Review

Targeted therapy for metastatic colorectal cancer

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ABSTRACT

Introduction: Outcomes in metastatic colorectal cancer are improving, with better understanding and use of targeted therapies.

Areas covered: A review of the literature and recent conference presentations was undertaken on the topic of systemic treatment of metastatic colorectal cancer. This article reviews the current evidence for targeted therapies in advanced colorectal cancer, including up-to-date data regarding anti-EGFR and anti-VEGF agents, the relevance of primary tumour location and novel subgroups such as BRAF mutated, HER2 amplified and mismatch-repair deficient cancers.

Expert commentary: EGFR-targeted and VEGF-targeted antibodies are now routinely incorporated into treatment strategies for mCRC. The use of EGFR-targeted antibodies should be restricted to patients with extended RAS wild-type profiles, and there is evidence that they should be further restricted to patients with left-sided tumours. Clinically, mCRC can be divided into subgroups based on RAS, BRAF, HER2 and MMR status, each of which have distinct treatment pathways.

Keywords: colorectal, sidedness, review, targeted, metastatic

1. **Introduction**

Improvements in outcome for patients in metastatic colorectal cancer (mCRC) have been achieved initially with the addition of oxaliplatin and irinotecan to fluoropyrimidine chemotherapy backbone, and subsequently with the introduction of anti-angiogenic agents and anti-EGFR antibodies. Survival has been further extended with the availability of third-line agents, such as regorafenib and TAS102, and integration of surgical resection of isolated metastases into clinical practice. RAS mutation status testing is now routinely used as a predictive factor to determine the application of anti-EGFR antibodies. With increased understanding of molecular subgroups and growing availability of biological agents, there is heightened interest in the development of prognostic and predictive biomarkers to guide treatment of mCRC.

This article reviews current clinical trial evidence and addresses issues regarding management of patients with mCRC. The review and its recommendations follow a formal consensus meeting among seven Australian specialist clinicians and three international CRC experts in September 2017.

2. **Goals of therapy**

Establishing treatment goals is important in mCRC to provide a benchmark of potential treatment benefits against which potential toxicities can be balanced. For the majority of patients with mCRC who have non-resectable disease, the mainstay of care is systemic treatment combined with supportive care. A minority of patients have resectable or potentially resectable disease, which typically corresponds to oligometastatic metastases limited to the liver and/or lung. These patients may be suitable for curative or potentially curative treatment involving complete resection of their metastatic disease, depending on their response to initial systemic therapy. Early multidisciplinary review of patient and tumour characteristics is an integral component of establishing goals of care and making decisions

about the potential opportunities for surgical resection of metastatic disease, first-line systemic therapies, and optimal sequencing.

3. Systemic treatment for metastatic CRC

3.1 Conventional Chemotherapy

3.1.1 Single agent chemotherapy and the sequential approach

Sequential use of cytotoxic chemotherapy may be a reasonable approach for patients with slowly progressing disease, in order to maximise survival and quality of life and reserve other treatments for later use.[1] Proponents of this approach typically select patients who have good performance status and are likely to be eligible for multiple lines of treatment, in whom: (i) there is low risk of rapid deterioration even with progressive disease, (ii) symptom control is not required, and (iii) there is no potentially resectable disease requiring rapid downsizing. Single agent chemotherapy may also be considered for patients who have multiple comorbidities or poor performance status and are unlikely to tolerate combination chemotherapy.

Several studies have demonstrated that initial single-agent fluoropyrimidine chemotherapy followed by combination chemotherapy is not inferior to upfront combination chemotherapy. Both the CAIRO and MRC FOCUS trials demonstrated that patients treated with first-line single-agent fluoropyrimidine did not have significantly different overall survival (OS) compared to patients receiving first-line combination chemotherapy.[2,3] A sequential treatment approach was further supported by the FFCD 2000-05 trial, in which upfront combination chemotherapy was more toxic and not more effective than the sequential use of first-line 5-FU/leucovorin followed by second-line and third-line combination therapy.[4]

3.1.2 Doublet Chemotherapy

Doublet chemotherapy is generally the standard first-line approach for mCRC patients. In particular, combination treatment should be advocated for patients who require immediate

tumour control of rapidly progressive disease and/or improvement of significant disease-related symptoms.

Combination chemotherapy comprises at least a doublet chemotherapy backbone, including a fluoropyrimidine. Apart from different toxicity profiles, there is little difference in efficacy between fluoropyrimidine/oxaliplatin-based and fluoropyrimidine/irinotecan-based regimens, which are generally considered interchangeable.[2,5,6] Several common acronyms are used to describe different combinations: FOLFOX (5-FU and oxaliplatin), FOLFIRI (5-FU and irinotecan), and when the oral 5-FU pro-drug capecitabine is substituted for infusional 5-FU, CAPOX (capecitabine and oxaliplatin) and CAPIRI (capecitabine and irinotecan). Recently, another option for doublet chemotherapy, comprising the oral fluoropyrimidine S-1 and irinotecan, was demonstrated to be non-inferior to FOLFOX or CAPOX with respect to PFS when given in the first-line setting with bevacizumab in the TRICOLORE trial.[7]

These chemotherapy combinations are the most common backbones of first-line systemic therapy in mCRC, and the selection of specific regimen will be influenced by factors such as patient preference, toxicity, prior adjuvant therapy and drug availability. The addition of biologic agents to monotherapy and combination chemotherapy regimens further improves outcomes, as discussed below, and are generally recommended over cytotoxic chemotherapy alone in first-line treatment.[8]

3.1.3 Triplet Chemotherapy

The combination of three cytotoxic agents as triplet therapy (FOLFOXIRI) in first-line treatment of mCRC has been investigated in phase 3 trials, which have not demonstrated consistent survival benefit compared to doublet chemotherapy. In a GONO study, FOLFOXIRI was found to increase OS (22.6 vs 16.7 months, HR 0.70, p=0.032), PFS (9.8 vs 6.9 months, HR 0.63, p=0.0006) and RR (60 vs 34%, p<0.0001) as well as R0 resection rates (15 vs 6%, p=0.033) compared to FOLFIRI.[9] This contrasts with the results from a HORG trial, which did not demonstrate superiority of FOLFOXIRI compared with FOLFIRI,

although the trial was arguably underpowered and demonstrated trends towards improved survival and RR with FOLFOXIRI.[10] The discrepancies between these two trial results may be attributable to differences in patient entry criteria. The superiority of FOLFOXIRI in the GONO trial may be related to the inclusion of patients with potentially resectable disease, in whom more aggressive systemic therapy with FOLFOXIRI allowed higher rates of metastectomy.[9]

FOLFOXIRI is infrequently used in mCRC, in part due to uncertainty regarding survival benefit, but mainly due to concerns regarding increased toxicity and lack of subsequent salvage options. However, triplet chemotherapy may be indicated in selected patients in whom maximising tumour response could facilitate curative surgery, where biological agents are unavailable or contraindicated, or in patients with bulky, symptomatic tumours.

3.2 Biological Agents in First-line Treatment

3.2.1 Anti-angiogenic Agents

Biological agents, either targeting the vascular endothelial growth factor (VEGF) pathway or the endothelial growth factor receptor (EGFR) pathway, should be considered standard options in first-and or second-line treatment of metastatic colon cancer.

Bevacizumab improves PFS when added to both oxaliplatin- and irinotecan-based combination chemotherapy regimens and fluoropyrimidine monotherapy regimens in first-line treatment of mCRC.[11-14] This advantage extended to increased OS when bevacizumab was given with irinotecan-based combination chemotherapy (IFL), compared to IFL alone.[11] However, one study that did not demonstrate a benefit with bevacizumab was the ITACa trial, which evaluated the effectiveness of adding bevacizumab to first-line FOLFIRI or FOLFOX4 chemotherapy.[15] Despite achieving a similar absolute increase in median PFS with the addition of bevacizumab as was seen in the NO16966 trial, this trial did not demonstrate significant improvements in median PFS, OS or response rate with bevacizumab. The results of this trial may have been weakened by poor patient recruitment

over its first 2 years, which necessitated a change in primary objective from OS to PFS, and also discontinuation of bevacizumab and/or fluoropyrimidines at patient/investigator discretion. Table 1 summarises key randomised studies investigating bevacizumab and other anti-angiogenic agents in first-line treatment of mCRC.

