EVIDENCE-BASED TREATMENT PLANNING IN mCRC: THE KEY TO MAXIMISING OUTCOMES

Summary of Presentations from the Roche Sponsored Satellite Symposium, European Cancer Congress 2013, Amsterdam, the Netherlands

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INTRODUCTION

This Roche sponsored satellite symposium was held as part of the European Cancer Congress 2013, and reviewed the current evidence available on treatment options for metastatic colorectal cancer and the application of this evidence to clinical practice.

Analysing the Current Treatment Landscape

Prof Eric Van Cutsem

Prof Van Cutsem began by presenting Phase III data from eight studies on first-line treatment regimens in metastatic colorectal cancer (mCRC), together with four observational studies. These studies compared overall survival (OS) and progression free survival (PFS) in patients treated with the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab, in combination with oxaliplatin and irinotecan-based chemotherapy regimens as well as triplet chemotherapy regimens. They found a consistent survival benefit with addition of bevacizumab to the treatment regimens.[1-14] Mutations in the *KRAS* gene are present in 35–45% of colorectal cancers and result in activation of proliferation pathways.[15] The *KRAS* gene is a member of the *RAS* gene family.[15] Bevacizumab activity in combination with other therapeutics in *KRAS* wild-type mCRC patients, demonstrated consistently high OS and PFS.[2,3,16-18] The AVEX study analysed patients over 70 years of age treated with capecitabine chemotherapy, with or without bevacizumab, and also demonstrated PFS improvements in patients treated with bevacizumab, with a hazard ratio (HR) of 0.53.[19]

The use of epidermal growth factor receptor (EGFR) antibodies in first-line treatment was also discussed. Studies on *KRAS* wild-type patients treated with EGFR inhibitors in combination with irinotecan and oxaliplatin demonstrated benefit from addition of EGFR inhibitors to irinotecan-based regimens, but a mixed response in oxaliplatin-based regimens.[20-23] The PRIME analysis demonstrated a PFS and OS benefit in *RAS* wild-type patients treated with FOLFOX (combination therapy consisting of folinic acid,

fluorouracil and oxaliplatin) together with the EGFR inhibitor panitumumab. This finding was particularly noteworthy as the initial trial had not shown a survival benefit.[23] Prof Van Cutsem noted that this study looked at all *RAS* mutations and the data suggested that colorectal cancer patients should be tested for the spectrum of *RAS* mutations, rather than *KRAS* mutations alone.

Prof Van Cutsem then discussed maintenance therapy. In the Phase III CAIRO trial, patients received capecitabine, oxaliplatin and bevacizumab and were then randomised to observation or to receive maintenance therapy of bevacizumab plus capecitabine.[24] Bevacizumab and capecitabine were reintroduced after disease progression. There was a median progression from the moment of randomisation (PFS1) of 8.5 months for maintenance therapy versus 4.1 months for observation. The primary endpoint of the study was the time from randomisation to progression upon any treatment containing capecitabine and bevacizumab, given after PFS1 (TT2P). This also showed a benefit for maintenance with bevacizumab with a stratified HR of 0.67.

Two head-to-head trials of bevacizumab versus EGFR inhibitors in *KRAS* wild-type patients were presented. PEAK is a Phase II first-line study of untreated, unresectable, wild-type *KRAS* patients randomised to FOLFOX plus bevacizumab or FOLFOX plus panitumumab.[25] PFS was similar in both groups (10.1 and 10.9 in the bevacizumab and panitumumab group, respectively, p=0.22). The larger FIRE-3 Phase III study randomised almost 600 patients to receive FOLFIRI (combination therapy containing folinic acid, fluorouracil and irinotecan) plus bevacizumab or FOLFIRI plus EGFR inhibitor cetuximab; the cetuximab group showed an increase in OS but not PFS.[18] Prof Van Cutsem noted that while the outcome from this study was important, before changing clinical practice it would be necessary to wait for the results of the CALGB study of cetuximab, with or without bevacizumab, in combination with chemotherapy in *KRAS* wild-type mCRC patients.[26] This study is ongoing and may provide results next year. While traditionally *KRAS* testing has looked to identify mutations in exon 2, it has been shown that there is a lack of efficacy in patients receiving first-line panitumumab who have mutations in *KRAS*, *NRAS* and *BRAF* outside of *KRAS* exon 2.[23,25] Prof Van Cutsem considered this indicated a need to expand testing to a broader range of mutations in *KRAS* but also in *NFAS* and *BRAF*.

