Editorial Commentary

Prognostic value of microsatellite instability (MSI)/deficient mismatch repair (MMR) and BRAFV600E mutation in recurring stage III colon cancer: insights from an ACCENT pooled analysis of seven adjuvant chemotherapy trials

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The rate of tumour recurrence in patients with stage III colon cancer treated with curative-intent surgery remains at ~30%, despite the use of adjuvant chemotherapy (1). Estimation of prognosis in patients with recurrent tumours guides clinical management decisions such as selection, intensity, and duration of palliative systemic therapy. Prognostication is largely based on observations made at diagnosis of advanced disease, considering clinicopathologic variables such as tumour grade, performance status, anatomic sites and extent of metastatic disease. In addition, molecular markers such DNA mismatch repair (MMR) status and mutations in *BRAF*, which have been associated with the risk of relapse (2,3), may further provide value for the prediction of survival after recurrence (SAR). However, the clinical utility of molecular biomarkers for estimation of SAR remains largely uncertain, with individual studies often underpowered due to the modest frequencies of both alterations and recurrence rates.

Deficient MMR (dMMR) status is caused by (epi-)genetic aberrations in MMR genes such as promoter methylation and silencing of *MLH1* or inherited mutations in *MLH1*, *MSH2*, *MSH6*, and *PMS2* (4,5). dMMR results in an increased incidence of insertion and/or deletion mutations producing a characteristic fingerprint at DNA microsatellite repeat sequences termed microsatellite instability (MSI) (6,7). Clinically, tumour MMR status is determined using either immunohistochemistry (IHC) for MMR proteins or by polymerase chain reaction (PCR) based typing of microsatellite markers. dMMR tumours occur in ~15% of patients with sporadic colon cancer and are associated with distinct clinicopathologic characteristics, such as location in the proximal colon, poor differentiation and a high degree of lymphocyte infiltration (8). In early-stage colon cancer, although dMMR has been associated with a lack of response to 5-FU based adjuvant chemotherapy (9), dMMR status is overall associated with a favourable prognosis (2). Consistent with a reduced metastatic potential, the prevalence of dMMR tends to be lower (~10%) in recurrent tumours (10). However, in contrast to early-stage colon cancer, data on the prognostic role of dMMR post-recurrence is limited.

BRAF, a member of the RAF kinase family, is a principal signal transducer of the mitogen-activated protein kinase (MAPK) signalling cascade. In colon cancer, *BRAF* is commonly activated by mutation, with BRAFV600E missense mutation occurring in ~15% of sporadic cases. BRAFV600E mutation occurs more frequently in tumours

with dMMR (~40%), but in contrast to dMMR status, shows a negative prognostic association with survival in both early-stage and stage IV colon cancer but with limited data for SAR (3,11).

Relatively few data are available on the utility of combined MMR and *BRAF* mutation testing for prediction of outcome post-colon cancer recurrence. Of the studies conducted, results have been inconsistent as a consequence of limited sample size and heterogeneity in tumour stages and adjuvant treatment use. To gain a better understanding of the prognostic value of MSI/dMMR and BRAFV600E molecular subgroups for SAR in stage III colon cancer patients treated with surgery and adjuvant chemotherapy, Taieb *et al*. report the largest meta-analysis to-date (n=2,630, 1987 of which contributed to multi-variate analyses) pooling data from seven adjuvant treatment trials (AVANT, MOSAIC, NCCTG NO147, NSABP C07, NSABP C08, PETACC3 and PETACC8) (10). In multivariate analysis for MMR and *BRAF* status adjusted for clinicopathologic variables (including age, gender, primary tumour location, T stage, N stage, histologic grade, performance status), interval to recurrence, *KRAS* mutation and with stratification by treatment groups within each study, patients with MSI/dMMR tumours were found to have significantly longer SAR than patients with microsatellite stable (MSS)/proficient mismatch repair (pMMR) tumours [adjusted hazard ratio (aHR), 0.82; 95% CI, 0.69–0.98]. This association remained significant when examining the subset of patients receiving standard-of-care doublet adjuvant chemotherapy (FP + oxaliplatin) (aHR, 0.76; 95% CI, 0.58–1.00). The authors commented that similar trends for SAR were found when analysing MSI/dMMR *vs.* MSS/pMMR status in tumours harbouring or lacking BRAFV600E mutation, although this did not reach statistical significance. Conversely, BRAFV600E mutation was associated with poor SAR (aHR, 2.06; 95% CI, 1.73–2.46) and this was also found in both MSI/dMMR tumours (aHR, 2.65; 95% CI, 1.67–4.21) and MSS/pMMR tumours (aHR, 2.12; 95% CI, 1.74–2.58).

