Editorial Commentary

A BEACON of hope for *BRAF*-mutant metastatic colorectal cancer

Jennifer Mooi[1], Belinda Lee[1,2,3,4]

[1]Medical Oncology, Northern Health, Melbourne, Australia; [2]Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia; [3]Faculty of Medicine and Dentistry, University of Melbourne, Melbourne, Australia; [4]Peter MacCallum Cancer Centre, Melbourne, Australia

Correspondence to: Jennifer Mooi. Medical Oncology, Northern Health, Melbourne, Australia. Email: jennifer.mooi@nh.org.au.

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Introduction

BRAF V600E-mutant metastatic colorectal cancer (CRC)

CRC is the second leading cause of cancer-related death, and the third most common cancer globally (1). Approximately 10–15% of CRC harbor a *BRAF* mutation (2). This molecular subtype of CRC is more commonly associated with right-sided tumours, more advanced stage at presentation, and mucinous histopathology (3). *BRAF*-mutant CRC are more frequently found in microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumours compared to microsatellite stable (MSS) tumours (4) and are associated with higher mutation burden and CpG island methylator phenotype (CIMP)-high status (5).

The presence of a *BRAF* mutation results in activation of *BRAF* kinase and sustained downstream activation of the RAS-RAF-mitogen-activated protein kinase (MAPK) signaling pathway. This disruption to key cellular responses drives cancer cell proliferation and survival, which in turn leads to more aggressive tumour biology (2). The presence of a *BRAF* mutation is considered a poor prognostic biomarker, translating to poor patient outcomes. Compared to *BRAF*-wildtype CRC, *BRAF*-mutant CRC are associated with a 70% increase in mortality (6) and a median overall survival (mOS) of 12 *vs.* 25 months in patients with *BRAF*-wildtype CRC (7).

BRAF targeted therapy

The most common *BRAF* mutation is the *BRAF* V600E substitution (8). This somatic point mutation provides an opportunity for targeted therapeutic inhibition. Early phase solid tumour clinical trials with first generation BRAF inhibitor, vemurafenib, demonstrated impressive response rates of 60–80% in *BRAF* V600E metastatic melanoma (9) but in contrast, was disappointing when assessed in *BRAF*-mutant metastatic CRC (mCRC) where markedly lower response rates of only 5% were reported (10).

The combination of second-generation RAF + MEK inhibition with dabrafenib and trametinib in a phase 2 clinical trial demonstrated a slight improvement, with response rates increasing to 12% in 43 patients with *BRAF* V600-mutant mCRC (11). Unlike in *BRAF*-mutant melanoma, where the concomitant use of MEK inhibition with a BRAF inhibitor blocked the paradoxical activation of ERK and brought about near-complete inhibition of the MAPK pathway, this synergistic effect was not fully appreciated in *BRAF*-mutant CRC (12).

Further translational efforts identified that rapid EGFR-mediated re-activation of the MAPK pathway was a key factor in the discrepancy between the solid tumour responses and the lack of efficacy of single agent *BRAF* inhibitors in *BRAF*-mutant CRC. To overcome this, a combination of RAF and EGFR inhibition in *BRAF*-mutant CRC was investigated. This led to more successful suppression of MAPK signalling and improved tumour responses (12,13). Preclinical and early phase clinical studies of triplet combinations of BRAF, MEK and EGFR inhibition subsequently provided more promise of sustained therapeutic responses and improved outcomes for this group of patients (14).

BEACON trial

BEACON was a randomized phase 3 trial investigating the use of a third-generation RAF inhibitor, encorafenib; combined with the EGFR inhibitor, cetuximab; with or without MEK inhibitor, binimetinib; compared to standard chemotherapy plus cetuximab in 665 patients with *BRAF* V600E-mutant mCRC whose disease had progressed following one or two prior regimens. Patients were randomly assigned in a 1:1:1 ratio to each of the three combinations [triplet (encorafenib, cetuximab and binimetinib; ECB): doublet (encorafenib and cetuximab; EC): control (chemotherapy and cetuximab)]. This study represents the largest cohort ever studied in *BRAF* V600E-mutant mCRC. At the pre-specified interim analysis, a confirmed response rate of 26% *vs.* 2%, with a clinically significant corresponding mOS of 9.0 *vs.* 5.4 months was demonstrated in the triplet arm compared to the control arm, respectively (15).

