

without chemotherapy, we must continue to focus not only on quantity of survival, but also its quality.

NBL has received institutional research funding from Array, AstraZeneca, Guardant Health, Merck Sharp & Dohme, Pfizer, and Roche; honoraria (continuing medical education lectures) from Bristol-Myers Squibb, Merck Sharp & Dohme, and Roche; and consulting fees from the Canadian Agency of Drugs and Technologies in Health and Excovery. ASF declares no competing interests.

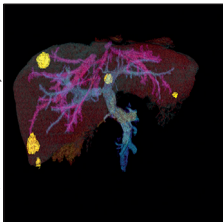
Andrea S Fung, \*Natasha B Leigh  
natasha.leigh@uhn.ca

Division of Medical Oncology/Hematology, Princess Margaret Cancer Centre, University of Toronto, ON M5G 1Z5, Canada (ASF, NBL)

- Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; **378**: 2078–92.
- Garassino MC, Gadgeel S, Esteban E, et al. Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2020; published online Feb 6. [https://doi.org/10.1016/S1470-2045\(19\)30801-0](https://doi.org/10.1016/S1470-2045(19)30801-0).
- Bezjak A, Tu D, Seymour L, et al. Symptom improvement in lung cancer patients treated with erlotinib: quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol* 2006; **24**: 3831–37.
- Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; **16**: 139–44.
- Mazieres J, Kowalski D, Luft A, et al. Health-related quality of life with carboplatin-paclitaxel or nab-paclitaxel with or without pembrolizumab in patients with metastatic squamous non-small-cell lung cancer. *J Clin Oncol* 2020; **38**: 271–80.
- Brahmer JR, Rodríguez-Abreu D, Robinson AG, et al. Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial. *Lancet Oncol* 2017; **18**: 1600–09.
- Reck M, Schenker M, Lee KH, et al. Nivolumab plus ipilimumab versus chemotherapy as first-line treatment in advanced non-small-cell lung cancer with high tumour mutational burden: patient-reported outcomes results from the randomised, open-label, phase III CheckMate 227 trial. *Eur J Cancer* 2019; **116**: 137–47.
- King-Kallimanis BL, Howie LJ, Roydhouse JK, et al. Patient reported outcomes in anti-PD-1/PD-L1 inhibitor immunotherapy registration trials: FDA analysis of data submitted and future directions. *Clin Trials* 2019; **16**: 322–26.
- Hansen AR, Ala-Leppilampi K, McKillop C, et al. Development of the Functional Assessment of Cancer Therapy-Immune Checkpoint Modulator (FACT-ICM): a toxicity subscale to measure quality of life in patients with cancer who are treated with ICMS. *Cancer* 2020; published online Jan 8. DOI:10.1002/cncr.32692.
- Insinga RP, Vanness DJ, Feliciano JL, Vandormael K, Traore S, Burke T. Cost-effectiveness of pembrolizumab in combination with chemotherapy in the 1st line treatment of non-squamous NSCLC in the US. *J Med Econ* 2018; **21**: 1191–205.



## EGFR antibodies in resectable metastatic colorectal liver metastasis: more harm than benefit?



Phantoms/Science Photo Library

The current standard of care for resectable liver-limited colorectal cancer is perioperative chemotherapy followed by curative resection, based on the EORTC trial, which showed a modest improvement in 3-year progression-free survival.<sup>1</sup> Since the addition of a biological agent to systemic therapy leads to increased proportions of patients achieving a response in the metastatic setting, a logical subsequent trial would investigate the role of biological agents in the perioperative setting.