The study by Taieb *et al*. broadly recapitulates the results previously reported for a pooled analysis of two of the trials included in the current report, NCCTG N0147 and NSABP C08 (12). As replicated by the current study, patients with MSI/dMMR had significantly better SAR (aHR, 0.70, 95% CI, 0.52–0.96), and patients with BRAFV600E tumours had significantly worse SAR (aHR, 2.45, 95% CI, 1.85–3.25). In analysis combining MMR/BRAF status, BRAFV600E mutation but not MMR status was highlighted as the major determinant of poor prognosis. Negative prognostic value of BRAFV600E mutation was shown for dMMR tumours, although analysis for pMMR tumours was not presented.

However, the NCCTG N0147/NSABP C08 pooled study also reported stratified analyses by primary tumour site and treatment arm, highlighting potentially important interactions which were not considered in the present study. In particular, the NCCTG N0147/NSABP C08 study identified a significant interaction between MMR status and location of primary tumour for SAR, with improved SAR limited to MSI/dMMR cancers from the proximal colon [aHR, 0.57, 95% CI, 0.40–0.83). Considering MMR and BRAF status together, the adjusted median SAR was shorter for patients with MSI/dMMR and BRAFV600E tumours of the distal *vs*. proximal colon. The NCCTG N0147/NSABP C08 study further reported a significant interaction with treatment, in that the improved SAR for patients with MSI/dMMR tumours apparent for FOLFOX-treated patients (aHR, 0.50, 95% CI, 0.31–0.81) was not found among those who also received cetuximab (aHR, 1.19, 95% CI, 0.78–1.82). A significant interaction for SAR was also identified between the trial treatment arms and the combined variable of MMR/BRAF. It would have been of interest for these interactions to be evaluated in the current expanded meta-analysis and to include details of the subset analysis for standard adjuvant chemotherapy (FP + oxaliplatin) beyond those presented for MMR status.

The relationship between MSI/dMMR status and improved SAR reported in the current study contrasts with a previous pooled analysis of four phase III studies in first-line metastatic colorectal cancer (mCRC) setting (CAIRO, CAIRO2, COIN, and FOCUS) (13). In this report, progression-free survival (PFS) and overall survival (OS) were found to be inferior for patients with MSI/dMMR compared with MSS/pMMR tumours (HR, 1.33; 95% CI, 1.12–1.57 and HR, 1.35; 95% CI, 1.13–1.61, respectively), although this was not adjusted for *BRAF* mutation which was assessed in a separate model and showed an association with poor outcome as in the current report (HR, 1.34; 95% CI, 1.17–1.54 and HR, 1.91; 95% CI, 1.66–2.19, respectively). In subgroup analyses, however, outcomes by MMR status were similar for tumours lacking or harbouring BRAFV600E mutation, leading the authors to propose that the poor prognosis of MSI/dMMR was principally driven by the BRAFV600E status. Interestingly, a recent meta-analysis of MMR and BRAFV600 status reported that for stage IV CRC, MSI/dMMR was associated with worse OS in *BRAF*

wild-type patients (HR, 1.49, 95% CI, 1.19–1.88), but not in *BRAF*-mutated patients (HR, 1.14, 95% CI, 0.79–1.66) (14). A potential explanation for the discrepancy with respect to MSI/MMR prognostic value may be that in the study by Taieb *et al.* all patients had recurrent disease and had previously received adjuvant therapy. Other possibilities may include the above noted interactions with tumour location and treatment, or potential roles of other confounders. With respect to the latter, the study by Taieb *et al.* showed a poor prognostic value for *KRAS* mutation status for SAR, but this was not stratified for in subset analyses.