Further published survival and post-hoc analyses of the BEACON trial has confirmed improvement in outcomes in the investigational targeted therapies combinations when compared to standard chemotherapy plus cetuximab, with mOS of 9.3 (triplet) *vs.* 9.3 (doublet) *vs.* 5.9 months (control) (hazard ratio =0.60, 0.61 *vs.* control, P<0.001, respectively). Median progression-free survival was 4.5 (triplet) *vs.* 4.3 (doublet) *vs.* 1.5 months (control) (hazard ratio =0.42, 0.44 *vs.* control respectively) (16). Safety profiles for both the triplet and doublet regimen combinations were acceptable and consistent with known toxicities associated with BRAF, EGFR and MEK inhibitors. The addition of binimetinib to the doublet regimen did not increase survival outcomes relative to EC and was associated with greater MEK-inhibition toxicity. Thus it was concluded that EC is the most appropriate regimen which improved survival for previously treated *BRAF* V600E-mutant mCRC, with Food and Drug Administration (FDA) approval granted for this indication in April 2020.

The authors of BEACON suggest that the triplet combination of ECB may be appropriate for higher risk subgroups such as those with higher burden of disease, partially or unresected primary tumours, and elevated C-reactive protein (CRP) levels; as these patients appeared to have better survival outcomes with the triplet *vs.* doublet regimen in the study's subgroup analyses. The higher response rates of 27% for triplet *vs.* 20% for the doublet; and when ECB is used in earlier treatment (one prior line *vs.* heavily pretreated: 34% *vs.* 26%) suggest additional studies are required to further define the place for the triplet combination.

Nonetheless, the EC doublet regimen which maximizes efficacy whilst minimizing toxicity, would be an appropriate backbone for the exploration of additional agents to the combination for further benefit.

Why are the results from BEACON important?

The findings of the BEACON study are significant for several reasons. It is the first to provide evidence of a novel therapeutic combination which improves survival outcomes specifically for *BRAF*-mutant mCRC, a group with high unmet need. The significance of this led to the US FDA granting breakthrough therapy designation for encorafenib in combination with binimetinib and cetuximab in 2018, based on data from the safety-lead-in analysis of the BEACON trial. Besides the advent of EGFR-inhibitors for *RAS*-wild type mCRC, the targeted therapies combinations demonstrated in BEACON are only the second approach we have against biomarker-defined populations in mCRC, with a decade in between these breakthroughs. The success of the targeted combinations given without chemotherapy in BEACON is even more notable given the field of mCRC treatment to date is predominantly "chemotherapy-driven".

The results of BEACON reinforce that combined BRAF and EGFR inhibition is a useful strategy in treating *BRAF*-mutant mCRC and establishes this approach as the new standard of care for previously treated *BRAF*-mutant mCRC. This strategy is further supported by additional pre-clinical and clinical studies using other inhibitors of the same class including vemurafenib combined with cetuximab (17) and combinations of dabrafenib, trametinib and panitumumab (18). The breakthrough in combining BRAF and EGFR inhibition to treat *BRAF*-mutant mCRC when the inhibition of either target alone in this disease was unsuccessful, is credit to the extensive pre-clinical work that has occurred in elucidating mechanisms of resistance and understanding the MAPK pathway.

Future directions

The prominent question on most clinicians' minds now is whether we will see combined BRAF + EGFR ± MEK inhibitors administered in first line treatment of *BRAF* V600E-mutant mCRC. This question is currently being addressed in several ongoing and upcoming trials.