In second-line Phase III studies, only those using anti-VEGF agents, such as bevacizumab and aflibercept, showed significant survival difference when compared to chemotherapy alone.[27–29] Prof Van Cutsem raised the question: "Is there rationale to continue VEGF inhibition beyond disease progression?" The TML study demonstrated PFS benefit for continuing bevacizumab post progression (5.7 versus 4.1 months), while the smaller Bevacizumab Beyond Progression trial also showed PFS benefit, although this was non-significant.[28,30] The VELOUR trial studied second-line VEGF inhibitor aflibercept in patients and found a PFS benefit (6.7 versus 3.9 months).[29]

Lastly, Prof Van Cutsem discussed the use of biologicals in third or subsequent-line therapy. Data from the CO.17 study and Study408 demonstrated an increase in OS and PFS with addition of cetuximab and panitumumab, respectively, compared to best supportive care (BSC).[31,32] He also presented data from the CORRECT study that demonstrated both an OS (6.4 versus 4.0 months) and PFS (1.9 versus 1.7 months) benefit with addition of the broad spectrum kinase inhibitor, regorafenib, compared to BSC.[33] The relative benefit of EGFR inhibitors is larger in later-line therapy than it is in early-line treatment. Prof Van Cutsem noted that this is a consideration in treatment planning and highlighted a need for more strategic trials to explore this.[20,22,23,31,32,34–36] From the current available data, it is evident that bevacizumab is the only biological with OS benefits in first and second-line therapy.

Prof Van Cutsem concluded that the selection of EGFR inhibitors is important as these have the strongest survival benefit in later lines of therapy. A broader *RAS* mutation status may be more important than *KRAS* to identify patients that are not suitable for panitumumab, and potentially for cetuximab. One of the main challenges to address in the successful treatment of mCRC is the understanding of the disease biology. It was Prof Van Cutsem's opinion that different tools are needed in order to accomplish this.

Evidence-Based Treatment Planning in Real Life

Dr Sharlene Gill

Dr Gill's presentation focused on the translation of evidence on treatment for mCRC into practice. She explained that there are a number of Phase III trials of biologicals in mCRC that may help to define an optimal strategy. The challenge for treating mCRC patients is to determine whether upfront planning of their treatment ensures the best possible outcome.

Dr Gill presented the case of a 61-year-old man diagnosed in 2009 with stage III adenocarcinoma of the sigmoid colon. He wished to pursue intensive treatment and underwent primary resection of the T3N1 tumour plus two positive lymph nodes, followed by 12 cycles of adjuvant FOLFOX. This was well-tolerated, with the exception of some grade 1 reversible neuropathy. In 2011, he presented with metastatic disease to the liver. A subsequent positron emission tomography scan confirmed para-aortic and portal adenopathy and, on this basis, it was deemed unresectable. He had wild-type *KRAS*. His Eastern Cooperative Oncology Group (ECOG) status (a scale to measure a patient's performance) was 0 (fully active, able to carry on all pre-disease performance without restriction) and he had elevation of tumour marker carcinoembryonic antigen (CEA) at 266 ng/mL with relatively few comorbidities; he had well-controlled hypertension and gastro-oesophageal reflux disease (GERD) with no history of cardiovascular disease or thrombotic events.

Dr Gill considered the evidence for first-line therapy if OS were the primary goal of treatment. Bevacizumab has shown survival benefit, irrespective of *KRAS* mutation status, and cetuximab has shown an OS benefit in *KRAS* wild-type patients; either choice would be reasonable for treatment of the patient.[6,16,20,23] However, Dr Gill also discussed the need to consider the continuum of care when choosing first-line treatment. The ESMO guidelines from 2012 recommend chemotherapy plus bevacizumab in first-line therapy, and at first progression, chemotherapy plus bevacizumab in second-line therapy.[37] Later lines of therapy can be dictated by *RAS* mutation status – wild-type *KRAS* patients could be offered EGFR inhibitor therapy at third-line followed by regorafenib at progression, or mutated *KRAS* patients could be offered regorafenib at third-line.[31,33]

As a result of the recommendations in the guidelines, the patient received FOLFIRI plus bevacizumab for 13 months, which was tolerated well. After some initial grade 1 diarrhoea, he had a partial response. He progressed at 13 months but maintained an ECOG score of 0. While moving to second-line therapy, Dr Gill questioned which biological agents were best at providing an OS benefit. While EGFR inhibitors have demonstrated response rate and progression-free survival activity, no statistical difference in overall survival is seen with their use in second-line treatment.[35,38] There is evidence that bevacizumab use beyond first-line progression improves survival.[27,28] Aflibercept data from the VELOUR study in second-line therapy had also shown improved survival.[29] In comparing the data on second-line aflibercept to that on second-line bevacizumab, similar differences in OS for the two regimens were identified and Dr Gill postulated that, in the absence of a head-to-head comparison, the efficacies of both seem comparable.[27-29] Considering this, she noted that toxicities were now a valid issue and that aflibercept is associated with increased chemotherapy-associated and anti-VEGF toxicity.[27-29] Therefore if a patient was tolerating bevacizumab well, there would be little rationale for moving to aflibercept. Her patient remained on bevacizumab and switched to FOLFOX from FOLFIRI, after which he experienced grade 2 neuropathy and was switched to bevacizumab plus capecitabine. His disease remained stable for 8 months and then progressed with an ECOG of 1 (some restrictions in activity).

