INTERVIEW

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Tracks 1-14

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Track 2 ML18147 (TML): A Phase III trial evaluating the addition of bevacizumab to crossover fluoropyrimidine-based chemotherapy for patients with mCRC experiencing disease progression on first-line chemotherapy/bevacizumab

Track 3 Targeting angiogenesis — bevacizumab, aflibercept and regorafenib — in the treatment of mCRC

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Track 5 Tumor responses to regorafenib therapy in mCRC

Track 6 Influence of K-ras G13D mutations on outcome in patients with mCRC treated with first-line chemotherapy with or without cetuximab

Track 7 Role of Onco*type* DX® and other genomic assays in early-stage colon cancer

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Track 13 Mechanism of action of ramucirumab — an IgG1 fully human monoclonal antibody targeting VEGFR-2

Track 14 Response, toxicities and mechanism of action of aflibercept, a potent angiogenesis inhibitor fusion protein

Select Excerpts from the Interview

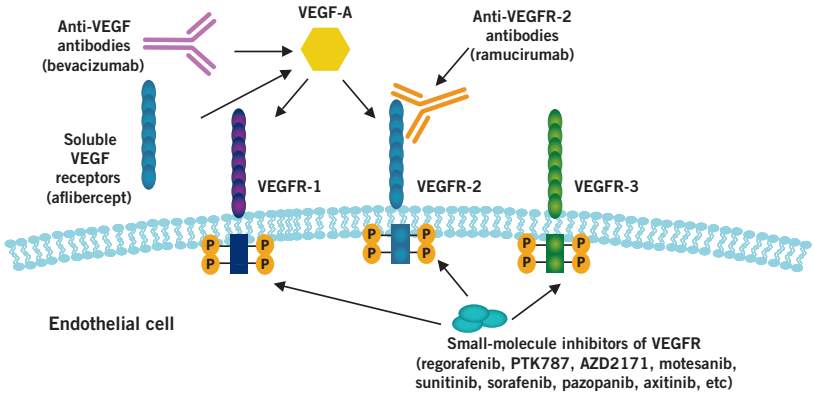
Tracks 1-4, 13-14

DR LOVE: Would you provide a brief overview of the mechanisms of action of some of the new anti-angiogenic agents under investigation in gastrointestinal cancer and how these compare to the mechanism of action of the anti-VEGF antibody bevacizumab (1.1)?

PROF VAN CUTSEM: We now have 3 novel angiogenesis inhibitors with evidence of activity, all with different mechanisms of action. Aflibercept is a fusion protein composed of parts of the different receptors (VEGFR-1 and VEGFR-2) that binds to and interferes with VEGF-A, VEGF-B and placental growth factor. Regorafenib is a

1.1

Agents Targeting the VEGF Pathway



Courtesy of John Mackey, MD.

novel multikinase inhibitor that mainly inhibits the action of VEGF through binding of VEGFR-2 and VEGFR-3.

Ramucirumab is a novel antibody that targets the VEGF receptor with broader activity. It doesn't bind to circulating VEGF as bevacizumab does. Whether that leads to a more profound clinical effect has yet to be shown in clinical trials.

DR LOVE: Would you summarize the results recently reported with each of these novel agents?

PROF VAN CUTSEM: Initial studies of ramucirumab were based on preclinical rationale, feasibility of the drug and knowledge that in gastric cancer blocking angiogenesis may be relevant (Spratlin 2010), so ramucirumab went directly to Phase III trials in gastric cancer. One ongoing Phase III trial is evaluating paclitaxel with or without ramucirumab for patients with metastatic gastric cancer (NCT01170663). An early-line trial with ramucirumab in gastric cancer is also ongoing.

Results from the Phase III CORRECT trial evaluating regorafenib in more than 700 patients with metastatic colorectal cancer (mCRC) with resistance to bevacizumab and anti-EGFR therapy were presented at the 2012 Gastrointestinal Cancers Symposium. The authors reported an improvement in survival for patients receiving regorafenib (Grothey 2012; [1.2]). So, in the continuum of care, having alternative anti-angiogenic agents may play an important role.

To my knowledge this is the first large trial in which a tyrosine kinase inhibitor has been studied as a single agent in patients with refractory CRC. The data are impressive because this patient population was optimally selected, needed to have clear indication of disease progression and needed to have been exposed to all agents available in colon cancer.