In the New EPOC study, the results of which were published by John A Bridgewater and colleagues in *The Lancet Oncology*, patients with resectable KRAS exon 2 wild-type colorectal liver-limited metastases were randomly assigned to perioperative chemotherapy (oxaliplatin plus fluorouracil, oxaliplatin plus capecitabine, or irinotecan plus fluorouracil) with or without addition of the epidermal growth factor receptor (EGFR) antibody cetuximab.<sup>2,3</sup> Although the concept was rational and the trial well designed, the initially reported results were rather unexpected and controversial.<sup>3</sup> Although the addition of cetuximab to chemotherapy numerically increased the proportion of patients with a response, it showed shorter progression-free survival, with a hazard ratio of 1.48 (95% CI 1.04–2.12; p=0.030)

in patients given chemotherapy with cetuximab versus those who had chemotherapy alone. Overall survival was similar (HR 1.49, 95% CI 0.86–2.60; p=0.16) but was not significant, conceivably because of short follow-up. On the basis of these data, the trial was stopped early. These results led to a controversial debate reflected in an exchange of letters in a different journal.<sup>4</sup> In their long-term analysis, Bridgewater and colleagues now confirm the initial results, showing shorter overall survival in patients given chemotherapy plus cetuximab compared with patients given chemotherapy alone (55.4 months [95% CI 43.5–71.5] vs 81.0 months [59.6 to not reached]; HR 1.45, 95% CI 1.02–2.05; p=0.036). The detrimental effects were more pronounced in patients with more favourable clinical tumour characteristics, potentially indicating an adverse effect in a true adjuvant (micrometastatic) setting. Finally, the results were largely driven by post-recurrence survival, suggesting either the development of a more aggressive disease phenotype or imbalances in post-recurrence treatment approaches.

Since the initial publication of the study, new insights into prognostic and predictive molecular signatures of metastatic colorectal cancer have emerged. In right-sided colon cancer, first-line cetuximab has shown to

Published Online  
January 31, 2020  
[https://doi.org/10.1016/S1470-2045\(20\)30003-6](https://doi.org/10.1016/S1470-2045(20)30003-6)  
See **Articles** page 398

decrease overall survival compared with bevacizumab.<sup>5</sup> Additionally, several studies suggest detrimental effects (ie, shorter survival) of anti-EGFR therapy in patients with other molecular alterations such as non-*KRAS* exon2 *RAS* mutations, *BRAF* mutations, *HER2* amplifications, and microsatellite instability.<sup>6</sup> In New EPOC, no significant differences were observed in the distribution of *RAS/RAF* mutations between treatment groups, but this observation does not rule out imbalances in other molecular alterations that could have affected sensitivity to EGFR antibody therapy. Moreover, the heterogeneity of the systemic therapy in the perioperative setting could be seen as a limitation since the detrimental effect was mainly seen in patients treated with oxaliplatin plus fluorouracil plus cetuximab. Importantly, only 10% of the patients within the cetuximab group received cetuximab as part of subsequent palliative therapy upon recurrence compared with 30% of patients in the chemotherapy alone group—a factor that might have led to lower overall survival because of decreased exposure to cetuximab upon recurrence.<sup>2</sup>

The authors offer the expression of the microRNA miR-31-3p in primary colorectal cancer of patients with metastatic disease treated with cetuximab or panitumumab as a potential explanation for resistance to EGFR inhibition and disease progression.<sup>7</sup> Some preclinical models suggest an epithelial–mesenchymal-like transition as potential mechanism of anti-EGFR therapy.<sup>8</sup> In vitro, a correlation between E-cadherin expression and growth inhibition by EGFR inhibitors was observed in colorectal cancer cells. Several other alterations, such as presence of *MET* amplification have been shown to play a role in anti-EGFR resistance.<sup>8</sup>

These hypotheses could point to potential biological mechanisms for cetuximab's association with poor outcomes in early-stage disease. In stage III colon cancer (according to the American Joint Committee on Cancer staging system), the addition of cetuximab to adjuvant fluorouracil plus oxaliplatin showed no difference in disease-free survival, although the hazard ratio point estimate suggested a detriment in survival, independent of *RAS* mutation status.<sup>9</sup> Multiple preclinical studies suggest that a substantial portion of the effects attributed to EGFR antibody treatment could be based on indirect effects beyond cancer cells, including the tumour microenvironment and immune–cancer cell interactions.<sup>10</sup> Various mechanisms of resistance to anti-EGFR therapy

exist in colorectal cancer, ranging from molecular and immune alterations to histological transformations, allowing for intratumoral heterogeneity, independent of the *RAS* mutation status.