Dr Gill discussed potential third-line therapies. She considered that EGFR inhibitors display better efficacy in later lines of therapy and that regorafenib in wild-type *KRAS* patients could be an option after EGFR inhibitor treatment and in subsequent lines of therapy.[31,33,39] Her patient was given irinotecan plus cetuximab and displayed partial response, but had significant toxicity with grade 2 diarrhoea, a rash, and a PFS of 5 months. He was then treated with fourth-line therapy regorafenib, but progressed after 2 months with toxicity. In total, the patient had approximately 26 months PFS on treatment and was entered onto a clinical trial where expected OS from time of diagnosis was approximately 30 months.

Dr Gill considered alternative scenarios for her patient. He could have received bevacizumab plus FOLFOX rather than FOLFIRI in first-line therapy.[1,2] Dr Gill noted that this would be a reasonable choice; however, FOLFOX is associated with toxicity and cumulative neurotoxicity should be considered if treating until progression. Bevacizumab plus FOLFOX followed by maintenance bevacizumab plus capecitabine could also be considered. Second-line therapy could be bevacizumab plus FOLFIRI.[28] Third-line therapy could be EGFR inhibition with cetuximab or panitumumab, and if the patient was well he could be offered regorafenib when other options were exhausted.[31–33]

Another alternative considered was triplet therapy FOLFOXIRI (a combination of folinic acid, fluorouracil, oxaliplatin, and irinotecan) plus bevacizumab in first-line, since patients treated with this combination have increased PFS compared to those treated with FOXFOX plus bevacizumab.[10] However, this regimen was associated with increased toxicity, resulting in diarrhoea, neutropaenia, and stomatitis and increased risk of neurotoxicity. The choice of second-line therapy would depend on the reason for switching; if the reason for switching was disease progression, then the likely option would be EGFR inhibitors, possibly with irinotecan followed by third-line regorafenib;[34-36] however, if switching was due to toxicity, it would be FOLFIRI plus bevacizumab and an EGFR inhibitor in third-line, regorafenib in fourth-line.[28,31–33] Thus, Dr Gill noted that upfront triplet therapy could reduce the number of subsequent lines of therapy available, but the data indicated that this would not impact survival.

Dr Gill concluded that in order to achieve the best outcome for mCRC patients, it is important to look at the best available evidence and define an upfront treatment strategy. There is strong Phase III data to support the efficacy of bevacizumab and, when used in first-line therapy, allows VEGF suppression in second-line therapy. It also saves EGFR inhibitor use for subsequent lines of therapy and is useful irrespective of *KRAS* status.

Panel Discussion

A panel discussion followed the presentations, which focused on the considerations given to treatment in the clinic and the discussion of treatment strategy with patients. Prof Van Cutsem felt that the use of an optimal strategy sequence was the best way to optimise patient survival; however, Dr Gill's opinion was that, while the entire sequence would need to be considered upfront, all potential lines of therapy would not necessarily be discussed with patients at the time of initiating treatment, partly because particular treatment options change over time. Moreover, while patients need to know that further therapeutic options are available, the specific details regarding later lines of therapy may be overwhelming. Chairperson Prof Arnold questioned how to change strategy after a treatment was stopped due to toxicity issues. Dr Gill noted that this is a challenge, but her preference was to maximise survival without exposing the patients to too much toxicity, and she would rarely use triplet therapy for unresectable mCRC. Finally, Prof Van Cutsem emphasised the need to expand the testing of *KRAS* to *RAS*, although this would not necessarily change first-line strategy, and noted that the upcoming CALGB study data would prove useful in this regard.

REFERENCES

1. Saltz LB et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26:2013–9.

2. Tol J et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med. 2009;360:563–72.

3. Hecht JR et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol. 2009;27:672–80.

4. Diaz-Rubio E et al. First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study. Oncologist. 2012;17:15–25.

5. Schmoll HJ et al. Cediranib with mFOLFOX6 versus bevacizumab with mFOLFOX6 as first-line treatment for patients with advanced colorectal cancer: a double-blind, randomized phase

III study (HORIZON III). J Clin Oncol. 2012;30:3588–95.