Our Phase III VELOUR study evaluated aflibercept versus placebo in combination with FOLFIRI as second-line therapy for patients with mCRC pretreated with oxaliplatin. All endpoints were met in this study. The primary endpoint was overall survival. The magnitude of benefit was not spectacular — median survival benefit was less than 2 months — but keep in mind that this was in the second-line setting. Improvements

1.2

CORRECT: A Phase III Trial of the Oral Multikinase Inhibitor Regorafenib with Best Supportive Care (BSC) versus Placebo with BSC for Patients with Metastatic Colorectal Cancer Who Experience Disease Progression After Standard Therapies*

Efficacy	Regorafenib + BSC (n = 505)	Placebo + BSC (n = 255)	Hazard ratio	*p*-value
Median progression-free survival	1.9 mo	1.7 mo	0.49	<0.000001
Median overall survival	6.4 mo	5.0 mo	0.77	0.0052
Disease control rate	44.8%	15.3%	—	<0.000001

	Regorafenib + BSC (n = 500)		Placebo + BSC (n = 253)	
Select adverse events (AEs)	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Hand-foot skin reaction	46.6%	16.6%	7.5%	0.4%
Fatigue	47.4%	9.6%	28.1%	5.1%
Hypertension	27.8%	7.2%	5.9%	0.8%
Diarrhea	33.8%	7.2%	8.3%	0.8%
Rash/desquamation	26.0%	5.8%	4.0%	0%
Mucositis, oral	27.2%	3.0%	3.6%	0%
AEs leading to permanent treatment discontinuation	8.2%		1.2%	

* Standard therapies were required to include 5-FU, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if K-ras wild type).

Grothey A et al. Gastrointestinal Cancers Symposium 2012;**Abstract LBA385**.

also were seen in response rate and prolongation of progression-free survival with the addition of aflibercept to a chemotherapy backbone (Van Cutsem 2011; [1.3]).

VEGF-related adverse events were not more pronounced with aflibercept compared to those previously reported with bevacizumab with regard to the frequency of hypertension, proteinuria and thrombosis. What was different compared to bevacizumab was that aflibercept increased the chemotherapy-related adverse events — stomatitis, diarrhea, neutropenia and fatigue. Those were more pronounced when aflibercept was combined with chemotherapy compared to chemotherapy alone (Van Cutsem 2011).

One third of the patients had received bevacizumab. In a subgroup analysis, we reported similar trends of benefit with the addition of aflibercept in the bevacizumab-pretreated population versus those not pretreated (Van Cutsem 2011). This raises some interesting questions: Is aflibercept more active than bevacizumab? Or is this the proof

1.3

VELOUR: A Phase III Randomized Study of Aflibercept versus Placebo in Combination with FOLFIRI as Second-Line Therapy for Metastatic Colorectal Cancer

Survival	FOLFIRI + aflibercept (n = 614)	FOLFIRI + placebo (n = 612)	Hazard ratio	*p*-value
Median progression-free survival	6.9 mo	4.7 mo	0.76	0.00007
Median overall survival	13.5 mo	12.1 mo	0.82	0.0032

Van Cutsem E et al. World Congress on Gastrointestinal Cancer 2011;**Abstract O-0024**.

or suggestion that postprogression continuation of an anti-angiogenic agent could be of benefit?

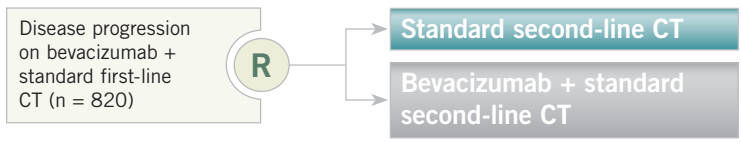
DR LOVE: Would you expand on that last question — the suggestion that postprogression continuation of anti-angiogenic therapy could provide benefit?

PROF VAN CUTSEM: Data from the BRiTE expanded access program published by Dr Axel Grothey have suggested that this approach is beneficial. This cohort study reported a prolongation in survival for patients receiving a second chemotherapy backbone and bevacizumab after disease progression on first-line therapy with a chemotherapy backbone and bevacizumab (Grothey 2008). However, these data do not provide hard scientific proof because this was not a randomized study.

A large prospective European trial is now under way evaluating continuation of bevacizumab beyond disease progression. More than 800 patients with CRC who had received first-line therapy with an oxaliplatin or irinotecan backbone and bevacizumab were eligible for this trial. Patients were randomly assigned to a different chemotherapy backbone and continuation of bevacizumab or no bevacizumab. The trial has a strong endpoint — overall survival – and should answer in an evidence-based fashion the question of whether bevacizumab should be continued after progression. Initial results are slated to be reported at ASCO 2012 (1.4). In view of the slightly higher toxicity reported with aflibercept compared to bevacizumab, this is going to be an important and relevant question in this setting and for our strategy in the treatment of CRC.

