prostate cancer. Even though these findings support the emerging role of chemotherapy plus hormonal treatment in the metastatic setting, their generalisability to men with non-metastatic prostate cancer might be questioned. Although androgen deprivation therapy is the standard of care in M+ disease, local treatments represent an important step of the therapeutic approach high-risk prostate cancer. Results have indeed been reported after local treatment alone in patients with high-risk disease. Similarly, about 25% of men with low nodal tumour burden do not have any recurrence after surgery alone. Moreover, even when recurrence occurs, up to 30% of these men develop pelvic, rather than systemic, recurrence. Therefore, these men are not invariably affected by systemic disease and might benefit from definitive treatments with or without systemic therapies. Unfortunately, in the study by James and colleagues, adequate treatment of the primary tumour that included only radiotherapy was planned in only 686 (60%) of 1138 men with M0 prostate cancer. This proportion decreases to 46% (203 of 441 men) in N+M0 patients. Surprisingly, no patient included in the trial received radical prostatectomy (appendix). Therefore, a substantial proportion of men received systemic treatments upfront without adequate local treatment. The administration of androgen deprivation therapy plus chemotherapy might represent a substantial overtreatment in this setting. The evaluation of only homogeneous cohorts of locally-advanced or N+ patients receiving treatment of the primary tumour before being considered for systemic treatments would address this issue.

We declare no competing interests.

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1 James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multarm, multinational, platform randomised controlled trial. Lancet 2016; 387: 1163–77

Authors’ reply
We thank Giorgio Gandaglia and colleagues for the comments about our Article.1 Radiotherapy was encouraged from the start of the trial, particularly for NOM0 patients, who were at the lower-risk end of the spectrum in our STAMPEDE trial.1 However, radiotherapy was only mandated for this subgroup after the results of the MRC PR07/NCIC PR-3 and SPCG7 trials showed a survival advantage with radiotherapy.2,3 The planned use of radiotherapy was a stratifying factor at randomisation. Use of radiotherapy thus reflects relevant contemporary practice during recruitment. There are no randomised trials supporting the use of radiotherapy in node-positive prostate cancer, hence the pattern of use reflects this ongoing uncertainty and cannot be described as undertreatment. There was no evidence in multivariate analysis that the treatment effects from docetaxel on failure-free survival or overall survival were affected by planned use or no use of radiotherapy.

No patients were planned for radical prostatectomy as part of their treatment within the trial, hence this outcome was not described in the protocol. Surgery is increasingly becoming a treatment option to be considered for patients at the higher-risk end of the spectrum. At present, there is no direct evidence from randomised controlled trials in this setting that shows any benefit to surgery over radiotherapy. Patients with high-risk relapse after previous prostatectomy or radiotherapy, or both, now starting long-term hormone therapy, were eligible for the trial.

We were deliberately cautious in the conclusion of our Article: “Standard of care should be updated to include docetaxel chemotherapy in suitable patients with metastatic disease, and docetaxel may be considered for men with high-risk non-metastatic prostate cancer with or without radiotherapy.”4 The National Health Service guidelines in England5 were rapidly changed after our publication and support the use of docetaxel in patients with metastatic prostate cancer. We would agree that, for patients with non-metastatic disease, improved treatment of the primary site might dilute any effect of systemic treatment on overall survival in a ceiling effect by reducing risk of death from prostate cancer.

We will report updated findings in the coming years when there will be more events, including from patients who initially had non-metastatic cancer and we will see whether the substantial advantage in failure-free survival translates to an advantage in survival the way it has for patients who had metastatic disease when joining the trial.

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Everolimus in ileum neuroendocrine tumours

James Yao (March 5, p 968) and colleagues' reported that everolimus was associated with significantly prolonged progression-free survival in patients with advanced, progressive neuroendocrine tumours in the lung or gastrointestinal tract. I would like to congratulate the authors for this well-designed phase 3 study. However, I have two main concerns regarding the study's interpretation, especially relating to ileum neuroendocrine tumours.

Firstly, disease progression at baseline with standard criteria is a key inclusion criteria, because the natural history of neuroendocrine tumours is highly heterogeneous. Although the definition of disease progression was well defined in the RADIANT-2 and RADIANT-3 studies\(^5\) (disease progression established by radiological assessment within the past 12 months preceding randomisation), this definition in the RADIANT-4 study is unclear (…were eligible for participation within 6 months from documented radiological disease progression.). How was the disease progression assessed? By Response Evaluation Criteria In Solid Tumors or by WHO criteria? By central radiological review? Over what time period (12 months as per the RADIANT-2 and RADIANT-4 studies or over 36 months as per the NETTER-1 study?) Stating the median time (range) between both exams showing disease progression at baseline would help readers to appreciate the aggressiveness of the disease.

Secondly, the RADIANT-4 study was first presented at the 2015 European Society for Medical Oncology meeting at the same time that another phase 3 study (NETTER-1\(^1\)) showed that peptide receptor radionuclide therapy significantly improves progression-free survival in patients with midgut neuroendocrine tumours. Clinicians are trying to establish how best to use both treatments (everolimus and peptide receptor radionuclide therapy) for midgut neuroendocrine tumours. In the RADIANT-4 study, authors reported prespecified subgroup analysis, including tumour origin, but grouped it into two strata never previously depicted in medical literature. Therefore, even if this subgroup analysis was not prespecified, the hazard ratio by primary tumour origin would also be helpful for readers, especially for the group of 71 patients with ileum neuroendocrine tumours, to better understand these good results. We can expect better hazard ratios for jejunum (n=27), duodenum (n=10), neuroendocrine tumours, or for an unknown primary origin (n=36) than for ileum neuroendocrine tumours. Indeed, the benefit of everolimus would probably be less notable for ileum neuroendocrine tumours with its well-known natural slow-growing history, for which fewer progression-free survival events occurred. This effect would be especially true if the time period needed to have a disease progression at baseline for ileum tumours was long (ie, <12 months).

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Authors’ reply

We thank Thomas Walter and Catherine Lombard-Bohas for their interest in our findings from the RADIANT-4 study.\(^1\) Eligible patients in our study had lung or gastrointestinal neuroendocrine tumours with radiological disease progression within 6 months before randomisation.\(^1\) Progression was determined by radiology report or by tumour measurements. Most patients (252 [83%] of 302) had...