Rectum

Use of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: Initial Results From the Pembrolizumab Arm of a Phase II Randomised Clinical Trial.

Rahma OE, Yothers G, Hong TS, Russell MM, You YN, Parker W, Jacobs SA, Colangelo LH, Lucas PC, Gollub MJ, Hall WA, Kachnic LA, Vijayvergia N, O'Rourke MA, Faller BA, Valicenti RK, Schefter TE, Moxley KM, Kainthla R, Stella PJ, Sigurdson E, Wolmark N, George TJ.

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IMPORTANCE

Total neoadjuvant therapy (TNT) is often used to downstage locally advanced rectal cancer (LARC) and decrease locoregional relapse; however, more than one-third of patients develop recurrent metastatic disease. As such, novel combinations are needed.

OBJECTIVE

To assess whether the addition of pembrolizumab during and after neoadjuvant chemoradiotherapy can lead to an improvement in the neoadjuvant rectal (NAR) score compared with treatment with FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) and chemoradiotherapy alone.

DESIGN, SETTING, AND PARTICIPANTS

In this open-label, phase II, randomised clinical trial (NRG-GI002), patients in academic and private practice settings were enrolled. Patients with stage II/III LARC with distal location (cT3-4 ≤ 5.0 cm from anal verge, any N), with bulky disease (any cT4 or tumour within 3.0 mm of mesorectal fascia), at high risk for metastatic disease (cN2), and/or who were not candidates for sphincter-sparing surgery (SSS) were stratified based on clinical tumour and nodal stages. Trial accrual opened on 1 August, 2018 and ended on 31 May 2019. This intent-to-treat analysis is based on data as of August 2020.

INTERVENTIONS

Patients were randomised (1:1) to neoadjuvant FOLFOX for four months and then underwent chemoradiotherapy (capecitabine with 50.4 Gy) with or without intravenous pembrolizumab administered at a dosage of 200 mg every three weeks for up to six doses before surgery.

MAIN OUTCOMES AND MEASURES

The primary end point was the NAR score. Secondary end points included pathologic complete response (pCR) rate, SSS, disease-free survival, and overall survival. This report focuses on end points available after definitive surgery (NAR score, pCR, SSS, clinical complete response rate, margin involvement, and safety).

RESULTS

A total of 185 patients (126 [68.1%] male; mean [SD] age, 55.7 [11.1] years) were randomised to the control arm (CA) (n = 95) or the pembrolizumab arm (PA) (n = 90). Of these patients, 137 were evaluable for NAR score (68 CA patients and 69 PA patients). The mean (SD) NAR score was 11.53 (12.43) for the PA patients (95% CI, 8.54-14.51) vs 14.08 (13.82) for the CA patients (95% CI, 10.74-17.43) (P = .26). The pCR rate was 31.9% in the PA vs 29.4% in the CA (P = 0.75). The clinical complete response rate was 13.9% in the PA vs 13.6% in the CA (P = 0.95). The percentage of patients who underwent SSS was 59.4% in the PA vs 71.0% in the CA (P = 0.15). Grade 3 to 4 adverse events were slightly increased in the PA (48.2%) vs the CA (37.3%) during chemoradiotherapy. Two deaths occurred during FOLFOX: sepsis (CA) and pneumonia (PA). No differences in radiotherapy fractions, FOLFOX, or capecitabine doses were found.

CONCLUSIONS AND RELEVANCE

Pembrolizumab added to chemoradiotherapy as part of total neoadjuvant therapy was suggested to be safe; however, the NAR score difference does not support further study.