of 140 participants in FAKTION with metastatic sample biopsies showed a median progression-free survival with and without capivasertib of 9·5 months versus 7·7 months in pathway-altered tumours and 12·1 months versus 10·3 months in pathway non-altered tumours. These data are consistent with improved progression-free survival with capivasertib in both groups, but the numbers are too small to draw firm conclusions.

A phase 3 study (CAPItello-291; NCT04305496), sponsored by AstraZeneca, is due to commence recruitment shortly and will evaluate the efficacy (progression-free survival) and safety of capivasertib plus fulvestrant versus placebo plus fulvestrant in patients in a similar population to that recruited to FAKTION. A key secondary endpoint is progression-free survival in the *PIK3CA/AKT1/PTEN*-altered subgroup. Entry to CAPItello-291 requires the most recently collected tumour tissue be sent for central testing, providing the opportunity for several exploratory analyses on blood and tissue samples.

We also thank Ethan B Ludmir and colleagues for their comments on the overall survival analysis, pointing out that the proportional hazards assumption might not be valid, given that the hazard curves overlap until month 12.

We can confirm that the restricted mean survival time analysis done by the authors is correct. We replicated the analysis using the last common observed time of 32·2 months in both groups and estimated the mean survival over this restricted time. Restricted mean survival time was 22·9 months (95% CI 19·7–26·0) in the capivasertib group and 18·6 months (16·1–21·1) in the placebo group. The observed difference between groups was 4·26 months (0·22–8·30; p=0·039).

We agree that this restricted mean survival time analysis does not require the proportional hazards assumption to be met, could be more efficient in detecting a difference in overall survival for the FAKTION trial, and is helpful in designing and planning future studies. However, this was not a prespecified analysis. Therefore, we did not include it in the original manuscript.

RHJ reports grants from AstraZeneca and Cancer Research UK, during the conduct of the study, and personal fees from Merck Serono and Roche, outside the submitted work. AC reports grants from AstraZeneca and Cancer Research UK and non-financial support from the sponsor of the study, during the conduct of the study. AF is a full-time employee at AstraZeneca receiving a salary and holding shares in AstraZeneca, during the conduct of the trial. SJH reports personal fees from Pfizer and Novartis and non-financial support from Evgen Pharma, outside the submitted work. MC declares no competing interests.

*Robert H Jones, Angela Casbard, Margherita Carucci, Andrew Foxley, Sacha J Howell
robert.hugh.jones@wales.nhs.uk

Velindre Cancer Centre, Cardiff, UK (RHJ); Centre for Trials Research, Cardiff University, Cardiff, UK (AC, MC); Oncology R&D, AstraZeneca, Cambridge, UK (AF); and Division of Cancer Sciences, The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK (SJH)

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