The role of bevacizumab as maintenance therapy in metastatic disease was first investigated in the MACRO study, which found no significant difference in PFS, OS or ORR between patients who continued chemotherapy and bevacizumab versus those who received single-agent maintenance bevacizumab, after induction chemotherapy with CAPOX and bevacizumab.[16] The pivotal CAIRO3 study provided evidence for continuation of bevacizumab after oxaliplatin-based induction chemotherapy, by demonstrating that maintenance capecitabine and bevacizumab prolonged PFS compared to observation in patients who achieved stable disease or better after first-line treatment with CAPOX and bevacizumab.[17] However, the optimal maintenance strategy following induction combination chemotherapy and bevacizumab remains unclear. Based on the PRODIGE9 trial, it appears the benefit of maintenance bevacizumab may be contingent on concurrent maintenance chemotherapy, as maintenance bevacizumab alone did not improve tumour control duration or survival compared to observation after induction FOLFIRI and bevacizumab.[18] On the other hand, maintenance bevacizumab alone was non-inferior to maintenance fluoropyrimidine and bevacizumab for the endpoint of time to failure of strategy in the randomised phase 3 AIO 0207 trial (HR 1.08, 95% CI 0.85-1.37, upper limit of the one-sided 98.8% CI 1.42, pre-specified non-inferiority margin one-sided 98.8% CI 1.43).[19] Furthermore, while combining VEGF-targeted and EGFR-targeted antibodies with chemotherapy in the first-line setting leads to inferior outcomes than bevacizumab and chemotherapy, combination biological agents may have a role in maintenance therapy.[20] In the GERCOR DREAM/OPTIMOX3 study, the addition of the EGFR-targeted tyrosine kinase inhibitor (TKI) erlotinib to bevacizumab as maintenance therapy improved OS (24.9

vs 22.1 months, HR 0.79, p=0.036) at the expense of increased rates of skin rash, diarrhoea and asthenia.[21]

In clinical practice, bevacizumab is generally well-tolerated and severe toxicities are rare. Most common adverse events, such as proteinuria and hypertension, are manageable with standard approaches and usually do not require dose interruption.[22] Table 2 summarises key studies investigating maintenance bevacizumab.

The role of bevacizumab needs to be considered in the context of patients' entire treatment journey, as there is inconsistent evidence for OS benefits with continuation of bevacizumab with second-line chemotherapy and during maintenance of first-line therapy in large randomised phase 3 clinical trials.[17,18,21,23] The use of bevacizumab in the first-line setting does not seem to affect response to treatment with other anti-angiogenic agents, such as aflibercept in second-line treatment or the small molecule TKI regorafenib in refractory mCRC.[24-26] It is important to note that there is inconsistent evidence for activity of single-agent bevacizumab as maintenance treatment and in the second-line setting, so bevacizumab should be used in conjunction with chemotherapy rather than as monotherapy.[18,19,27] Ongoing investigation to identify reliable predictive biomarkers will provide guidance regarding optimal use of bevacizumab and other VEGF-directed anti-angiogenic agents.

3.2.2 RAS Wild Type: EGFR-targeted Antibodies in the First-line Setting

Currently there is no evidence for the benefit of anti-EGFR therapy used in combination with fluoropyrimidines alone, or with capecitabine regimens as clinical trials testing these combinations have yet to be reported. Therefore, anti-EGFR agents should be primarily used with intravenous 5-FU-based doublet chemotherapy in the first-line setting. Patients with RAS and BRAF wild type and left-sided tumours have the greatest range of therapeutic options available to them, so careful consideration should be given to the chemotherapy backbone as well as planned sequencing of VEGF-targeted treatments in relation to anti-

EGFR antibodies in this population. Table 3 summarises data for anti-EGFR agents in the first-line setting.

CRYSTAL was a randomised phase 3 trial that investigated the addition of the anti-EGFR monoclonal antibody cetuximab to first-line FOLFIRI chemotherapy.[28-30] Cetuximab was associated with significantly improved PFS (9.9 vs 8.7 months, HR 0.68, p=0.02) and response rate (59.3 vs 43.2%, OR 1.91, 95% CI 1.24 to 2.93), with a trend to improved OS (24.9 vs 21.0 months, HR 0.84, 95% CI 0.64-1.11) in patients who were KRAS exon 2 wild-type. Pooled analysis of individual patient data from CRYSTAL and OPUS, a randomised phase 2 study comparing first-line FOLFOX/cetuximab to FOLFOX alone, confirmed that adding cetuximab to combination chemotherapy results in significant improvement in OS (HR 0.81, p=0.0062), PFS (HR 0.66, p<0.001) and RR (OR 2.16, p<0.0001) in KRAS WT tumours.[31] In contrast, no PFS or OS benefit was observed with the addition of cetuximab to chemotherapy in the MRC COIN and NORDIC-VII studies.[32,33] Inconsistencies in these trial results are likely related to a number of factors, including use of different chemotherapy backbones and selection of patients based on KRAS exon 2 status only in earlier studies.

For the initial mutation analysis in the anti-EGFR trials, tumours were only screened for KRAS mutations in codons 12 and 13 of exon 2 of the KRAS gene, as these were the first to be identified to be associated with resistance to anti-EGFR targeted therapy in mCRC.[34] Subsequent retrospective analyses of non-randomised data suggested that patients harbouring activating mutations in exons 3 and 4 (codons 61, 117 and 146) of the KRAS gene or exons 2, 3 and 4 (codons 12, 13, 61) of the NRAS gene also confer resistance to EGFR-targeted antibodies.[35,36] The predictive value of extended RAS analysis was first demonstrated in the PRIME trial.[37] Extended RAS analysis of PRIME, in which mutational status for KRAS exons 2-4, NRAS exons 2-4 and BRAF codon 60 was ascertained in 90% of the study population, revealed that the addition of panitumumab to first-line FOLFOX chemotherapy resulted in significant improvements in PFS (10.1 vs 7.9 months, HR 0.72, p=0.004) and OS (26.0 vs 20.2 months, HR 0.78, p=0.04) in extended RAS WT patients.[38]

Conversely, the addition of panitumumab to FOLFOX in patients with extended RAS mutations was associated with poorer PFS (HR 1.31, 95% CI 1.07-1.60) and OS (HR 1.25, 95% CI 1.02-1.55). Importantly, an interaction test looking for a difference in the effect of adding panitumumab between RAS WT patients and RAS mutant patients was statistically significant for PFS and OS (p=0.01), confirming the role of extended RAS status as a predictive biomarker for EGFR-targeted therapy. A meta-analysis confirmed that the patients were unlikely to significantly benefit from anti-EGFR therapy if their tumours featured any of these additional RAS mutations.[39]

A systematic review summarised several trials (COIN, PRIME, OPUS and CRYSTAL) that addressed the question of whether the addition of an anti-EGFR agent to first-line chemotherapy improves outcomes amongst patients with extended RAS WT tumours. This meta-analysis demonstrated that adding an anti-EGFR agent significantly improved PFS (p<0.0001) and RR (p<0.001), with a trend towards longer OS (p=0.07), compared with chemotherapy alone.[40] It is clear that extended RAS mutations confers lack of benefit from EGFR-targeted treatment and may even be associated with harm, and extended RAS status testing has rapidly been adopted as standard of care in patients with mCRC being considered for anti-EGFR therapy. Unlike the data for maintenance anti-VEGF therapy, the evidence for the role of maintenance anti-EGFR therapy in mCRC remains unclear.

