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Questions About a Clinical Trial Evaluating the Addition of Cetuximab to Definitive Chemoradiation Therapy With Paclitaxel and Cisplatin for Patients With Esophageal Cancer

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In Reply We read with interest the Letters to the Editor from Liu and Yue as well as Adenis and Lordick, and we appreciate the opportunity to provide a response. We agree with Liu and Yue that this phase 3 trial¹ was not designed or powered to assess the primary end point within the histology subsets. The Statistical Considerations section of the article describes the rationale for stratifying patients based on histologic type. In addition, it describes the required clinical complete response rate that would have to be achieved in order to continue to accrue patients with a specific histologic type. The Results section provides the outcome for patients with adenocarcinoma. The failure to meet the required end point of a 12% improvement in clinical complete response rate led to the mandated cessation of accruing patients with adenocarcinoma histologic type. The subsequent decision to discontinue accruing patients with squamous cell carcinoma histologic type and close the trial early came as a result of the publication of the United Kingdom SCOPE1 trial² in January 2013, which failed to document a benefit of the addition of cetuximab to chemoradiation therapy in a similar cohort. Again, this is described in the Results section of the article.¹ We did not perform toxicity, survival, or local failure analyses between treatment arms within histology subsets because these were not considered part of the primary end point of the trial and, therefore, not appropriate for this article.¹ We note that the results of the phase 2 multi-institutional trial mentioned by the authors describe a clinical complete response rate of 64%, which is consistent with the findings of the control arm of RTOG 0436, and does not provide level 1 evidence to support a benefit associated with the addition of cetuximab. We look forward to the publication of the results of their phase 3 trial ().

Adenis and Lordick note our decision to use a paclitaxel and cisplatin weekly chemotherapy regimen, and take issue with our statement that the toxicity profile on both arms provides support for this weekly regimen rather than fluorouracil. We agree that this trial was not designed to directly compare these chemotherapy regimens, but do believe that these data provide a rationale for consideration of its use in the non-operative setting. The near-

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identical performance of a taxane platinum regimen in our trial compared with historical data for fluorinated pyrimidine/platinum therapy, despite the absence of a head-to-head comparison, justifies use of this regimen as an alternative. The impressive results from CROSS,³ albeit an operative trial, with a near 50% pathologic complete response rate, a median survival of 84 months in squamous cancer, also support this option. It is also important to note that the National Comprehensive Cancer Network endorses carboplatin–taxane–radiation therapy as a preferred regimen in both the operative and nonoperative management of patients. A comparative trial of this regimen vs fluorinated pyrimidine/platinum therapy will likely never be performed.

While we appreciate the perspectives provided by these authors, we do not believe that these comments change the conclusions presented in this report.

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