Conclusions: Early on-treatment ctDNA dynamics are a surrogate for PFS. Dynamic ctDNA assessment has the potential to substantially enhance early drug development through targeted therapy and biomarker evaluation.

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6O | **Utility of early circulating tumour DNA dynamics as a surrogate for progression free survival in the BEECH phase I/II trial in metastatic breast cancer**

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Background: Dynamic changes in circulating tumour DNA (ctDNA) levels may predict long-term outcome of therapy. We utilised samples from a phase I/II randomised trial (BEECH) to assess ctDNA dynamics as a surrogate for progression free survival (PFS) and early predictor of drug efficacy.

Methods: Patients with oestrogen receptor positive advanced metastatic breast cancer (ER+ mBC) in the BEECH study were randomised to paclitaxel plus placebo versus paclitaxel plus AKT inhibitor capivasertib. Plasma samples were collected for ctDNA analysis at baseline and at multiple timepoints in the development cohort (safety run-in, part A) and validation cohort (randomised, part B). Baseline sample ctDNA sequencing identified mutations for longitudinal analysis, and mutation specific digital droplet PCR (ddPCR) assays were utilised to assess change in ctDNA allele fraction between baseline and 872 on-treatment samples. Early suppression of ctDNA assessment was used to define criteria in the development cohort and independently evaluated in the validation cohort.

Results: In the development cohort, suppression of ctDNA was evident after 8 days of treatment ($p = 0.014$), with cycle 2 day 1 (4 weeks) identified as the optimal timepoint to predict PFS from early ctDNA dynamics. In the validation cohort, median PFS was 11.1 months in patients with suppressed ctDNA at 4 weeks and 6.4 months in patients with high ctDNA (HR = 0.20, 95% CI $0.083 - 0.50$, $p < 0.0001$). No difference in the level of ctDNA suppression was observed between patients randomised to capivasertib or placebo overall ($p = 0.904$) nor in the PIK3CA mutant subpopulation ($p = 0.071$). Clonal haematopoiesis of indeterminate potential (CHIP) was evident in 30% (18/59) baseline samples and had no effect on tolerance of chemotherapy nor on PFS.