Authors' reply

Birgitte Offersen and Jens Overgaard argue that 26 Gy in five fractions is biologically inferior to 40 Gy in 15 fractions on the basis of α/β point estimates; however, therapeutic ratio is better defined clinically. In the FAST-Forward trial,[1] pre-defined non-inferiority of the 1 week schedule, compared with a 15 fraction control for ipsilateral breast tumour relapse, was substantiated. Combined with similar rates of late adverse effects for patients allocated to the 26 Gy schedule, why not be guided by the data?

Point estimates of α/β values for late normal tissue effects scored by clinicians, patients, and photographic assessments in the FAST-Forward[1], START,[2] and FAST[3] trials have 95% CIs that overlap for each endpoint in all five trials; however, let us assume that the estimated α/β value of 2 Gy for late normal tissue effects of the 5 day schedule is accurate. In this case, 26 Gy in five fractions is equivalent to 47 Gy in 2 Gy fractions, causing 10–15% fewer late adverse effects than the earlier standard 50 Gy in 25 fractions still in use. Based on a tumour α/β value of 3·5 Gy estimated directly in the START-P and START-A trials, 40 Gy in 15 fractions should have also been biologically inferior; however, it was clinically non-inferior for ipsilateral breast tumour relapse (hazard ratio 0·77, 95% CI 0·51–1·16) and slightly milder for late normal tissue effects, including clinician-assessed breast shrinkage (0·80, 0·67–0·96).[2] Post-hoc analysis suggests a significant overall time effect for ipsilateral breast tumour relapse only, corresponding to a wasted dose of 0·6 Gy/day (95% CI 0·10–1·18, p=0·02) when the 5 week schedule is used.[4] If true, something similar could be considered in the FAST-Forward trial. Repopulation is the probable biological mechanism if surgical resection, systemic therapies, or both, stimulate tumour

proliferation in the weeks or months before radiotherapy.

Offersen and Overgaard also raise the need for radiotherapy in subgroups of patients at low risk; such consideration is a separate question and is addressed in other ongoing trials.

Michael Douek and colleagues question the trial design of FAST-Forward. The purpose of the two-test group design is that a regimen of five fractions can be found to be isoeffective with control, by interpolation if necessary. Hazard ratios for late normal tissue effects in the START trials did not change between 5 years and 10 years.[2] Intraoperative radiotherapy is not relevant to our trial and the questions that it addresses.

We welcome comments from Shearwood McClelland III; although results from the FAST-Forward trial are applicable to all subgroups of patients tested, the Correspondence highlights access to radiotherapy and favourable therapeutic ratio as the most important clinical considerations.

We declare no competing interests.

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1 Brunt AM, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet* 2020; **395:** 1613–26.

2 Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013; **14:** 1086–94.

3 Brunt AM, Haviland JS, Sydenham M et al. Ten-year results of FAST: a randomized controlled trial of 5-fraction whole breast radiotherapy for early breast cancer. *J Clin*

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4 Haviland JS, Bentzen SM, Bliss JM, Yarnold JR, on behalf of the START Trial Management Group. Prolongation of overall treatment time as a cause of treatment failure in early breast cancer: an analysis of the UK START (Standardisation of Breast Radiotherapy) trials of radiotherapy fractionation. *Radiother Oncol* 2016; **121:** 420–23.