3.2.3 RAS Wild Type: First-line VEGF versus EGFR antibodies in an all RAS population

Several studies have sought to define the optimal biologic agent for use in first-line treatment in patients with all RAS WT tumours. There is increasing evidence to suggest that primary tumour location in the left versus right colon should be considered when selecting a first-line biological agent; this is discussed further in Novel Subgroups below.

In the phase II PEAK study, 285 KRAS exon 2 wild type patients were randomised to receive mFOLFOX6/bevacizumab or mFOLFOX6/panitumumab in the first-line setting, with a primary endpoint of non-comparative analysis of PFS.[41] When molecular analysis was

extended to include KRAS exons 3 and 4 and NRAS exons 2-4, a positive effect was observed with panitumumab treatment for both PFS (13.0 vs 10.1 months, HR 0.65, 95% CI 0.44-0.96, p=0.29) and OS (41.3 vs 28.9 months, HR 0.63, 95% CI 0.39-1.02, p=0.58) among 170 extended RAS WT patients, in contrast to the negative effect among 51 patients with KRAS exon 2 WT/other RAS mutant tumours (median PFS 7.8 vs 8.9 months, HR 1.39, 95% 0.73-2.64, p=0.318).

The randomised phase 3 FIRE-3 study compared cetuximab and bevacizumab in KRAS exon 2 WT mCRC patients, using FOLFIRI as the chemotherapy backbone.[42] Five hundred and ninety-two patients were recruited to provide 80% power to detect a 12% absolute increase (from 50% to 62%) in investigator-assessed RECIST objective response rate, which was the primary endpoint. FIRE-3 was negative for the primary endpoint, with only a trend towards increased RR of 62% in the cetuximab arm versus 58% in the bevacizumab arm (p=0.18). Although there was no significant difference in PFS (10.0 months cetuximab arm vs. 10.3 months bevacizumab arm, HR 1.06, 0.88-1.26, p=0.55), OS was significantly longer in the cetuximab arm (28.7 vs. 25.0 months, HR 0.77, 95% CI 0.62-0.96, p=0.017). An exploratory analysis of extended RAS status (KRAS/NRAS exons 2-4) was conducted in the FIRE-3 study population.[43] Of 475 KRAS exon 2 WT patients that could be sequenced, 75 (16%) harboured mutations in one or more of the RAS genes tested, and the remaining 400 were extended RAS WT. In the final extended RAS WT group, the OS difference between FOLFIRI/cetuximab and FOLFIRI/bevacizumab became more pronounced, favouring the cetuximab arm (33.1 vs 25.0 months, HR 0.70, 95% CI 0.54-0.90, p=.0059), while investigator-assessed PFS and RR remained comparable between arms.

The phase 3 CALGB 80405 trial is the third study of head-to-head comparison of first-line anti-EGFR agent to bevacizumab in mCRC.[44] The trial initially randomised unselected mCRC patients receiving FOLFIRI or FOLFOX chemotherapy to cetuximab, bevacizumab or both biological agents. The study was subsequently amended to enrol only patients with

KRAS exon 2 (codon 12 and 13) WT tumours and to close the dual antibody group. Among the 1137 KRAS exon 2 WT patients in the final study population, and in contrast to the FIRE-3 trial, there was no significant difference between the chemotherapy/cetuximab versus chemotherapy/bevacizumab group in OS (30.0 vs 29.0 months, HR 0.88, 95% CI 0.77-1.01, p=0.08), PFS (10.5 vs 10.6 months, HR 0.95, 95% CI 0.84-1.09, p=0.45) or RR (59.6 vs 55.2%, difference 4.4%, 95% CI 1.0-9.0%, p=0.13). A possible explanation for the dissimilar results between the two phase 3 trials is the different proportions of patients with right-sided tumours, defined as those proximal to the splenic flexure, in FIRE-3 (22%) and CALGB 80405 (30%).[44,45] In post hoc subgroup analysis for the expanded RAS subset, OS (HR 0.88, 95% CI 0.72-1.08) and PFS (HR 1.03, 95% CI 0.86-1.24) remained similar between cetuximab and bevacizumab arms in CALGB 80405.

Head-to-head comparison data of bevacizumab versus anti-EGFR antibodies in first-line mCRC are summarised in Table 4. All three randomised studies (PEAK, FIRE-3, CALGB 80405) comparing first-line anti-EGFR agents versus bevacizumab were included in a meta-analysis, which found improvements in OS (HR 0.77, 95% CI 0.63-0.95, p=0.016) and RR (OR 1.46, 95% CI 1.13-1.90, p=0.004) with anti-EGFR agents compared to bevacizumab in an extended RAS WT population, but no difference in PFS (HR 0.92, 95% CI 0.71-1.18, p=0.5).[46] The unusual finding of significant OS difference without a PFS advantage, as noted in the FIRE-3 study and the meta-analysis, is unexpected for oncology studies in the metastatic setting, where PFS benefit is typically easier to demonstrate because OS is affected by subsequent lines of therapy. A possible explanation may be that choice of first-line therapy affects treatment with and efficacy of further line and salvage therapies. In the FIRE-3 trial, survival differences began to appear at around 24 months, after most patients had completed first-line therapy, and duration of second-line treatment was longer in the cetuximab arm (4.6 vs 3.2 months, p=0.007), as was PFS from start of second-line therapy (PFS2, 6.5 vs 4.7 month, HR 0.68, 95% CI 0.54-0.85) and OS from start of second-line therapy (OS2, 16.3 vs 13.2 months, HR 0.70, 95% CI 0.55-0.88, p=0.0021).[47,48]

In addition to considerations regarding efficacy, the choice of biological agents may also be influenced by potential toxicity and logistical factors. The EGFR- and VEGF-targeted agents have different side effect profiles, with anti-EGFR antibodies causing a severe and distressing acneiform rash in some patients. Furthermore, due to time and tissue requirements for RAS mutation testing, treatment may need to commence before results become available, with bevacizumab becoming the default biological agent in patients with RAS status unknown tumours.

3.2.4 RAS Wild Type: Combinations of Bevacizumab with an EGFR-targeted agent and chemotherapy

Despite promising preclinical and early Phase II trials, studies testing the addition of anti-EGFR monoclonal antibodies to chemotherapy and bevacizumab in the first-line setting did not demonstrate any advantages with two biological agents. In the CAIRO2 trial, there was no significant difference in PFS, OS or RR between KRAS WT patients treated with fluoropyrimidine-based chemotherapy, bevacizumab and cetuximab, and those treated with chemotherapy and bevacizumab.[20] Similarly, the addition of panitumumab to bevacizumab and chemotherapy in the PACCE study resulted in increased toxicity and decreased PFS.[49] Therefore, the use of combinations of EGFR-targeted and VEGF-targeted in mCRC is not recommended based on current evidence. Hypothesised explanations for the observed detrimental effect of combining two targeted agents include direct negative interactions between antibodies, decreased dose intensity of chemotherapy, as well as inclusion of patients with NRAS and KRAS exon 3 and 4 mutated tumours in the aforementioned studies.

3.3 Second-line and Subsequent Treatment

Decision-making when patients progress following initial treatment is becoming more complex, partly due to the blurring of traditional ‘line-based’ treatment approach where patients were treated until progression and then switched to salvage therapies.

