TP53 Mutational Status and Cetuximab Benefit in Rectal Cancer: 5-Year Results of the EXPERT-C Trial

Francesco Scafani, David Gonzalez, David Cunningham, Sanna Hulkkil Wilson, Clare Peckitt, Josep Taberneroc, Bengt Glimelius, Andrés Cervantes, Alice Dewdney, Andrew Wotherspoon, Gina Brown, Diana Tait, Jacqueline Oates, Ian Chau

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Correspondence to: David Cunningham, MD, Department of Medicine, The Royal Marsden NHS Foundation Trust, Dovins Rd, Sutton, Surrey, SM2 5PT, UK (e-mail: david.cunningham@rmh.nhs.uk).

In this updated analysis of the EXPERT-C trial we show that, in magnetic resonance imaging–defined, high-risk, locally advanced rectal cancer, adding cetuximab to a neoadjuvant treatment strategy with neoadjuvant CAPOX followed by chemoradiotherapy, surgery, and adjuvant CAPOX is not associated with a statistically significant improvement in progression-free survival (PFS) and overall survival (OS) in both KRAS/BRAF wild-type and unselected patients. In a retrospective biomarker analysis, TP53 was not prognostic but emerged as an independent predictive biomarker for cetuximab benefit. After a median follow-up of 65.0 months, TP53 wild-type patients (n = 69) who received cetuximab had a statistically significant better PFS (89.3% vs 65.0% at 5 years; hazard ratio [HR] = 0.23; 95% confidence interval [CI] = 0.07 to 0.78; two-sided P = .02 by Cox regression) than TP53 wild-type patients who were treated in the control arm. An interaction between TP53 status and cetuximab effect was found (P < .05) and remained statistically significant after adjusting for statistically significant prognostic factors and KRAS.


TP53 mutations occur in approximately 50% of colorectal cancers (1) and largely result in inactivation of p53 (2). Functional p53 may predict radiosensitivity (3), and an association between p53 and activity of anti-EGFR agents has been reported (4,5). We analyzed TP53 in EXPERT-C (ISRCTN registration: 99828560), a randomized, phase II trial of neoadjuvant CAPOX followed by chemoradiotherapy (CRT), surgery and adjuvant CAPOX ± cetuximab in magnetic resonance imaging–defined, high-risk rectal cancer (RC) (6).

The study was approved by local ethics committees, and written informed consent was obtained from each patient. TP53 mutations in exons 4 to 9 were screened for by capillary electrophoresis–single strand conformational analysis (7) and characterized by bidirectional Sanger sequencing analysis performed on an independent polymerase chain reaction. Patients with TP53 mutations in either pretreatment biopsy or surgical specimen were categorized as TP53 mutant. Kaplan–Meier methods, log-rank analysis, and Cox regression were used. Log minus log plots were investigated. All statistical tests were two-sided, and a P value of less than .05 was considered statistically significant. An interaction test was also performed, and prognostic variables (P < .10) were entered in multivariable Cox regression models.

The EXPERT-C trial recruited 164 eligible patients and 90 of 149 (60.4%) were KRAS/BRAF wild-type (CAPOX = 44; CAPOX-C = 46) (6). After a median follow-up of 63.8 months (95% confidence interval [CI] = 61.4 to 66.2), in KRAS/BRAF wild-type patients the 5-year progression-free survival (PFS) rates were 67.8% (95% CI = 53.9 to 81.7) and 75.4% (95% CI = 62.9 to 87.9); hazard ratio [HR] = 0.62, 95% CI = 0.29 to 1.35, P = .23) and the 5-year overall survival (OS) rates were 72.3% (95% CI = 59.0 to 85.6) and 84.3% (95% CI = 73.5 to 95.1; HR = 0.56, 95% CI = 0.23 to 1.38, P = .20) for CAPOX and CAPOX-C, respectively. In the overall population, the 5-year PFS rates were 64.3% (95% CI = 53.7 to 74.9) and 69.4% (95% CI = 59.4 to 79.4; HR = 0.77, 95% CI = 0.45 to 1.31; P = .34) and the 5-year OS rates were 68.5% (95% CI = 58.3 to 78.7) and 77.8% (95% CI = 68.8 to 86.8; HR = 0.64, 95% CI = 0.35 to 1.15; P = .13) (no interaction between KRAS/BRAF status and treatment effect). No differences in terms of local and distant progression rates were observed between treatment groups (data not shown).

One hundred forty-four patients were assessable for TP53 (n = 199 of 236 samples successfully analyzed) and representative of the trial population. Sixty-nine (47.9%) were TP53 wild-type and 75 (52.1%) were mutant (Supplementary Table 1, available online). Concordance for TP53 status in paired specimens was observed in 33 of 35 case patients (60.0%). Baseline characteristics were balanced in all subgroups and not associated with TP53 status (univariable analysis: P > .20) (Supplementary Table 2, available online).