Strengths of the study by Taieb *et al.* include the large combined patient cohort with gold-standard data collection and mature recurrence and survival data, assembled by pooling seven major adjuvant treatment trials. One limitation pointed out by the authors is that only 54% of recurring patients were analysed due to lack of informed consent or inadequate BRAF and MMR testing. Notably, this may have introduced some selection bias, as multiple variables (including age, total evaluated lymph nodes, total nodes examined, *KRAS* status, performance score and time-to-recurrence) showed differences between excluded and included study populations. Heterogeneity for variables further appeared evident between trials, although this was not formally evaluated.

Further limitations include non-uniformity of methodology for detecting MSI status and *KRAS* mutation across studies, although for BRAFV600E mutation this was stated to have been done consistently using allele-specific PCR. Mutation detection was further limited to BRAFV600E and *KRAS* codons 12 and 13. Given the nature of the trials, the use of adjuvant treatment regimens was not uniform and involved experimental treatment arms which might affect SAR; for example, through cross-resistance or an imbalance in the use of chemotherapy after relapse due to adjuvant treatment regimens potentially influencing choice of subsequent treatments. Importantly, no data were available on patient management after tumour recurrence including surgery and lines of treatment, all of which would have impacted SAR. Changes in treatment approaches over the time course of included studies might also have impacted outcomes. Other variables which have previously been linked to SAR but were not available for the current study include metastatic site, resectability of metastasis or oligometastatic disease (15). Biomarkers such as white blood cell count, alkaline phosphatase, platelets, haemoglobin have further been implicated as potential predictors (16,17). There is strong evidence that tumour biology and pathology differ between proximal and distal colon tumours (18), and—as outlined above—analyses within these major subgroups would have been a valuable addition. Similarly, interactions with treatment were not formally considered, although these were indicated from previous work (12). Another bias inherent to biomarker analyses on clinical trials is that patient tend to be younger and of good performance status, and prognostic findings may not readily translate to a typical patient population seen in oncology clinics.

Prognostic biomarkers for recurrent patients have the potential to refine palliative management. In the meta-analysis by Taieb *et al.*, BRAFV600E mutations were associated with significantly poorer SAR in patients with either MSI/dMMR or MSS/pMMR tumours, suggesting a need for more intensive first-line treatment or novel therapies in these individuals. BRAFV600E mutation separated patient survival by a median of ~1 year, further highlighting *BRAF* status as a potential stratification marker for clinical trials, which rarely exhibit survival differences by treatment arm exceeding 2–3 months. Although dMMR tumours showed more favourable SAR in multivariate analyses, median SAR was similar within both the BRAFV600E [MSI/dMMR, 0.8 (0.7–1.1) years, MSS/pMMR, 0.9 (0.8–1.2) years] and BRAF wild-type groups (MSI/dMMR, 2.4 (1.9–3.5) years, MSS/pMMR, 2.3 (2.2–2.4) years) and clinical utility with respect to patient stratification would appear less certain. Furthermore, immunotherapy is emerging as an effective new therapeutic option in patients with metastatic MSI/dMMR colon cancer (19).