ECB, the same triplet combination used in BEACON, is being tested in a treatment-naive *BRAF* V600E-

mutant mCRC population in a single arm, phase II study (ANCHOR-CRC), with preliminary results of the first 40 evaluable patients showing an overall response rate of 50%, with a median PFS of 4.9 months (19) (ClinicalTrials.gov identifier: NCT03693170). Although more mature results with additional study participants are awaited, the initial PFS reported here seems disappointing for a first-line setting, suggesting that alternative agents outside of MAPK targets may be needed in addition to combined BRAF + EGFR inhibition.

Do we still need chemotherapy with the combined targeted therapies? SWOG 1406, a randomized phase II study, assessed the addition of vemurafenib to irinotecan + cetuximab in previously treated *BRAF* V600E-mutant mCRC (17). Their positive findings of improved PFS and response rate for the addition of vemurafenib to irinotecan + cetuximab adds to the collective support for combined BRAF + EGFR inhibition, but in contrast to other studies, this was the first to use chemotherapy with the combined targeted therapies. Of particular interest, is the correlative circulating tumour DNA (ctDNA) data collected in SWOG 1406, which suggested that unlike other studies of targeted therapies without chemotherapy, mechanisms of resistance in vemurafenib, cetuximab + chemotherapy did not involve acquired RAS mutations.

Looking forward, the phase III trial comparing EC *vs.* EC + chemotherapy (FOLFOX or FOLFIRI) *vs.* investigator's choice of standard chemotherapy ± bevacizumab in previously untreated *BRAF* V600E-mutant mCRC (BREAKWATER, ClinicalTrials.gov identifier: NCT04607421), should provide greater insights into the questions above (20).

Microsatellite instability (MSI) is often found in CRC with *BRAF* mutations owing to epigenetic inactivation of the mismatch repair protein MLH-1, associated with CpG island hypermethylation or CIMP-high states. Furthermore, when subtyped by transcriptional signatures, the majority of *BRAF*-mutant CRC are found to be consensus molecular subtype 1 (CMS1) (21) which are characterized by hypermutation and immune-activation (22). These associations suggest a role for immune checkpoint inhibitors (ICI), and indeed several trials are underway testing combinations of MAPK-targeted therapies with ICI in *BRAF* V600E-mutant mCRC (ClinicalTrials.gov identifiers: NCT03668431, NCT04017650, NCT04294160).

The investigators and participants of both BEACON and SWOG 1406 trials should be congratulated on their efforts for including collections of bio-samples for correlative study. SWOG 1406 has already reported interesting findings from these correlates including concordance of *BRAF* V600E mutation in tissue and ctDNA (high concordance, with the reported sensitivity of ctDNA in the range of 70–80%), and serial ctDNA as markers of treatment response and resistance (17). Given the challenges of tissue collection in this patient population with advanced, often inoperable and rapidly progressive disease, validation of ctDNA technology is ever more critical and should be prioritised in all future studies of *BRAF*-mutant mCRC. Correlative tissue and plasma data from BEACON study are yet to be reported. These samples will form a precious resource from a rare patient population, from which we can hopefully glean more understanding about the impact of this new treatment paradigm of simultaneous inhibition of multiple MAPK targets in *BRAF* V600E-mutant mCRC.

Summarising comments

Combined BRAF and EGFR inhibition in the MAPK signalling pathway is now established as the new standard of care for *BRAF* V600E-mutant mCRC who have failed previous standard therapy. The inhibition of a third target in this pathway, MEK, may have a role in earlier treatment or in a subgroup of patients with poor prognostic factors. The success of combined inhibition of multiple MAPK targets in the treatment of *BRAF*-mutant CRC illustrates the merits of collaborative preclinical and translational cancer research in bringing breakthrough therapies to the clinic. Moving forward, the addition of alternative agents including chemotherapy or immunotherapy to the BRAF + EGFR inhibitors combination, deserves to be explored. Correlative studies involving tissue and plasma collection, with technologies such as next-generation sequencing and ctDNA are critical in helping to refine and advance this new treatment paradigm for *BRAF*-mutant mCRC.

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