Certainly, the study has some limitations surrounding surgical quality, including imbalances in the number of patients not undergoing surgery (21 in the chemotherapy plus cetuximab group vs 15 in the chemotherapy alone group) and the use of ablation rather than resection (11 vs 5). Despite these limitations, surgery was done in high-volume expert centres and randomisation conceivably helped to balance these factors.

We commend the authors for completing a large interdisciplinary trial addressing important clinical and biological questions. Despite the limitations mentioned above, it is unlikely that the final outcomes of the study were affected by these factors. Although historically good responses have been achieved with more aggressive therapies in the advanced setting, cetuximab and cytotoxic therapy (oxaliplatin plus fluorouracil) in resectable stage IV and III colorectal cancers apparently might have a detrimental effect on survival.

At this point in time, EGFR antibodies should not be used as a component of neoadjuvant or perioperative therapy in resectable stage IV colorectal cancer. Although we believe that EGFR antibodies added to chemotherapy still play a role in the preoperative conversion setting, when high anatomical response are desired, we caution against their use as postoperative therapy after resection of metastatic disease. As the field of molecular targeting treatment and understanding of resistance mechanisms continue to evolve, novel combination treatment strategies should be explored. Additional studies with predefined subgroups (eg, sidedness or different molecular and immune profiles) and novel combination treatment strategies are warranted in patients with operable colorectal liver metastases.

We declare no competing interests.

Copyright © 2020 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY-NC-ND 4.0 license.

\*Sepideh Gholami, Axel Grothey  
sgholami@ucdavis.edu

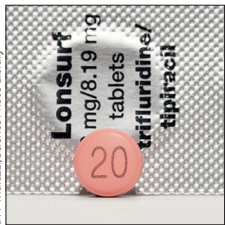
Department of Surgery, University of California, Davis, Sacramento, CA 95817, USA (SG); and West Cancer Center and Research Institute, Germantown, TN, USA (AG)

- 1 Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; **14**: 1208–15.

- 2 Bridgewater JA, Pugh SA, Maishman T, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2020; published online Jan 31. [https://doi.org/10.1016/S1470-2045\(19\)30798-3](https://doi.org/10.1016/S1470-2045(19)30798-3).
- 3 Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol* 2014; **15**: 601–11.
- 4 Nordlinger B, Poston GJ, Goldberg RM. Should the results of the new EPOC trial change practice in the management of patients with resectable metastatic colorectal cancer confined to the liver? *J Clin Oncol* 2015; **33**: 241–43.
- 5 Venook AP, Niedzwiecki D, Lenz HJ, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. *JAMA* 2017; **317**: 2392–401.
- 6 Løes IM, Immervoll H, Sorbye H, et al. Impact of KRAS, BRAF, PIK3CA, TP53 status and intraindividual mutation heterogeneity on outcome after liver resection for colorectal cancer metastases. *Int J Cancer* 2016; **139**: 647–56.
- 7 Manceau G, Imbeaud S, Thiébaud R, et al. Hsa-miR-31-3p expression is linked to progression-free survival in patients with KRAS wild-type metastatic colorectal cancer treated with anti-EGFR therapy. *Clin Cancer Res* 2014; **20**: 3338–47.
- 8 García-Foncillas J, Sunakawa Y, Aderka D, et al. Distinguishing features of cetuximab and panitumumab in colorectal cancer and other solid tumors. *Front Oncol* 2019; **9**: 849.
- 9 Huang J, Nair SG, Mahoney MR, et al. Comparison of FOLFIRI with or without cetuximab in patients with resected stage III colon cancer; NCCTG (Alliance) intergroup trial N0147. *Clin Colorectal Cancer* 2014; **13**: 100–09.
- 10 Giordano G, Remo A, Porras A, Pancione M. Immune resistance and EGFR antagonists in colorectal cancer. *Cancers (Basel)* 2019; **11**: E1089.



