correspondence

Reply to A. Kurreck et al and M.S. Copur et al

We are grateful for the interest in our report of the FOCUS4-N trial of capecitabine maintenance in patients with metastatic colorectal cancer (CRC) who have stable or responding disease after induction chemotherapy.[1] Both Kurreck et al[2] and Copur et al[3] raise the question of treatment intensity in our trial and link the relatively short outcomes of our patients to a lack of the use of the most active agents in CRC and whether active monitoring (AM) is an adequate treatment plan after initial induction doublet or triplet therapy.

Our primary conclusion from the study was that capecitabine is effective as a maintenance therapy with a hazard ratio of 0.38 compared with AM. Previous evidence has shown that the combination of capecitabine plus bevacizumab had similar hazard ratios versus observation,[4] suggesting that it may be the capecitabine element of the combination that is most effective. It has been shown that single-agent bevacizumab is both ineffective and highly uneconomic.[5] Thus, like the older Optimox studies,[6,7] we show that it is the fluoropyrimidine that carries great effects in this setting. The swimmer plots in the FOCUS4-N article[1] provide some useful insights into individual patient benefits, with about one third of patients in each group progressing at the first scan, suggesting that this one third of patients are fluoropyrimidine-refractory whereas two thirds seem to double their time to progression or greater, suggesting fluoropyrimidine sensitivity.

It is in the context of two meta-analyses that we make the conclusion that AM is an evidence-based approach to management. Copur et al[3] reference the network analysis by Sonbol et al.[8] Rather than extracting a trend in one of the calculations, we note the overall conclusion, "For patients with metastatic CRC, there is no benefit to continuing the full induction regimen until progression, without a period of either observation or maintenance treatment. A maintenance strategy with a fluoropyrimidine, with or without the addition of bevacizumab, is preferred. However, given the lack of a clear overall survival (OS) benefit, shared decision-making should include observation as an acceptable alternative." To this, we now add the individual patient meta-analysis from more than 4,000 patients,[9] which clearly shows the lack of OS benefit from the use of maintenance therapy with the conventional agents used in metastatic CRC.

Should patients with poor prognostic features be considered for a treatment break? Copur et al[3] suggest that patients with poorer prognosis should not be considered for a break or de-escalation in therapy. This question has been addressed in the CAIRO,[4] COIN,[10] and FOCUS4[1] trials, which include sustained induction therapy and AM and maintenance strategies, and none have found any consistent evidence that poorer prognostic factors predict a detriment from a de-escalation of therapy.[11]

In FOCUS4-N, there was a subtle skew in molecular subgroups (12% *BRAF* and 54% *RAS* mutant) because of the access to the parallel molecularly selected studies. However, we do not feel that these are exceptionally different from patients in CAIRO3 (7% *BRAF*-mutant and 56% *RAS*-mutant),[12] and as discussed above, these are unlikely to affect the outcome in the maintenance/AM setting, contrary to our expectations. We note that FOCUS4-N has recruited from a broad range of real-world patients and that additional poor prognostic factors are represented more frequently in FOCUS4-N and similar trial such as COIN (eg, FOCUS4-N *v* CAIRO3 > 1 site of metastases 68% *v* 60% and complete response/partial response after induction 60% *v* 65%). In terms of intensity of therapy, there is little to distinguish: the duration of induction chemotherapy was 16 weeks for FOCUS4-N and 18 weeks for CAIRO3, whereas the scan frequency was 8 weekly for FOCUS4-N and 9 weekly for CAIRO3. We also note in the ARCAD collaborative article on the impact of geography that in first-line randomized controlled trials of metastatic CRC, the United Kingdom has significantly worse outcomes in OS and progression-free survival (PFS) compared with mainland Europe and the United States and explore the various reasons for this in this article.[13]

In reference to the specifics of the use of epidermal growth factor receptor monoclonal antibodies in the interval, the referenced studies[14,15] provide excellent data for further scrutiny, but we do not see that these change or challenge our overall conclusions. It is agreed that more active therapies in the interval will be very likely to result in a prolongation of PFS before returning to induction therapy. Indeed, this was the basis of the FOCUS4 trial concept,[16] in that if a novel agent could prolong the PFS interval, it would potentially provide the signal to encourage further evaluation and that if it did not show this efficacy in a patient group with a rationally selected molecular biomarker, then it was unlikely to have significant activity in a wider group of patients. We question whether the approach of more is better for the patient using our current therapies will enable us to reach the bar of improving quality of life with the same survival benefit. The phase II studies simply emphasize this further with Pietrantonio et al (Valentino trial)[15] demonstrating no OS benefit but a more than doubling of G3-4 toxicities from 20% to 42% and Modest et al (Panama trial)[14] also demonstrating no OS benefit with

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G3-4 toxicities increasing from 26% to 43% with the doublet versus single-agent approach. Some patients and their clinicians will find these toxicities acceptable, but many others will not, and this is reflected across trials in a reduction in patients in the more intense arm recommencing full-dose induction therapy on progression.

