**ESPAC-4: RESPONSE TO LANCET COMMENTARY BY DEPLANQUE AND DEMARTINES**

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**Editor,**

**The Lancet**

Dear Sir,

We appreciate the commentary on our article by Dr Gaël Deplanque and Professor Nicolas Demartines concluding that the ESPAC-4 trial1 “…clearly establishes the combination of gemcitabine and capecitabine as a new standard of care in the adjuvant setting of pancreatic ductal adenocarcinoma.”2

We would caution against the approach taken by the commentators that attempts to interpret the findings in terms of a ‘cure’. In our discussion we comment only on the grounds of extending overall survival which must be the primary outcome worthy of discussion in a condition with such a poor prognosis. Further to this, it is dangerous to extrapolate cure from measures of relapse free survival and tumour recurrence from this analysis as it is not possible to predict what will happen to the patients still at risk. Further analyses with longer follow-up are required to get a better estimate of the number of patients who remain alive and disease free after an extended period.

The estimates of the number needed to treat should follow Altman and Andersen’s3 method for time-to-event outcomes which gives an estimate of needing to treat 15 patients with the combination of gemcitabine and capecitabine rather than gemcitabine, and not 25, in order to save one more life. We would also counter the claim that no patients had crossed the 5-year survival boundary. Between November 10th 2008 and March 9th 2011 there were 162 patients randomised into the trial so permitting a minimum follow up of five years in these patients by the time of the data cutoff date of March 9th 2016.

We would like to reiterate the need raised by the commentators to improve not only the number of patients who are suitable for surgery but also to improve the outcomes of patients following surgery. Adjuvant chemotherapy clearly has a place in a condition that was once considered chemo-resistant and the data show here, as they have with previous ESPAC trials, that patients with better surgical outcomes (typically R0 and N0) are more likely to benefit from adjuvant chemotherapy. Not only is more surgery required then, but surgery with better outcomes.4 The role of neoadjuvant therapy also needs defining notably to increase the overall and R0 and N0 resection rates.5

The primary endpoint was overall survival, measured as the time from randomisation until death from any cause. The median (range) time from surgery to randomisation was 64 (21–111) days so the actual estimated survival from the time of surgery is a median of an 64 additional days to the estimated median 25·5 months and 28.0 months in the two groups.1

As the reviewers note, fitter patients are more likely to tolerate 6 cycles of adjuvant chemotherapy and it has been shown using data from the ESPAC-3 trial 6 that completing all 6 cycles is an important factor in ensuring that the impact of adjuvant therapy is realised and may mean waiting sometime after eight weeks after surgery. In the ESPAC-3 trial the estimated median (interquartile range) from surgery to randomisation was 45 (29-57) days and from randomization to the start of chemotherapy was 10 (5-18) days for the fluorouracil plus folinic acid group and 8 (5-14) days for the gemcitabine group. Thus effective survival with adjuvant chemotherapy can be started up to 18 weeks post-surgery to achieve an optimum result with six cycles of chemotherapy.

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