3.3.1 Second-line Chemotherapy Strategy

Most patients who progress following a first-line oxaliplatin doublet will switch to irinotecan-based therapy, and vice versa. When chemotherapy is used alone, similar OS outcomes are produced irrespective of whether oxaliplatin-based or irinotecan-based chemotherapy is sequenced first, although responses are less frequent and PFS is shorter with second-line therapy with both approaches.[5]

3.3.2 Second-line Biologic Strategy

The choice of biological agent in the second-line setting is influenced by various factors, including biologic agent use in the first-line, RAS status and increasingly other molecular characteristics such as BRAF and HER2 status, as described below. Randomised trials of EGFR-targeted antibody panitumumab in the second- and third-line setting have reported outcomes by extended RAS mutational status among KRAS exon 2 WT patients. Similar to results from first-line studies described above, patients with RAS mutations have similar or inferior outcomes when treated with panitumumab compared to FOLFIRI alone, irinotecan alone or best supportive care.[46, 47, 48] Tables 3 and 5 summarise current data for second-line use of anti-EGFR and anti-VEGF agents, respectively.

3.3.3 Beyond Second-line and Newer Approaches

As anti-EGFR agents cetuximab and panitumumab are associated with clear survival advantages in later lines of therapy, their use should be standard of care in RAS WT patients who have not previously been exposed to these agents. The ASPECCT trial demonstrated that panitumumab is non-inferior to cetuximab in terms of OS, PFS, toxicity and RR.[50] Comparable efficacy and tolerability between panitumumab and cetuximab was confirmed in a retrospective series of patients receiving anti-EGFR therapy combined with irinotecan in later lines of treatment.[51] However, there are many patients who remain relatively well despite exhausting existing treatment options, for whom new agents and strategies are needed for third and later lines for treatment.

Regorafenib is an oral multi-tyrosine kinase inhibitor that was compared with placebo in salvage setting in the CORRECT study.[25] Treatment with regorafenib resulted in a statistically significant but clinically modest improvement in OS (6.4 vs 5.0 months, HR 0.77, 95% CI 0.64-0.94, p=0.0052). The main toxicities requiring dose modifications and delays were diarrhoea and asthenia, but quality of life in both study arms were similar. The benefit of regorafenib in a treatment refractory mCRC patients was corroborated by CONCUR, a phase 3 trial conducted in an Asian population only, which confirmed the survival advantage associated with regorafenib (HR 0.55, p<0.0001).[52]

The RECOURSE trial investigated TAS102, a synthetically engineered fluoropyrimidine, in patients who had received at least 2 prior lines of chemotherapy including fluoropyrimidine, oxaliplatin, irinotecan and bevacizumab, and for patients with KRAS WT tumours, cetuximab or panitumumab. Compared to placebo, TAS102 prolonged OS from 5.3 to 7.1 months (HR 0.68, 95% CI 0.58-0.81, p<0.001) and PFS from 1.7 to 2.0 months (HR 0.48, 95% CI 0.41-0.57, p<0.001), and delayed time to deterioration in performance status from 4.0 to 5.7 months (HR 0.66, 95% CI 0.56-0.78, p<0.001).[53] The most common toxicities were haematological, including ≥Grade 3 neutropaenia in 38% of patients receiving regorafenib and febrile neutropaenia in 4%.

Fruquintinib is an oral VEGF-targeted kinase inhibitor that was studied in the third line setting amongst Chinese patients in a phase 3 trial. Compared to placebo, fruquintinib prolonged OS (9.3 vs 6.6 months, HR 0.65, 95% CI 0.51-0.83, p<0.001) and was associated with increased rates of ≥Grade 3 hypertension (21.6%), hand-foot reaction (10.8%), proteinuria (3.2%) and diarrhoea (3.2%).[54]

Novel approaches to treatment sequencing are being investigated to maximise the clinical utility of existing agents. For instance, a phase 2 trial of cetuximab rechallenge demonstrated RR of 54% when irinotecan-refractory patients who had clinical benefit with a line of

cetuximab- plus irinotecan-based therapy, followed by a different chemotherapy and progression, were retreated with the same cetixumab- plus irinotecan-based therapy.[55]

3.4 Novel Subgroups

3.4.1 Left versus Right Side

3.4.1.1 Clinical, pathologic and molecular characteristics

There is accumulating data that right- and left-sided colon cancers should be considered different entities, with distinct clinical, demographic and histological features. Right-sided cancers, defined as those proximal to the splenic flexure, tend to occur in female and older patients, and are associated with poorly differentiated and locally advanced tumours, peritoneal carcinomatosis and worse prognosis.[56] These characteristics were corroborated in a retrospective analysis of the NCIC CO.17 trial, which was designed to compared cetuximab versus best supportive care in chemotherapy-refractory mCRC and found that patients with right-sided cancers had more poorly differentiated, KRAS mutant and BRAF WT tumours, and shorter interval between diagnosis and study entry.[57] Furthermore, among KRAS wild-type patients in CO17, patients with left-sided tumours had significantly improved PFS when treated with cetuximab (5.4 vs 1.8 months, HR 0.28, 95% CI 0.18-0.45, p<0.0001) whereas those with right-sided tumours did not (1.9 vs 1.9 months, HR 0.73, 95% Ci 0.42-1.27, p=0.26).

3.4.1.2 Predictive and prognostic relevance

A recent meta-analysis of first-line clinical trials in mCRC confirmed that primary tumour location was predictive of survival benefit from the addition of an anti-EGFR antibody to standard chemotherapy in RAS WT tumours (left-sided OS HR 0.69, p<0.0001; right-sided OS HR 0.96, p=0.802).[58] With respect to choice of first-line biologic agent, patients with RAS wild-type left-sided cancers had a significant benefit from anti-EGFR treatment compared to anti-VEGF treatment (HR 0.71, 95% CI 0.58-0.85, p=0.0003) while patients

with right-sided cancers had a non-significant improvement in OS with bevacizumab-based treatment (HR 1.3, 95% CI 0.97-1.74, 0.081). A pooled analysis of six randomised trials (CRYSTAL, FIRE-3, CALGB 80405, PRIME, PEAK, 20050181) investigated the prognostic and predictive effects of tumours side in patients with RAS WT mCRC receiving first- or second-line chemotherapy with EGFR-targeted antibodies.[59] This meta-analysis not only reinforced the poorer prognosis associated with right-sided tumours, but also confirmed that anti-EGFR treatment prolonged OS (HR 0.75, 95% CI 0.67-0.84, p<0.001) and PFS (HR 0.78, 95% CI 0.70-0.87, p<0.001) and improved RR (OR 2.12, 95% CI 1.77-2.55) in left-sided tumours only. The test for interaction between primary tumour location and EGFR-targeted antibodies was significant for OS (p<0.001) and PFS (p=0.002) and trended towards significance for RR (p=0.07). Although first-line trials provide most of the evidence for the predictive role of primary tumour location, the second-line 20050181 trial investigating the addition of panitumumab to FOLFIRI reported similar associations between tumour side and OS and ORR, suggesting that tumour location may influence treatment decisions beyond first-line therapy.[59,60] Further evidence for differential responses to EGFR-targeted treatment based on tumour location is provided by the phase 2 AIO VOLFI trial, which reported RR of 90.6% versus 60.0% for left and right-sided mCRC treated with FOLFOXIRI and panitumumab.[61] It is biologically plausible that primary tumour location may response to EGFR-targeted therapy, as cetuximab response signatures such as amplification of the ErbB family and stronger EGFR signalling are observed more frequently in left-sided KRAS wild-type mCRC.[62]

3.4.1.3 Implications for Clinical Practice

With growing evidence regarding the predictive role of primary tumour side, it appears that only patients with left-sided mCRC derive long term survival benefits from anti-EGFR therapy. In line with these findings, mCRC guidelines published by the National Comprehensive Cancer Network (NCCN) in the United States of America and the National Health and Medical Research Council (NHMRC) of Australia recommend that anti-EGFR

agents should only be used routinely in left-sided RAS WT tumours.[63,64] However, for potentially resectable RAS WT patients where conversion to resectability is the goal, current European Society for Medical Oncology (ESMO) guidelines for mCRC recommend intensified treatment with cytotoxic doublet plus an anti-EGFR antibody to maximise R0 resection rates with no caveats on primary tumour location.[65] Until the predictive value of primary tumour location is validated in prospective studies, the question of whether EGFR-targeted therapies should be offered to patients with RAS WT right-sided tumours is likely to remain controversial.