We disagree that clinical judgment is a good indicator for therapeutic choice in this setting, which may suffer the unconscious bias of fee per cycle of therapy by some individuals in certain health care systems. As implied by Copur et al, we believe that it is a common misrepresentation of the evidence that all patients with worse prognostic features need to be maintained on active but toxic combination therapies for longer. We are pleased, however, to see that the individual characteristics of the patient are an area that we have consensus over but would wish to emphasize that this is an assessment guided by the clinician listening to and guiding the patient rather than a molecular or biologically measurable parameter. We do agree, however, that further evaluation to identify subgroups of patients who have an optimal continuous, maintenance, or AM strategy is required, and indeed, we plan to undertake this through the ARCAD collaborative group.

In summary, there is overwhelming level-one evidence from individual patient meta-analysis, including 4,000 patients, that AM is an appropriate approach to be considered for patients responding to first-line induction therapy. This results in less time on therapy, lower toxicity, and in a number of studies, better quality of life, which are very important end points for many patients. Such a strategy also has both economic benefits and societal benefits, which should not be underestimated.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Adams RA, Fisher DJ, Graham J, et al: Capecitabine versus active monitoring in stable or responding metastatic colorectal cancer after 16 weeks of first-line therapy: Results of the randomized FOCUS4-N trial. J Clin Oncol 39:3693-3704, 2021
2. Kurreck A, Stintzing S, Modest DP, et al: Efficacy, molecular biology, quality of life or economic aspects: What do we really FOCUS oN? J Clin Oncol 2022 10.1200/JCO.21.02310
3. Copur MS, Kelly J, Tun SM: Treatment break versus maintenance in metastatic colorectal cancer. J Clin Oncol 2022 10.1200/JCO.21.02420
4. Simkens LH, van Tinteren H, May A, et al: Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): A phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. Lancet 385:1843-1852, 2015
5. Matter-Walstra K, Schwenkglenks M, Betticher D, et al: Bevacizumab continuation versus treatment holidays after first-line chemotherapy with bevacizumab in patients with metastatic colorectal cancer: A health economic analysis of a randomized phase 3 trial (SAKK 41/06). Clin Colorectal Cancer 15:314-320.e2, 2016
6. Tournigand C, Cervantes A, Figer A, et al: OPTIMOX1: A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer—A GERCOR study. J Clin Oncol 24:394-400, 2006
7. Chibaudel B, Maindrault-Goebel F, Lledo G, et al: Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 study. J Clin Oncol 27:5727-5733, 2009
8. Sonbol MB, Mountjoy LJ, Firwana B, et al: The role of maintenance strategies in metastatic colorectal cancer: A systematic review and network meta-analysis of randomized clinical trials. JAMA Oncol 6: e194489, 2020
9. Adams R, Goey K, Chibaudel B, et al: Treatment breaks in first line treatment of advanced colorectal cancer: An individual patient data meta-analysis. Cancer Treat Rev 99:102226, 2021
10. Adams RA, Meade AM, Seymour MT, et al: Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first-line treatment of advanced colorectal cancer: Results of the randomised phase 3 MRC COIN trial. Lancet Oncol 12:642-653, 2011
11. Goey KKH, Elias SG, Hinke A, et al: Clinicopathological factors influencing outcome in metastatic colorectal cancer patients treated with fluoropyrimidine and bevacizumab maintenance treatment vs observation: An individual patient data meta-analysis of two phase 3 trials. Br J Cancer 117: 1768-1776, 2017
12. Goey KKH, Elias SG, van Tinteren H, et al: Maintenance treatment with capecitabine and bevacizumab versus observation in metastatic colorectal cancer: Updated results and molecular subgroup analyses of the phase 3 CAIRO3 study. Ann Oncol 28:2128-2134, 2017
13. Yin J, Dawood S, Cohen R, et al: Impact of geography on prognostic outcomes of 21,509 patients with metastatic colorectal cancer enrolled in clinical trials: An ARCAD database analysis. Ther Adv Med Oncol 13: 17588359211020547, 2021
14. Modest DP, Karthaus M, Fruehauf S, et al: Panitumumab plus fluorouracil and folinic acid versus fluorouracil and folinic acid alone as maintenance therapy in *RAS* wild-type metastatic colorectal cancer: The randomized PANAMA trial (AIO KRK 0212). J Clin Oncol 40:72-82, 2022
15. Pietrantonio F, Morano F, Corallo S, et al: Maintenance therapy with panitumumab alone vs panitumumab plus fluorouracil-leucovorin in patients with RAS wild-type metastatic colorectal cancer: A phase 2 randomized clinical trial. JAMA Oncol 5:1268-1275, 2019
16. Kaplan R, Maughan T, Crook A, et al: Evaluating many treatments and biomarkers in oncology: A new design. J Clin Oncol 31:4562-4568, 2013

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