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Commentary: Immuno-chemo-radio-therapy before esophagectomy: Our next standard?

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CENTRAL MESSAGE

PALACE-2 is a protocol manuscript for a multicenter trial in which patients with locally advanced esophageal squamous cell carcinoma receive preoperative pembrolizumab with chemoradiotherapy.

The authors present the PALACE-2 (Pre-Operative Pembrolizumab + Chemoradiation in Patients With Locally Advanced Esophageal Squamous Cell Carcinoma) protocol design of a multicenter, single-arm phase 2 study of preoperative pembrolizumab combined with chemoradiotherapy (PPCT) for locally advanced and surgically resectable esophageal squamous cell carcinoma (ESCC).[1] Patients receive chemoradiotherapy according to the CROSS (Chemoradiotherapy for Esophageal cancer followed by Surgery) regimen with carboplatin and nab-paclitaxel with the addition of the immune checkpoint inhibitor pembrolizumab, which targets programmed cell death protein-1.[2,3] The primary end point of this study is pathologic complete response (pCR). The authors plan to accrue 143 patients from 5 centers.

The authors previously completed a single-center, phase 2 study, the PALACE-1, in which they enrolled 20 patients to investigate the safety and feasibility of PPCT.[4] They found that this regimen was safe and feasible to administer before surgery, given that 18 of 20 patients proceeded to surgical resection. In addition, they noted pCR in 55.6% of the resected specimens. Based on this pCR rate, the authors designed an expanded trial to detect a difference in pCR between PPCT and historical control data for chemoradiotherapy of 43.2% for an Asian population with ESCC.

The authors should be commended for completing the PALACE-1 trial then expanding to the multi-institutional, ongoing PALACE-2 trial. Based on the PALACE-2 results, the authors are planning a multicenter, randomized controlled trial (PALACE-3) to directly compare PPCT with conventional chemoradiotherapy. The progression from a single institutional, phase 2 study, to a multi-institutional phase 2 study, and finally the multi-institutional phase 3 study is logical and helps coordinate multiple centers; however, the necessity of the PALACE-2 trial is debatable. Over the past few years, the experience with chemoimmunotherapy has increased, and the authors safely treated 20 patients with this regimen. Therefore, proceeding directly to the randomized design is justifiable without additional phase 2 safety and feasibility data. If the authors were concerned that additional safety data are warranted, then the first cohort in the PPCT randomized arm could be assessed for safety with predesigned stopping points. Regardless, the authors are successfully accruing to the PALACE-2 trial while planning PALACE-3; therefore, they should acquire the phase 3 data in a reasonable time.

This publication is a protocol manuscript that presents a trial design rather than the results of a study. Given time required for protocol design, regulatory approval, patient

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accrual, maturation of data, and publication, publication of prospective trial designs should be encouraged. These manuscripts allow other investigators to avoid performing redundant trials and potentially participate in ongoing trials. In addition, these manuscripts may help referring physicians and patients find centers of excellence asking important questions in complex diseases such as ESSC.

Lastly, the authors should be commended for not only executing PALACE-1 and accruing on PALACE-2 but also for running a program with the patient volume to accrue to these trials while providing exceptional care. The authors are asking important questions that may change the standard approach for managing patients with ESCC.

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