3.4.2 BRAF Mutations

The serine/threonine-protein kinase BRAF is a component of the RAS/RAF/MEK/MAP signal transduction pathway, which mediates signals from cell surface receptors to the nucleus to regular cell growth, differentiation and survival. BRAF is downstream of RAS, and is responsible for phosphorylation and activation of MEK1 and MEK2.[66] Mutations in BRAF, which are detected in approximately 10% of CRC patients overall, are mutually exclusive of KRAS mutations and occur more frequently in patients with mismatch repair deficiency (dMMR).[67-70] The most common BRAF mutation is V600E, which results in an amino acid change from valine (V) to glutamic acid (E), leads to constitutive activation of BRAF by mimicking tyrosine kinase phosphorylation.[66]

3.4.2.1 Clinical, pathologic and molecular characteristics

BRAF mutations in CRC are associated with female gender, older age and right-sided tumours with more advanced TNM stage, poor differentiation, mucinous histology and dMMR.[71,72] BRAF mutated CRC also tends to metastasise more commonly to the peritoneal cavity and lymph nodes, which in one series occurred in approximately 50% of BRAF mutant patients compared to 25-35% of BRAF WT patients.[67]

3.4.2.2 Prognostic relevance

BRAF V600E mutated colorectal cancers are associated with poorer prognosis, with median survival approximately half that of BRAF WT tumours (10-15 months).[72,73] The poorer survival associated with BRAF mutations may be related to lower response rates to first-line chemotherapy, but is also likely driven by subsequent rapid progression that precludes many patients from receiving second-line therapies. There is also evidence that patients with BRAF mutations rarely have patterns of metastatic spread that are amenable to surgical resection with curative intent, and those that do undergo resection have a higher rate of subsequent relapse compared to BRAF WT patients.[74]

Despite the evidence for poorer prognosis associated with the most prevalent BRAF mutation V600E, the presence of a BRAF mutation does not refer to a homogenous group of patients with identical clinical behaviour. There are clearly some patients that fare better and are able to receive second and subsequent lines of therapy, although the molecular and clinical factors underlying this heterogeneity are yet to be well delineated. In this regard, recent research into BRAF mutations outside of codon 600, such as codons 594 and 596, suggest other mutations do not share clinical features with the V600E mutation and may even be associated with more favourable prognosis.[75]

3.4.2.3 Predictive relevance

BRAF mutation status does not appear to be predictive of the RR and PFS benefit afforded by the addition of bevacizumab to first-line chemotherapy in mCRC patients.[76] The utility of BRAF mutation status as a predictive marker of benefit from anti-EGFR directed therapy is more controversial. There have been no randomised studies designed primarily to address this issue prospectively, but retrospective analyses of randomised trials have attempted to investigate the effect of anti-EGFR antibodies in BRAF mutant patients. Two meta-analyses have analysed the predictive role of BRAF mutation status in RAS WT patients receiving anti-EGFR therapy.[77,78] Neither demonstrated a statistically significant difference in PFS

or OS between BRAF mutant and WT subgroups, with aggregate HRs approximating 0.9. In one of the meta-analyses an interaction test was performed which did not demonstrate a significant effect of BRAF mutation status on the survival benefit associated with EGFR targeted therapies in mCRC.[77] BRAF mutant patients receiving anti-EGFR antibody monotherapy in later lines of treatment rarely have a RECIST-defined tumour response.[79] However, the fact that BRAF mutations predominantly occur in right-sided tumours substantially confounds the analysis.

3.4.2.4 Implications for clinical practice

The clinical utility of knowing patients' BRAF status is now accepted among oncologists, with clinical practice guidelines recommending that BRAF mutational status be ascertained in mCRC patients for prognostic stratification.[80] Knowledge of a patients' BRAF status not only offers valuable prognostic information but also may facilitate early referral for clinical trial participation.

Given that BRAF V600E mutations are associated with poor prognosis, lower response rates and lower chance of proceeding to subsequent treatment lines, it could be inferred that patients should be treated with as many agents in the first-line setting as oncologists deem tolerable. In pre-planned subgroup analysis of the TRIBE study, which investigated a 'triplet' first-line approach with the addition of oxaliplatin to FOLFIRI/bevacizumab, patients with BRAF mutant tumours appeared to benefit from intensified treatment (median OS: 19 vs 10.7 months, HR 0.54, 95% CI 0.24-1.20), although patient numbers were too small (n=28) to establish statistical significance.[81] Nevertheless, BRAF status is only one of many factors that need to be considered when choosing a treatment protocol. Furthermore, there is currently insufficient evidence for routinely withholding anti-EGFR therapy based on BRAF status. While patients with BRAF mutations are likely to have less benefit than RAS/RAF wild-type patients, it is reasonable to treat them with EGFR-targeted agents, particularly when other options are not available.

There is active research investigating the newer treatment approaches involving BRAF-targeted biological agents in patients with BRAF mutations. However, unlike in melanoma, single agent BRAF inhibitors have limited activity in mCRC.[82] The mechanism of resistance to BRAF inhibitors in mCRC is believed to be related to feedback reactivation of the EGFR receptor, resulting in ongoing stimulation of the MAPK pathway.[83] Subsequent research has focused on combination approaches to inhibit the MAPK pathway at multiple levels, inhibiting parallel pathways and/or the EGFR receptor. Evidence of safety and activity have been demonstrated in early phase trials of combinations of BRAF with MEK inhibitors, EGFR inhibitors, PI3K inhibitors and/or chemotherapy.[84-88]

On the basis of RR of 35% observed in a phase 1b trial of the combination of vemurafenib, irinotecan and cetuximab, the phase 2 SWOG 1406 study randomised 106 pre-treated mCRC patients with extended RAS wild-type and BRAF V600E mutation to receive cetuximab and irinotecan (IC), with or without vemurafenib.[86,89] The addition of vemurafenib was associated with longer PFS (4.3 vs 2.0 months, HR 0.48, 95% CI 0.31-0.75, p=0.001), higher disease control rate (67 vs 22%, p<0.001) and a trend to improved OS (9.6 vs 5.9 months, HR 0.73, 95% CI 0.45-1.17, p=0.19), notwithstanding the fact that 48% of patients in the IC arm crossing over to the vemurafenib arm on progression. Interestingly, the addition of vemurafenib was associated with benefit in patients crossing over to the vemurafenib arm after progression on IC alone, with median PFS of 5.8 months and OS of 12.1 months. SWOG 1406 provides evidence supporting the use of BRAF inhibitor vemurafenib in combination with irinotecan and cetuximab in 2nd or later line treatment of mCRC with BRAF V600E mutations.