6. Hurwitz H et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350:2335–42.

7. Sobrero A et al. Phase IV study of bevacizumab in combination with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) in first-line metastatic colorectal cancer. Oncology. 2009;77:113–19.

8. Fuchs CS et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: updated results from the BICC-C study. J Clin Oncol. 2008;26:689–90.

9. Fuchs CS et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol. 2007;25:4779–86.

10. Falcone A et al. FOLFOXIRI/bevacizuman (bev) versus FOLFIR/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group. Abstract 3505, presented at ASCO 31 May–4 June 2013, Illinois, USA.

11. Arnold D et al. First-line treatment with bevacizumab plus chemotherapy for patients with metastatic colorectal cancer: Results from a large German community-based observational cohort study. Poster discussion PD-0006, presented at WCGC 30 June–3 July 2010, Barcelona, Spain.

12. Kozloff M et al. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: the BRiTE observational cohort study. Oncologist. 2009:14:862–70.

13. Van Cutsem E et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. Ann Oncol. 2009;20:1842–7.

14. Bendell JC et al. Treatment patterns and clinical outcomes in patients with metastatic colorectal cancer initially treated with FOLFOX-bevacizumab or FOLFIRI-bevacizumab: results from ARIES, a bevacizumab observational cohort study. Oncologist. 2012;17:1486–95.

15. Tan C, Du X. KRAS mutation testing in metastatic colorectal cancer. World J Gastroenterol. 2012;18:5171–80.

16. Hurwitz HI et al. The clinical benefit of bevacizumab in metastatic colorectal cancer is independent of K-ras mutation status: analysis of a phase III study of bevacizumab with chemotherapy in previously untreated metastatic colorectal cancer. Oncologist. 2009;14:22–8.

17. Price TJ et al. Impact of KRAS and BRAF gene mutation status on outcomes from the Phase III AGITG MAX trial of capecitabine alone or in combination with bevacizumab and mitomycin in advanced colorectal cancer.J Clin Oncol. 2011;29:2675–82.

18. Heinemann V et al. Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wildtype metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3). Abstract LBA3506, presented at ASCO 31 May–4 June 2013, Illinois, USA.

19. Cunningham D et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol. 2013;14:1077–85.

20. Van Cutsem E et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol. 2011;29:2011–9.

21. Tveit KM et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. J Clin Oncol. 2012;30:1755–62.

22. Maughan TS et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet. 2011;377:2103–14.

23. Douillard JY et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med. 2013;369:1023–34.

24. Koopman M et al. Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC): The phase III CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG) Abstract 3502, presented at ASCO 31 May–4 June 2013, Illinois, USA.

25. Schwartzberg LS et al. Analysis of KRAS/NRAS mutations in PEAK: A randomized phase II study of FOLFOX6 plus panitumumab (pmab) or bevacizumab (bev) as first-line treatment (tx) for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC). ASCO 31 May–4 June 2013, Chicago, Illinois. Abstract 3631, presented at ASCO 31 May–4 June 2013, Illinois, USA.

26. Venook AP. Abstract discussion: Subsets of patients with colorectal cancer – who benefits and who does not? Presented at the 15th WCGC 6 July 2013, Barcelona, Spain.

27. Giantonio BJ et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007;25:1539–44.

28. Bennouna J et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol. 2013;14:29–37.

29. Van Cutsem E et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012;30:3499–506.

30. Salvatore L et al. Bevacizumab beyond progression in metastatic colorectal cancer patients receiving a first-line treatment containing bevacizumab: Update of BEBYP trial by GONO. Abstract number O-0027. Presented at the 15th WCGC 6 July 2013, Barcelona, Spain.

31. Karapetis CS et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008;359:1757–65.

32. Amado RG et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol. 2008;26:1626–34.

33. Grothey A et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381:303–12.

34. Seymour MT et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. Lancet Oncol. 2013;14:749–59.

35. Langer C et al. Mutations in patients with metastatic colorectal cancer receiving cetuximab in combination with irinotecan: results from the EPIC trial. ESMO 2008, Abstract 385P. Ann Oncol. 2008;19(8):viii133.

36. Peeters M et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol. 2010;28:4706–13.

37. Schmoll HJ et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol. 2012;23:2479–516.

38. Sobrero AF. Final results from study 181: Randomized phase III study of FOLFIRI with or without panitumumab (pmab) for the treatment of second-line metastatic colorectal cancer (mCRC). Abstract number 387. Oral abstract session, presented at ASCO 19 January 2012, San Francisco, California.

39. Jonker DJ et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med. 2007;357:2040–8.

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