## TAS-102 plus bevacizumab: a new standard for metastatic colorectal cancer?



DRP Marazzi/Science Photo Library

Published Online  
January 27, 2020  
[https://doi.org/10.1016/S1470-2045\(20\)30009-7](https://doi.org/10.1016/S1470-2045(20)30009-7)

See [Articles](#) page 412

For patients with surgically unresectable metastatic colorectal cancer, a continuum of care is offered to improve their overall outcome. Few treatment options exist apart from oxaliplatin and irinotecan-based therapies; even fewer exist for patients with RAS mutations, who account for 30–60% of all patients with metastatic colorectal cancer.<sup>1</sup> When the oral agent, TAS-102, was approved by the US Food and Drug Administration in 2017, it offered another potential option for patients with surgically unresectable, metastatic colorectal cancer.<sup>2</sup> Often incorrectly touted as a modified oral fluorouracil, TAS-102 differentiates itself by being comprised of two components: trifluridine, a nucleoside analogue, and tipiracil hydrochloride, a thymidine phosphorylase inhibitor, combined in a 1:0:0:5 ratio. Tipiracil prevents rapid degradation of trifluridine resulting in increased bioavailability. The phase 3 RECURSE trial<sup>3</sup> randomly assigned patients (2:1) with metastatic colorectal cancer (n=800) to receive either TAS-102 (35 mg/m<sup>2</sup>, days 1–5 and 8–12) or placebo. The primary endpoint of overall survival was met, with longer median overall survival in the TAS-102 group (7.1 months vs 5.3 months in the placebo group) with a hazard ratio (HR) of 0.68 (95% CI 0.58–0.81; p<0.001). Progression-free survival was also longer in the TAS-102 group than in the placebo group (2.0 months vs 1.7 months [0.48, 0.41–0.57; p<0.001]); and a response was achieved in 1.6% of patients in the TAS-102 group versus 0.4% in the placebo group (p=0.29). The duration of response with TAS-102 ranged from 0.1–78 weeks. The most common adverse event

in the TAS-102 group was grade 3 or 4 neutropenia occurring, in 35.9% of patients.

Despite its oral formulation and ease of administration, overall enthusiasm for TAS-102 in the metastatic colorectal cancer treatment arsenal was subdued because the overall survival benefit was only 1.8 months compared with placebo in a heavily pretreated patient population. Furthermore, this improvement in overall survival did little to distinguish TAS-102 from the oral multikinase inhibitor regorafenib (absolute improvement in overall survival of 1.4 months compared with placebo). Given the small improvement in overall survival, progression-free survival, and response compared with placebo, consideration of cost must be taken into account. The average cost for one TAS-102 treatment cycle is reported to be US\$10 947.70 for an individual with a body surface area of 1.7 m<sup>2</sup>.<sup>4</sup>

In their Article in *The Lancet Oncology*, Per Pfeiffer and colleagues<sup>5</sup> report the results from the first randomised phase 2 study comparing TAS-102 plus bevacizumab with TAS-102 alone in patients with refractory metastatic colorectal cancer, done in Denmark. Unique to this setting is that anti-VEGF therapy with aflibercept and ramucirumab in the second-line setting, and regorafenib in the refractory setting, are not approved in Denmark. The patients were heavily pretreated (the majority of patients received more than 3 lines of previous therapy). The treatment provided was a standard dose of TAS-102 (35 mg/m<sup>2</sup> twice daily on days 1–5 and 8–12) alone or in combination with 5 mg/kg bevacizumab on days 1 and 15 of each 28-day cycle. The primary endpoint