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Detecting a Survival Benefit to Dose Escalation.

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entries, as in the case of changing ambiguous outcome definitions to specific ones. In addition, multivariable analyses of the factors associated with changes in ClinicalTrials.gov entries were not feasible owing to the small number of studies included in the analysis.

Among trials supporting FDA approval of cancer drugs, modifications in study design after patient accrual has begun are common, often unreported, and associated with breakthrough therapy designation, accelerated approval, and single-arm trials. Health care professionals, reviewers, journal editors, and regulators should demand more transparent justification for changes to the trial design after commencement of patient accrual.

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Acquisition, analysis, or interpretation of data: Shepshelovich, Tibau, Molto, Goldvaser, Šeruga, Amir.
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COMMENT & RESPONSE

Detecting a Survival Benefit to Dose Escalation

To the Editor We commend Michalski et al[1] for reporting the anticipated results of RTOG 0126, and in particular, for reporting the incidences of both all-cause and cause-specific mortality. Surprisingly, many trials do not report this vital information.[2] The incidence of prostate cancer mortality was unexpectedly low in their trial, possibly owing to improvement in salvage therapies and changes in the patient population. We are concerned that the proposed effect size (hazard ratio, 0.77) on overall survival (OS) was, in retrospect, mathematically infeasible, and therefore the true power of this study to detect an OS benefit with dose escalation is much lower than 90%.

The incidences of all-cause mortality and prostate cancer mortality at 8 years were 25% and 4%, respectively, for a relative incidence of cancer-specific to all-cause mortality of approximately 0.16 (0.04/0.25). This relative incidence bounds the maximum effect a cancer treatment can have on a primary end point. Unless one postulates that mortality from cancer and noncancer causes are positively correlated or that dose escalation somehow reduces mortality from noncancer causes, the maximum achievable hazard ratio in this population is greater than 1 – 0.16 = 0.84, even if dose escalation were to entirely eliminate death from prostate cancer.[3] The relative cause-specific incidence would be much higher, of course, for biochemical progression-free survival, which would make an effect size of 0.77 more plausible. Thus, this trial seems underpowered for an OS primary end point and possibly overpowered for a biochemical progression-free survival primary end point.

A power estimate is misleading if it proposes effect sizes that are impossible. Post hoc, we estimate that even if dose escalation perfectly eliminated cancer deaths in this population, about 5000 patients would be needed for 90% power with a 1-sided α of 0.025; with 1500 patients, this trial would have had less than 50% power to observe any benefit on OS. Because OS is such a problematic primary end point in populations with heavy competing risks,[4] we propose that future trials use methods to identify populations with a comparatively lower relative incidence of competing mortality when OS is the desired primary end point.[5] Before undertaking analysis, it may also be helpful to check the expected relative incidence against the hypothesized effect size to ensure that it is feasible.

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In Reply We thank Dr Zakeri and colleagues for their interest in the NRG/RTOG 0126 trial.[1] After design, how a clinical trial plays out depends on accurate projections of several key parameters. As mentioned by Zakeri et al and described in the report,[1] the overall survival (OS) was much better than anticipated, owing largely to better-than-expected prostate cancer prognosis. This result, in turn, has major bearing on the hazard ratio (HR) for the composite end point of OS. Indeed, the benefit on OS is bounded, and a simplified way to conceptualize this,[2] similar to the argument by Zakeri et al, is that the HR of the composite outcome is a weighted average of effects on constituent end points:

$$HR_{OS} = \text{Proportion prostate cancer deaths} \times HR_{\text{prostate cancer}} + \text{Proportion other deaths} \times HR_{\text{other deaths}}$$

One can reasonably assume a moderate to large effect on prostate cancer deaths and no effect on other-cause death. Assuming that 30% to 40% of deaths are attributable to prostate cancer, a 23% reduction in mortality (HR, 0.77) would be mathematically achievable but ambitious. Revisiting the power calculation, the key determinants are the failure rate (events/time) and rate ratio (ie, HR); thus, sample size was based on these quantities. At the planned total of 715 events for definitive analysis, power for HR of 0.77 would be 93% (using the Shoenfeld formula[3]; an alternate determination that was based on time-varying event rates was used, yielding the original 90%). The same number of events would afford 80% power for an HR of 0.81 and 70% power for an HR of 0.83. Thus, we cannot confirm the statement that "with 1500 patients, this trial would have less than 50% power to observe any benefit on OS." However, we do agree that the planning HR of 0.77 was unrealistic in light of the much better-than-expected prognosis of the patients, and less than 90% for more realistic HRs. Given the detailed development in the study protocol (available via supplemental materials),[1] there was certainly no intention to present a misleading power assessment, but we acknowledge that, based on the observed study data, an unachievable target HR at 90% power was specified.

As described, the trial was reported early (at 58% of events) owing to crossing of a futility monitoring boundary and additional considerations that indicated little chance of the OS for the high-dose radiation therapy (RT) arm proving to be superior to a clinically material degree in this trial; this finding is unequivocal and not owing to a lack of statistical power. Given the low mortality rate and that high-dose RT has already been widely adopted, it was deemed useful to report the results at this time. Further follow-up (in which the relative proportion of prostate cancer deaths may increase) will bear out the ultimate findings with respect to other end points, where benefits are already apparent (eg, large prostate-specific antigen [PSA] failure reduction, leading to avoidance of salvage therapy) or emerging (eg, distant metastasis, cause-specific mortality). A PSA failure-based primary end point, while attractive because it would have indeed led to a smaller trial, would then result in lower power for the more substantive clinical end points. Thus, in conjunction with our partners at the National Cancer Institute, OS was selected as the primary end point.

The ultimate determination of the worth of high-dose RT rests on weighing the realized benefits and risks, as observed in the trial. Design of future studies must strive to address the challenging problem of identifying clinically meaningful interventions for cancer patients with relatively low risk of cancer mortality. Many, including Zakeri et al and others,[4] continue to work on creative potential solutions to this problem.

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Competing Risks for a Diagnosis of Invasive Breast Cancer

To the Editor In their recent article in *JAMA Oncology*, Brentnall et al[1] reported on long-term results from a praiseworthy cohort study that observed women who completed a breast cancer risk assessment until the diagnosis of invasive breast cancer or censoring. Women were censored at death, diagnosis of ductal carcinoma in situ, when they reached 75 years of age, or at the end of study follow-up.

It is unclear if and how many women subsequently underwent risk-reducing interventions, such as chemopro-