3.4.3 Defective Mismatch Repair mCRC

Microsatellite instability (MSI) refers to deviations in the number of short tandem repeats of nucleosides in specific genomic sites that arise due to defects in the mismatch repair (MMR) mechanism, which normally detects and repairs DNA replication mistakes and maintains

stability of microsatellite length. It is hypothesised that MMR deficiency results in higher mutational burdens in MSI-high (MSI-H) tumours, producing neoantigens that increase their responsiveness to immune checkpoint inhibitors.[90,91] This is supported by evidence of high T lymphocyte infiltrates and upregulation of immune checkpoints, including programmed cell death 1 (PD-1) receptor and programmed cell death 1 ligand (PD-L1), in the microenvironment of MSI mCRC.[92] Current clinical guidelines recommend universal MMR or MSI testing in all patients with a personal history of colon or rectal cancer.[63]

The phase 2 KEYNOTE-016 study evaluated the activity of anti-PD-1 checkpoint inhibitor pembrolizumab in treatment-refractory advanced CRC with and without MMR deficiency.[91] The ORR in patients with MMR deficient (dMMR) mCRC was 52%, including complete responses in 12% of patients, compared to ORR of 0% in MMR proficient (pMMR) mCRC.[93] Patients with dMMR mCRC also had longer PFS (not reached vs 2.2 months, HR 0.10, $p<0.001$) and OS (not reached vs 5.0 months, HR 0.22, $p=0.05$) than patients with pMMR mCRC. The efficacy of pembrolizumab has subsequently been confirmed in MSI-H pre-treated advanced colorectal and non-colorectal cancers, with ORR of 38% in the latter.[94] On the basis of these results, pembrolizumab was granted accelerated approval by the United States Food and Drug Administration for treatment of advanced solid tumours with MSI-H or dMMR, representing the first time the agency has given tumour site-agnostic approval based on a common biomarker rather than the tumour's location of origin. A phase 3 trial is currently under way comparing pembrolizumab versus standard of care chemotherapy in the first-line setting in patients with dMMR or MSI-high mCRC (NCT02563002).[95]

Other immune checkpoint inhibitors, alone and in combination, have also been investigated MSI-H mCRC. In the phase 2 CheckMate-142 study, patients with treatment-refractory dMMR/MSI-H mCRC were treated with single agent nivolumab, a PD-1 immune checkpoint inhibitor, achieving a RR of 31%.[96,97] Patients treated with combination immunotherapy with nivolumab and ipilimumab (a cytotoxic T-lymphocyte-associated-4 [CTLA-4] immune

checkpoint inhibitor) achieved RR 41% and DCR 78%, at the expense of a high rate (37%) of Grade 3-4 treatment-related adverse events (AE).[98] The PD-L1 inhibitor atezolizumab was tested with bevacizumab in 10 patients with MSI-H mCRC in a phase Ib study, resulting in RR of 30% and Grade 3-4 AE rate of 40%.[99] Atezolizumab is currently being tested in the early colon cancer setting in the ATOMIC/Alliance A021502 trial, where atezolizumab/FOLFOX is being compared to FOLFOX alone in patients with MSI-H/dMMR stage III colon cancer (NCT02912559).[100]

Given that only a minority of CRC patients have dMMR as a biomarker predicting response to checkpoint inhibitors, there is substantial interest in developing methods to transform immunologically “cold” tumours into “hot” ones that will benefit from immunotherapy.[101] One strategy is to combine immunotherapy with molecularly targeted therapy, which can produce favourable immune effects in the tumour microenvironment such as increased antigen and HLA expression, increased T cell infiltrate, reduced immunosuppressive cytokines and improved T cell function.[102] In a phase 1b trial of the MEK inhibitor cobimetinib and atezolizumab in patients with pre-treated microsatellite stable (MSS) mCRC, 17% of patients had an objective response, paving the way for a phase 3 study of atezolizumab alone and in combination with cobimetinib in patients with treatment-refractory MSS mCRC (NCT02788279).[103] The effect of chemotherapy and anti-angiogenic agents on the tumour immune milieu was examined in an early phase trial of FOLFOX, bevacizumab and atezolizumab as first-line therapy in mCRC, resulting in RR of 52%.[104] Furthermore, CD8+ T cells and PD-L1 expression were increased in tumours following administration of FOLFOX, as well as after combined administration of all 3 agents, suggesting that cytotoxic chemotherapy and/or VEGF-targeted agents may help promote immune-related activity in mCRC, potentiating the efficacy of immune checkpoint inhibitors. In a phase 2 trial evaluating the combination of FOLFOX chemotherapy and pembrolizumab in patients with untreated mCRC, irrespective of MMR status, objective responses were reported in 16 of 30 patients (53%).[105] The PD-L1 checkpoint inhibitor atezolizumab has

been tested with CEA CD3 TCB, a novel T-cell bispecific antibody targeting CEA on tumours cells and CD3 on T cells, in a Phase 1a/1b trial of patients with advanced CEA-positive, chemorefractory CRC, producing responses in 1 of 5 patients receiving this combination.[106]

3.4.4 HER2 amplified tumours

Human epidermal growth factor (HER2; also known as ERBB2) is a member of the epidermal growth factor (EGFR) family of transmembrane tyrosine kinase receptors, which are involved in various cellular functions such as proliferation, apoptosis, adhesion, migration and differentiation. HER2-targeted agents, such as trastuzumab, are well-established as standard-of-care in HER2-amplified breast cancer. Based on this and evidence of activity with combination HER2-targeted agents in mouse models of HER2-amplified mCRC, the HERACLES trial was proof-of-concept phase 2 trial assessing the efficacy of trastuzumab and lapatinib in HER2-positive, KRAS exon 2 wild-type mCRC patients resistant to standard therapies including cetuximab.[107] After screening 914 patients with KRAS exon 2 wild-type mCRC, 48 HER2-positive patients (defined as having either 3+ HER2 score by immunohistochemistry (IHC), or 2+ HER2 score by IHC and FISH positive in >50% of cells) were identified and 27 were treated with dual-targeted anti-HER2 therapy. Eight patients (30%) achieved an objective response, with 7 of 8 responses seen in patients with tumours with HER2 IHC 3+ (as opposed to HER2 IHC 2+ and FISH positivity). The combination was well-tolerated, with toxicities limited to mainly Grade 2 diarrhoea, fatigue and rash. The results of this study provide evidence to support the investigation of HER2-targeted therapy in earlier lines of treatment in patients with HER2-positive mCRC. The MyPathway Phase IIa multiple basket study included an arm investigating dual HER2 blockade with trastuzumab and pertuzumab in advanced solid tumours with HER2 amplification or overexpression.[108] Amongst the 37 patients with HER2-positive colorectal cancer, ORR was 38% and median duration of response was 11 months. Among HER2-amplified KRAS WT patients ORR was

52%, while no responses were observed in HER2-amplified KRAS mutated patients, providing predictive data that may facilitate more targeted use of anti-HER2 therapy.[109]

HER2 amplification in colorectal cancer is associated with resistance to anti-EGFR antibodies, thereby limiting the role of these agents in HER2-positive patients.[110] Of note, HER2 overexpression occurs more commonly in left-sided colon and rectal tumours than right-sided colon tumours, and thus may have significant clinical relevance for treatment choice.[111]

3.4.5 Gene Expression Signature-defined Molecular Subgroups

Gene expression signatures are garnering increasing interest as tools to refine classification of CRC and facilitate clinical prognostication and development of expression signature-based targeted therapies. The best known of these classification systems is the Consensus Molecular Subtypes (CMS) developed by the CRC Subtyping Consortium.[112] The CMS system classifies CRC into 4 subtypes based on gene expression signatures. Each of the 4 subtypes is associated with particular biological characteristics, which suggests that responsiveness to therapies is also likely to differ for each subtype. The prognostic role of CMS subtypes has been confirmed in retrospective analyses of the CALGB 80405 and FIRE-3 studies comparing the first-line combinations of chemotherapy with EGFR- versus VEGF-targeted agents.[113,114] However, the prognostic and potentially predictive value of CMS subtypes needs to be validated prospectively in future trials, as there is currently insufficient evidence for using CMS subgroups to inform clinical decision making.