Ultimately, in order to optimally utilise combined clinicopathologic and molecular biomarkers for prognostication in clinical practice, integrated algorithms will be required. Accordingly, recent years have seen increased efforts in the development of nomograms for the prediction of prognosis of colon cancer. These include predictors for stage IV disease (16,20), survival after hepatectomy for liver metastasis (21), pulmonary resection for lung metastasis (22) and, recently, survival after relapse (15). The study by Taieb *et al.* provides important data towards these efforts.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Shi Q, Andre T, Grothey A, et al. Comparison of outcomes after fluorouracil-based adjuvant therapy for stages II and III colon cancer between 1978 to 1995 and 1996 to 2007: evidence of stage migration from the ACCENT database. J Clin Oncol 2013;31:3656-63.
2. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol 2005;23:609-18.
3. Zhu L, Dong C, Cao Y, et al. Prognostic Role of BRAF Mutation in Stage II/III Colorectal Cancer Receiving Curative Resection and Adjuvant Chemotherapy: A Meta-Analysis Based on Randomized Clinical Trials. PLoS One 2016;11:e0154795.
4. Wijnen JT, Vasen HF, Khan PM, et al. Clinical findings with implications for genetic testing in families with clustering of colorectal cancer. N Engl J Med 1998;339:511-8.
5. Herman JG, Umar A, Polyak K, et al. Incidence and functional consequences of hMLH1 promoter hypermethylation in colorectal carcinoma. Proc Natl Acad Sci U S A 1998;95:6870-5.
6. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. Science 1993;260:816-9.
7. Ionov Y, Peinado MA, Malkhosyan S, et al. Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. Nature 1993;363:558-61.
8. Alexander J, Watanabe T, Wu TT, et al. Histopathological identification of colon cancer with microsatellite instability. Am J Pathol 2001;158:527-35.
9. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med 2003;349:247-57.
10. Taieb J, Shi Q, Pederson L, et al. Prognosis of microsatellite instability and/or mismatch repair deficiency stage III colon cancer patients after disease recurrence following adjuvant treatment: results of an ACCENT pooled analysis of seven studies. Ann Oncol 2019;30:1466-71.
11. Yokota T, Ura T, Shibata N, et al. BRAF mutation is a powerful prognostic factor in advanced and recurrent colorectal cancer. Br J Cancer 2011;104:856-62.
12. Sinicrope FA, Shi Q, Allegra CJ, et al. Association of DNA Mismatch Repair and Mutations in BRAF and KRAS With Survival After Recurrence in Stage III Colon Cancers : A Secondary Analysis of 2 Randomized Clinical Trials. JAMA Oncol 2017;3:472-80.
13. Venderbosch S, Nagtegaal ID, Maughan TS, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res 2014;20:5322-30.
14. Yang Y, Wang D, Jin L, et al. Prognostic value of the combination of microsatellite instability and BRAF mutation in colorectal cancer. Cancer Manag Res 2018;10:3911-29.
15. Kawai K, Nozawa H, Hata K, et al. Nomogram Predicting Survival After Recurrence in Patients With Stage I to III Colon Cancer: A Nationwide Multicenter Study. Dis Colon Rectum 2018;61:1053-62.
16. Kohne CH, Cunningham D, Di Costanzo F, et al. Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. Ann Oncol 2002;13:308-17.
17. Díaz R, Aparicio J, Gironés R, et al. Analysis of prognostic factors and applicability of Kohne's prognostic groups in patients with metastatic colorectal cancer treated with first-line irinotecan or oxaliplatin-based chemotherapy. Clin Colorectal Cancer 2005;5:197-202.
18. Stintzing S, Tejpar S, Gibbs P, et al. Understanding the role of primary tumour localisation in colorectal cancer treatment and outcomes. Eur J Cancer 2017;84:69-80.

19. Marcus L, Lemery SJ, Keegan P, et al. FDA Approval Summary: Pembrolizumab for the Treatment of Microsatellite Instability-High Solid Tumors. Clin Cancer Res 2019;25:3753-8.
20. Kawai K, Ishihara S, Yamaguchi H, et al. Nomograms for predicting the prognosis of stage IV colorectal cancer after curative resection: a multicenter retrospective study. Eur J Surg Oncol 2015;41:457-65.
21. Kattan MW, Gonen M, Jarnagin WR, et al. A nomogram for predicting disease-specific survival after hepatic resection for metastatic colorectal cancer. Ann Surg 2008;247:282-7.
22. Kanemitsu Y, Kato T, Hirai T, et al. Preoperative probability model for predicting overall survival after resection of pulmonary metastases from colorectal cancer. Br J Surg 2004;91:112-20.

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