1.4

TML (ML18147): A Phase III Trial Evaluating the Addition of Bevacizumab to Crossover Fluoropyrimidine-Based Chemotherapy (CT) for Patients with Metastatic Colorectal Cancer Experiencing Disease Progression on a First-Line CT/Bevacizumab Combination



- **Primary endpoint:** Overall survival
- **Secondary endpoints:** Progression-free survival, overall response rate and safety
- **Status:** Completed, first data expected for ASCO 2012

Press release (January 26, 2012): "Bevacizumab-based regimen extends survival when continued beyond initial treatment in patients with metastatic colorectal cancer."

www.clinicaltrials.gov. Identifier NCT00700102, April 2012.

Tracks 10-11

DR LOVE: What new directions are we headed in regarding HER2-positive gastric cancer?

PROF VAN CUTSEM: No new data from large randomized trials have been reported since those from the ToGA trial, which evaluated the addition of trastuzumab to a chemotherapy backbone of 5-FU or capecitabine in combination with cisplatin (Bang 2010). The Phase III LOGIC trial is evaluating capecitabine/oxaliplatin with or

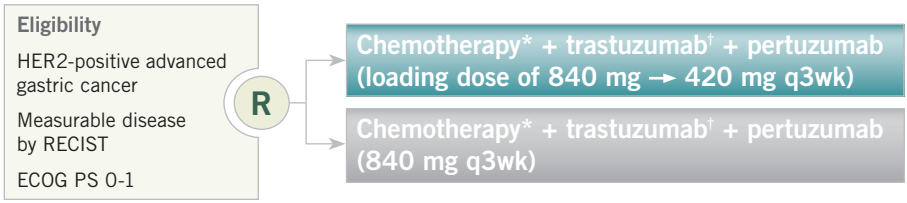
without lapatinib as first-line therapy for HER2-positive advanced gastric cancer. We now have also initiated a protocol combining trastuzumab with pertuzumab. We're performing a Phase I run-in because we're using a slightly different chemotherapy backbone — capecitabine/cisplatin. We don't expect any problems in Phase I, but we need to evaluate a few dose levels in this setting. Then the main part of this protocol will be a Phase II trial of capecitabine/cisplatin/trastuzumab in combination with pertuzumab for patients with HER2-positive advanced gastric cancer (1.5).

An impressive improvement has already been reported with trastuzumab/pertuzumab and docetaxel in the HER2-positive breast cancer arena (Baselga 2012). Mechanistically, there are some explanations. Pertuzumab and trastuzumab bind to different epitopes of the HER2 receptor, but even keeping that fact in mind, the magnitude of the benefit with the combination was larger than what many expected. That's why it's important to also evaluate this combination in patients with HER2-positive gastric cancer. ■

1.5

Phase IIA Study Evaluating 2 Different Doses of Pertuzumab in Combination with Trastuzumab and Chemotherapy for HER2-Positive Advanced Gastric Cancer

Protocol ID: NCT01461057 **Target Accrual:** 30 (Open)



* Cisplatin 80 mg/m^2 on day 1 of each cycle in combination with capecitabine 1,000 mg/m^2 twice daily
† Loading dose 8 mg/kg for cycle 1; 6 mg/kg for subsequent cycles

www.clinicaltrials.gov, April 2012.

SELECT PUBLICATIONS

Bang YJ et al. **Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial.** *Lancet* 2010;376(9742):687-97.

Baselga J et al. **Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer.** *N Engl J Med* 2012;366(2):109-19.

Grothey A et al. **Results of a phase III randomized, double-blind, placebo-controlled, multicenter trial (CORRECT) of regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients (pts) with metastatic colorectal cancer (mCRC) who have progressed after standard therapies.** Gastrointestinal Cancers Symposium 2012;**Abstract LBA385**.

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Spratlin JL et al. **Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2.** *J Clin Oncol* 2010;28(5):780-7.

Tabernero J et al. **Results from VELOUR, a phase 3 study of aflibercept versus placebo in combination with FOLFIRI for the treatment of patients with previously treated metastatic colorectal cancer.** European Multidisciplinary Congress 2011;**Abstract 6LBA**.

Van Cutsem E et al. **Intravenous (IV) aflibercept versus placebo in combination with irinotecan/5-FU (FOLFIRI) for second-line treatment of metastatic colorectal cancer (MCRC): Results of a multinational phase III trial (EFC10262-VELOUR).** World Congress on Gastrointestinal Cancer 2011;**Abstract O-0024**.