4. Chemotherapy and Liver Dominant mCRC

4.1 Resectable and Potentially Resectable Disease

Complete resection of oligometastatic disease, with or without perioperative chemotherapy, is currently the only potentially curative treatment for mCRC, with a 5-year survival rate of 40-60% after hepatectomy.[115-117] Conversion therapy is systemic treatment that is given

to patients with potentially resectable disease with a view to 'convert' unresectable metastases to resectability.[65] As resection rate after neoadjuvant chemotherapy has been found to correlate with tumour response rate (RR) according to RECIST criteria, conversion therapy should comprise aggressive combination chemotherapy and an appropriate biological agent to aim for maximal tumour downsizing.[118-120]

4.2 Unresectable Liver Dominant mCRC

Non-surgical liver-directed therapies have been investigated in trials enrolling mCRC patients with unresectable liver metastases. The prospective, randomised phase 2 CLOCC study compared radiofrequency ablation (RFA) plus chemotherapy versus chemotherapy alone in 119 mCRC patients with <10 unresectable liver metastases and no extrahepatic disease. The trial met its primary end point with an improved 30-month OS of 61.7% in the combination arm compared to 57.6% in the chemotherapy only arm.[121] This corresponded to an increase in median OS in favour of the RFA and chemotherapy (45.6 vs 40.5 months, HR 0.57, 95% CI 0.38 to 0.88, p=0.01). These results need to be interpreted with caution, as patients in the RFA arm had better baseline prognostic characteristics than the control arm, with a lower proportion of patients with ≤3 metastases and higher proportion of patients with metachronous tumours.

Selective internal radiation therapy (SIRT) involves the delivery of targeted radiation to liver tumours via injection of yttrium-90-labelled resin microspheres (SIR-spheres) through the hepatic artery. SIRFLOX was a phase 3 study that assessed the safety and efficacy of the addition of SIR-spheres to first-line chemotherapy (FOLFOX ± bevacizumab) in patients with unresectable liver only or liver dominant mCRC.[122] While the primary endpoint of PFS by RECIST 1.0 was not met (10.7 with SIRT vs 10.2 months without SIRT, HR 0.93, 95% CI 0.77-1.12, p=0.43), the trial demonstrated improvements in secondary end points such as liver-specific PFS (20.5 vs 12.6 months, HR 0.69, 95% CI 0.55-0.90, p=0.002). A pre-planned combined analysis of SIRFLOX with 2 other SIRT studies (FOXFIRE and FOXFIRE-

Global) evaluated the addition of SIRT to first-line FOLFOX ± biological agent in 1103 systemic treatment-naïve patients with mCRC. This negative study confirmed that improvements in liver-specific PFS conferred by the addition of SIRT do not translate to improvements in OS, echoing data nearly two decades earlier utilising hepatic arterial chemotherapy.[123,124] There is currently therefore no evidence to support SIRT as an adjunct to routine first-line systemic therapy in mCRC, irrespective of primary tumour location. However, SIRT may be useful in later lines of treatment in patients with liver only metastases who have failed chemotherapy.[125]

5. Expert Commentary & Five-year View

This consensus review examines current evidence for the use of targeted therapy in mCRC in different settings. There is well-established evidence for the use of EGFR-targeted and VEGF-targeted antibodies, which should routinely be incorporated into treatment strategies for mCRC. The introduction and ongoing management of these biological agents should be managed to derive maximal benefit from their use. The goal of treating mCRC is to utilise all available drugs across multiple lines of therapy, when possible, and this requires careful assessment of patient and tumour characteristics to inform selection and sequencing of agents.

The use of EGFR-targeted antibodies should be restricted to patients with extended RAS wild-type profiles (NRAS 2-4 wild-type and KRAS 2-4 wild-type). For this group of patients, the choice of bevacizumab versus anti-EGFR therapy in the first-line setting now appears clearly based on side of primary. Based on retrospective analyses of randomised trials, left-sided tumours appear to derive greater benefit from EGFR-targeted antibodies compared to right-sided tumours. Therefore, primary tumour location should be taken into consideration when selecting biological treatments, which is a recommendation that is already reflected in some colorectal cancer treatment guidelines.

Novel subgroups and classification systems are gaining interest as tools to aid better characterisation, prognostication and development of targeted therapies in mCRC. While BRAF mutations in mCRC are associated with poor prognosis and less likelihood of progressing to subsequent treatment lines, these mutations represent a potential target for biological treatment. Novel treatment combinations of BRAF and MEK inhibitors have started to demonstrate activity in early phase trials of BRAF V600E mutant mCRC. MMR deficiency is recognised as being predictive of benefit from immune checkpoint inhibitors, which have now been approved for use in later lines in this molecular subgroup, not only in mCRC but across all solid tumours. HER2 amplifications also represent fertile domain for developing targeted treatments in mCRC. Finally, CMS subgroups are likely to play a more prominent role in prognosticating and personalising treatment for mCRC patients once prospective data is available from future trials.

In terms of novel treatment modalities, despite early promise with evidence of improvements in liver specific PFS, localised radiotherapy via SIRT has not achieved clinically meaningful improvements in OS, although this remains an option for patients with liver only metastases who have failed chemotherapy.

Key Issues

- The treatment strategy for advanced colorectal cancer should include early molecular assessment and multidisciplinary review to determine the potential for resection of metastasis, as this will inform best use and sequence of available agents.
- Results of extended RAS status testing will determine suitability for treatment with EGFR-targeted patients, with extended RAS wild-type patients achieving median overall survival up to 30 months and 5 year survival in excess of 10%.
- Site of primary is now accepted by a number of guidelines (NCCN, ESMO and Australian NHMRC) as a guide to treatment choice in RAS WT mCRC, with left-sided

tumours best treated with an anti-EGFR/chemotherapy combination, and right-sided tumours with bevacizumab/chemotherapy combination

- Mismatch repair (MMR) status should be routinely tested in mCRC patients as MMR deficiency predicts benefit from immune checkpoint inhibitors in the treatment-refractory setting.
- Patients with BRAF mutations or HER2 amplifications may be amenable to treatment with molecularly targeted agents, pending further clinical trial evidence.
- Currently there is evidence that mCRC could be divided into 6 distinct clinical/molecular subgroups which have distinct treatment pathways; 1. Left sided RAS WT, 2. Right sided RAS WT, 3. RAS MT, 4. BRAF MT, 5. HER2 over expressed, and 6. dMMR (noting some cross over with BRAF MT).

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Table 1: First-line Phase III trials with anti-angiogenic agents

BIOLOGIC	Treatment	n	RR (%)	Median PFS months (HR)	Median OS months (HR)	Comment
Bevacizumab [11]	IFL V IFL/ bev	813	35 v 45 +	6.2 v 10.6 (0.54) +	15.6 v 20.3 (0.66) +	No randomised data available for FOLFIRI

Bevacizumab (NO16966) [12]	Oxaliplatin/ Fluoropyrimidine V Oxaliplatin/fluoropyrimidine/ bev	1401	38 v 38 -	8.0 v 9.4 (0.83) +	19.9 v 21.3 (0.89) -	Suboptimal use of drugs
Bevacizumab (MAX) [13]	Capecitabine v capecitabine (mitomycin)/ bev	471	30 v 36 -	5.7 v 8.5 (0.63) +	18.9 v 16.4 -	
Bevacizum	Capecitabine	280	10	5.1	16.8	Cape/bev

ab (AVEX) [14]	v capecitabine/bev		v 19 +	v 9.1 (0.53) +	v 20.7 (0.78) -	more toxic but well tolerated in elderly (age >70 years)
Bevacizumab +/- Panitumumab (PACCE) [49]	Doublet chemotherapy /bev v Doublet chemotherapy/bev/pan	823	48 v 46 -	11.4 v 10.0 (1.27) -	24.5 v 19.4 (1.43) -	Combined Abs inferior Trend to inf RR, PFS , OS in KRAS WT
Bevacizum	Oxaliplatin/capecitabine/b					

ab +/- cetuximab (CAIRO2) [20]	ev v Oxaliplatin/capecitabine/bev/cet	736	50 v 52.7 -	10.7 v 9.4 (1.22) +	20.3 v 19.4 -	Combined Abs inferior
Bevacizumab (TRIBE) [81]	FOLFIRI/bev v FOLFOXIRI/bev	508	54 v 65	9.7 v 12.3 (0.77) +	25.8 v 29.8 (0.80) +	OS in RAS/BRAF WT and RAS/ BRAF mutated subgroups presented in update
Bevacizumab (ITACa) [15]	Doublet chemotherapy V	376	50.0 v	8.4 v	21.3 v	