There was no difference in response to neoadjuvant chemotherapy (NACT), CRT, and complete response rate between the treatment groups according to TP53 status (Supplementary Table 3, available online). After a median follow-up of 65 months (95% CI = 62.8 to 67.2), no differences in PFS (HR = 1.21; 95% CI = 0.60 to 0.46) and OS (HR = 0.97; 95% CI: 0.44 to 2.13; P = .94) were observed between treatments within TP53 mutant patients. However, in TP53 wild-type patients, the use of cetuximab was associated with a statistically significant improvement in PFS (HR = 0.23; 95% CI = 0.07 to 0.78; P = .02) and OS (HR = 0.16; 95% CI = 0.04 to 0.70; P = .02). Five-year PFS and OS were 65.0% (95% CI = 50.3 to 79.7) and 67.5% (95% CI = 53.0 to 82.0) with CAPOX and 89.3%
(95% CI = 77.9 to 100) and 92.7% (95% CI = 82.9 to 100) with CAPOX-C, respectively (Figure 1). An interaction between TP53 status and cetuximab effect was found for PFS (P = .02) and OS (P = .04) and remained statistically significant after adjusting for prognostic factors and KRAS.

The effect of cetuximab in TP53 wild-type patients was consistent across all biomarker subgroups (Figure 2).

The analysis of outcome by TP53 status in patients with preoperative biopsy only (n = 102) showed a similar, slightly weaker interaction between TP53 status and cetuximab effect, likely because of the smaller numbers (PFS: P = .05).

This updated analysis of EXPERT-C further supports the hypothesis that NACT may improve the outcome of high-risk rectal cancer (8). The survival outcomes observed in this high-risk population compare favorably with those reported with standard CRT in risk-unselected patients (9). The use of cetuximab was associated with a numerically better survival in both KRAS/BRAF wild-type and unselected patients. Nevertheless, these results are hypothesis-generating and the definitive role of NACT (with or without cetuximab) can be clarified only by evaluating this strategy against standard CRT in a well-powered, randomized trial.

We found that TP53 was not prognostic but predictive for cetuximab benefit. The interaction between TP53 status and cetuximab effect was independent of other prognostic variables and, although potentially affected by the small numbers, did not appear to be influenced by the status of other biomarkers. The KRAS-independent activity of cetuximab observed in our study is in line with the radiosensitizing properties of this agent (10). However, a numerically higher response with cetuximab in TP53 wild-type patients after NACT (62.1% vs 47.5%; P = .23), which was not observed after CRT (75.9% vs 72.5%; P = .75), would rather suggest that EGFR inhibition may have played a role in the treatment of early micrometastases. This hypothesis is confirmed by the low incidence of distant failure (10.7%) in TP53 wild-type, cetuximab-treated patients.

Caution is necessary when interpreting the results of retrospective analyses of trials that are not powered to detect survival differences. Our findings contrast with the evidence supporting the key role of KRAS in determining resistance to anti-EGFR antibodies in the metastatic setting (11–14). Several questions on the mechanisms of p53-mediated response to cetuximab, especially for KRAS-mutated tumours, remain unanswered. Functional p53 was shown to inhibit the PTEN/PI3K/AKT pathway and promote negative feedback signals to the MAPK pathway (15–17). The chemotherapy backbone and radiation treatment may impact on the ability of p53 to modulate the response to EGFR inhibition. The activity of cetuximab seems to be influenced by the companion chemotherapy agent (18,19), and oxaliplatin-induced DNA damage may trigger p53-mediated signalling pathways, ultimately resulting in increased tumor sensitivity.

**Figure 1.** Kaplan–Meier curves for progression-free survival in the TP53 mutant (A) and TP53 wild-type (B) population. Kaplan–Meier curves for overall survival in the TP53 mutant (C) and TP53 wild-type (D) population. Tables of the numbers of patients at risk in each group at various time points are below each graph. CAPOX = capecitabine-oxaliplatin treatment arm; CAPOX-C = capecitabine-oxaliplatin-cetuximab treatment arm; CI = confidence interval; HR = hazard ratio.

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to EGFR blockade (15,20–22). Moreover, tumor repopulation and antiapoptotic effects deriving from the radiation-induced activation of EGFR may be inhibited by the use of cetuximab beyond the end of CRT (23). This theory suggests a crucial role for the systemic effect of cetuximab therapy and potentially explains the disconnection observed between treatment response and survival. Finally, the beneficial effects of cetuximab in TP53 wild-type patients may relate to the mechanism of antibody-dependent cellular cytotoxicity, possibly enhanced by p53-mediated cellular senescence (24,25).

We recognize the limitations of this analysis (retrospective design, small numbers, TP53 discordance rate between biopsies and surgical specimens) and acknowledge that our findings are hypothesis generating and not practice changing. Gold-standard validation of TP53 as predictive biomarker for cetuximab requires a prospective, randomized study with a marker-by-treatment-interaction design and stratification by TP53 status (26). However, we appreciate that further retrospective validation is needed before launching such a confirmatory trial. In the absence of other randomised trials evaluating anti-EGFR–based strategies in resectable rectal cancer, useful information could be provided by the analysis of TP53 in randomized controlled trials in the setting of adjuvant colon cancer and metastatic colorectal cancer. The results of these retrospective biomarker analyses would also inform whether our findings may apply to different colorectal cancer populations and treatment settings.

References

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**Affiliations of authors:** Department of Medicine, The Royal Marsden NHS Foundation Trust, London and Surrey, UK (FS, DG, DC, SHW, SP, AD, AW, GB, DT, JO, IC); Medical Oncology Department, Vall d’Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain (JT); Department of Radiology, Oncology and Radiation Science, Akademiska Sjukhuset Uppsala, Uppsala, Sweden (BG); Department of Hematology and Medical Oncology, INCLIVA Biomedical Research Institute, University of Valencia, Hospital Clinico de Valencia, Valencia, Spain (AC).