	Double chemotherapy/bev		50.6 -	9.6 (0.86) -	20.8 (1.13) -	
Tyrosine Kinase Inhibitors	vatalanib , sunitinib, sorafenib, cedaranib	No clinical benefit seen				

NB + is statistically significant, - is not, bev=bevacizumab

Table 2. Maintenance Phase III trials with anti-angiogenic agents

Biologic	**First-line Induction Treatment**	**Treatment**	**n**	**Median PFS months (HR)**	**Median OS months (HR)**	**Comment**
Bevacizumab (MACRO) [16]	18 weeks CAPOX/ bev	CAPOX/bev vs. bev	480	10.4 Vs. 9.7 (1.10) -	23.2 Vs. 20.0 (1.05) -	Non-inferiority endpoint for PFS not met Randomisation occurred before induction treatment

Bevacizumab (CAIRO3) [17]	18 weeks CAPOX/bev	Capecitabine/bev Vs. Observation	558	8.5 Vs. 4.1 (0.40) +	25.9 Vs. 22.4 (0.83) -	Positive for primary endpoint of time to second progression (HR 0.67, p<0.0001) Randomisation occurred after induction treatment
Bevacizumab (PRODIGE 9) [18]	24 weeks FOLFIRI/bev	Bevacizumab Vs. Observation	494	9.2 Vs. 8.9 (0.92) -	21.65 Vs. 21.98 (1.05) -	Randomisation occurred before induction treatment
Bevacizumab (AIO	24 weeks Fluoropyrimid	Fluoropyrimidine/bev	837	6.3 vs.	20.2 vs.	Non-inferiority demonstrated for primary endpoint (failure of strategy) for bev compared to

0207) [19]	ine/oxaliplatin/bev	Vs. Bev Vs. Observation		4.6 vs. 3.5 +	21.9 Vs. 23.1 -	fluoropyrimidine/bev (HR 1.08, 95% CI 0.85-1.37) Randomisation occurred after induction treatment
Bevacizumab/ erlotinib (GERCOR DREAM; OPTIMOX 3) [21]	24 weeks Fluoropyrimidine/oxaliplatin/bev or FOLFIRI/bev	Bev/erlotinib Vs. Bev	700	5.4 Vs. 4.9 (0.81) -	24.9 Vs. 22.1 (0.79) +	Randomisation occurred after induction treatment

NB + is statistically significant, - is not, bev=bevacizumab

Table 3: Phase 3 Trials adding EGFR antibodies to chemotherapy (+ is statistically significant; - is not)

FIRST-LINE	**TREATMENT**		**KRAS exon 2 wild type analysis**				**Extended RAS wild type analysis**			
			n	RR %	PFS m; (HR)	OS m; (HR)	n	RR %	PFS m; (HR)	OS m; (HR)
Cetuximab (Crystal) [28-30]	FOLFIRI/cetuximab V FOLFIRI		666	57 v 40 +	9.9 v 8.4 (0.696) +	23.5 v 20.0 (0.796) +	367	66 v 39 +	11.4 v 8.4 (0.56) +	28.4 V 20.2 (0.69) +

Panitumumab (PRIME) [37,38]	FOLFOX/panitumumab V FOLFOX		656	57 v 48 +	9.6 V 8.0 (0.80) +	23.9 V 19.7 (0.83) -	512	NR	10.1 v 7.9 (0.72) +	26 v 20.2 (0.78) +
Cetuximab (NORDIC) [32]	Nordic FLOX/Cetuximab V Nordic FLOX		303	46 v 47 -	7.9 v 8.7 -	20.1 v 22.0 -	N/A	N/A	N/A	N/A
Cetuximab (COIN) [33]	Oxaliplatin/FU/ cetuximab v		729	64 v 57 +	8.6 v 8.6	17.0 v 17.9	N/A	N/A	N/A	N/A

	oxaliplatin/FU				-	-				
Cetuximab (TAILOR) [126]	FOLFOX/cetuximab V FOLFOX		N/A	N/A	N/A	N/A	393	61 v 40 +	9.2 V 7.4 +	20.7 V 17.8 +
SECOND-LINE	**TREAMENT**	**Prior Bev**	**KRAS exon 2* wild type analysis**				**Extended RAS wild type analysis**			
			n	RR%	PFS HR	OS HR	n	RR%	PFS HR	OS HR
Panitumumab (PICCOLO)* [127]	Irinotecan vs Irinotecan + panitumumab	2% 2%	460 (KRAS exons 2 and 3)	12 v 33 +	0.78 +	1.01 -	323	12 v 44 +	0.68 +	0.92 -

Panitumumab 20050181 [128]	FOLFIRI V FOLFIRI/ panitumumab	20% 18%	597	10% V 35% +	0.73 +	0.85 -	421	10% V 41% +	0.70 +	0.81 -
Cetuximab (Study CA225006) [129]	Irinotecan V Irinotecan/ cetuximab	N/A N/A	192	N/A	0.773 -	1.29 -	N/A	N/A	N/A	N/A

* patients in the PICCOLO study were wild type for KRAS exons 2 and 3

NB + is statistically significant, - is not

Table 4: Head –to- head first-line trials comparing anti EGFR mab with bevacizumab: (+ is statistically significant; - is not)

Trial	Treatment	**KRAS exon 2 wild type analysis**				**Extended RAS wild type analysis**			
		n	**RR %**	**PFS Months (HR)**	**OS Months (HR)**	**n**	**RR %**	**PFS Months (HR)**	**OS Months (HR)**
PEAK Phase II [41]	FOLFOX/bev V FOLFOX/pa	285	54 v 58	10.1 v 10.9	24.3 v 34.2	170	60 v 64	9.5 v 13.0	28.9 v 41.3

	n			(0.87) -	(0.62) +			(0.65) +	(0.63) -
FIRE3 Phase III [42]	FOLFIRI/bev V FOLFIRI/cet	592	58 v 62	10.0 v 10.3 (1.06)	25.0 v 28.7 (0.77)	342	60 v 66	10.2 v 10.4 (0.93)	25.6 v 33.1 (0.70)

			-	-	+		-	-	+
CALGB80405 Phase III [44] FOLFOX or FOLFIRI doublet backbone (73% FOLFOX)	Doublet/bev V Doublet/cet	1137	55.2 V 59.6 - -	10.6 v 10.5 (0.95) -	30.0 v 29.0 (0.88) -	526	56 v 68.8 +	11.0 v 11.2 (1.03) -	31.2 v 32.0 (0.88) -

Table 5: Second-line trials with antiangiogenic agents

	Treatment	N	Prior Bevacizumab	PFS Months (HR)	OS months (HR)
Aflibercept (VELOUR) [26]	FOLFIRI + aflibercept v. FOLFIRI + placebo	612 614	30.4% 30.5%	6.9 V 4.7 (0.758) +	13.5 V 12 (0.82) +

Bevacizumab	FOLFIRI + bevacizumab	No data from randomized controlled trial available			
Bevacizumab (ECOG 3200) [27]	FOLFOX + bevacizumab vs FOLFOX	293 292	0% 0%	7.3 V 4.7 (0.61) +	12.9 V 10.8 (0.75) +

Bevacizumab (ML18147) [23]	Oxali-/Iri-CT + bevacizumab vs Oxali-/Iri- CT alone	409 411	100% 100%	5.7 V 4.1 (068) +	11.2 V 9.8 (0.81) +
Ramicirumab (RAISE) [130]	FOLFIRI + ramucirumab	536	100%	5.7 V	13.3 v

	Vs FOLFIRI	536	100%	4.5 (0.793) +	11.7 (0.844) +

CT: Chemotherapy