INTERVIEW

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Tracks 1-4

DR LOVE: What is your approach to making adjuvant treatment decisions for patients with Stage II colon cancer?

PROF VAN CUTSEM: The outcome for patients with Stage II colon cancer is already quite good and is improving. We still use the concept of high-risk versus low-risk Stage II disease and take different factors into account. If fewer than 12 lymph nodes are removed and examined by the pathologist, the patient is classified as having high-risk disease. We also consider differentiation grades. Patients with poorly differentiated tumors fare worse.

Other factors taken into account include bowel obstruction at initial presentation, T4 tumors, tumors with lymphatic vessel, perineural or vascular invasion, young patients and patients with elevated CA19.9 levels. These criteria are used to categorize patients as having high-risk Stage II disease.

In addition to these features, we now have microsatellite instability (MSI) testing. Patients with MSI unstable (MSI-H) status have a good prognosis, and those with microsatellite stable (MSS) status have an unfavorable prognosis. If a patient has Stage II colon cancer without the poor characteristics previously mentioned and an MSI-H

status, we do not treat. We discuss the treatment options with patients and inform them that the benefit of adjuvant chemotherapy is limited.

For a patient with an MSS tumor with one or more of the poor characteristics, we discuss adjuvant chemotherapy with 5-FU or capecitabine. In exceptional cases, such as a young patient with several poor prognostic characteristics and MSS status, we consider 5-FU/oxaliplatin.

DR LOVE: How do you care for elderly patients and those with Stage III colon cancer?

PROF VAN CUTSEM: For Stage III disease, treatment decisions are easier to make. Most of these patients are offered adjuvant 5-FU/oxaliplatin for 6 months without biologics. That's the standard treatment in this situation. An important discussion is whether to offer that to all patients with Stage III colon cancer.

For elderly patients, 3 factors come into play: the biology of the disease, other comorbidities and physiological age. Age by itself is not a crucial decision factor. One must also consider the concomitant pathology and diseases that the patient has. I would offer a 75-year-old fit patient with clear Stage III colon cancer without any concomitant adverse pathology 5-FU/oxaliplatin. For a 70-year-old patient who has a physiological age above 70 with T2N1 disease, poor kidney function and myocardial infarction, I may offer only 5-FU.

DR LOVE: What do you envision as the current and/or future role of multigene assays such as the Onco*type* DX assay in this decision-making paradigm?

PROF VAN CUTSEM: Increasing evidence suggests that they may play a role in the treatment algorithm for patients with Stage II disease in addition to consideration of the different factors I have mentioned.

Although these different clinical factors are more prognostic and they are not proven to be predictive, we still use them in making our clinical decisions to predict benefit of a treatment. The same holds true with these gene signatures — they have a prognostic role, but they are not predictive of benefit from 5-FU or 5-FU/oxaliplatin. These assays are currently used more in the United States than elsewhere. At the moment we don't use gene signatures as much in Europe, but I believe they have some utility. I believe that in 5 to 10 years we will integrate them much more. Some work is being done in this regard to try to prove predictive value, but we do not yet have the data.

DR LOVE: In your practice, do you perform routine RAS tests for patients with metastatic colorectal cancer (mCRC)? What is the clinical effect of knowing the RAS status of the disease in making treatment decisions for patients with mCRC?

PROF VAN CUTSEM: I believe that expanded RAS testing is mandatory for patients with mCRC. The biology of the disease and evidence from preclinical and retrospective studies are all going in the same direction. Even though we must be cautious with data from retrospective studies, if all the evidence is consistent with the biology and pointing in the same direction, it should be believed.

RAS testing is important for a number of different reasons. First, we can increase the likelihood of benefit from an anti-EGFR antibody. This is true for both cetuximab and panitumumab. Second, if a patient with a rare RAS mutation receives treatment, especially with an oxaliplatin-based regimen, it may be harmful. Data on the combination of oxaliplatin with panitumumab or cetuximab for patients with rare RAS mutations show a deleterious or harmful effect (Douillard 2013). Third, it is economically advanta-

geous to not administer treatment to patients who will not benefit from therapy. Fourth, it prevents unnecessary exposure to the toxic side effects of the drug or drugs.

Track 5

DR LOVE: Would you discuss the results of the Phase III CALGB/SWOG-80405 trial for patients with untreated metastatic adenocarcinoma of the colon and rectum (2.1)?

PROF VAN CUTSEM: Several important lessons and messages came out of this study. First, it showed that the overall survival for patients with mCRC has become longer, at about 30 months. If you go back to the 5-FU era 15 years ago, the median survival was 10 to 11 months. With incremental steps, the survival is improving. I believe that this is mainly because of strategic thinking and treatment with different agents. Also, the multidisciplinary approach to therapy contributes to the improved survival observed. Every time a new agent is integrated into therapy, we see an incremental benefit.

Second, the CALGB/SWOG-80405 study did not confirm the results of the FIRE-3 trial, which reported that survival for patients who received chemotherapy/cetuximab was longer than that with chemotherapy/bevacizumab (Heinemann 2014). Instead, it tells us that we have equivalent options, including oxaliplatin-based and irinotecan-based chemotherapy. In theory, we can combine oxaliplatin or irinotecan with bevacizumab or an anti-EGFR antibody. Third, the data pertain to patients with wild-type KRAS exon 2 colon cancer. The results did not change my standard practice because I administer

2.1

CALGB/SWOG-80405: Results of a Phase III Trial of FOLFIRI or mFOLFOX6 with Bevacizumab (Bev) or Cetuximab (Cet) for Patients with KRAS Wild-Type Untreated Metastatic Adenocarcinoma of the Colon or Rectum

	Chemo + bev (n = 559)	Chemo + cet (n = 578)	HR	*p*-value
Median OS	29.0 mo	29.9 mo	0.92	0.34
Median PFS	10.8 mo	10.4 mo	1.04	0.55
ORR	57.2%	65.6%	NR	0.02
KRAS wt exon 2/all RAS mt*	n = 42	n = 53	HR	*p*-value
Median OS	22.3 mo	28.7 mo	0.74	0.21
FOLFOX-based chemo (all RAS wt)	**FOLFOX + bev** (n = 192)	**FOLFOX + cet** (n = 198)	HR	*p*-value
Median OS	29.0 mo	32.5 mo	0.86	0.2
Median PFS	11.0 mo	11.3 mo	1.1	0.3
FOLFIRI-based chemo (all RAS wt)	**FOLFIRI + bev** (n = 64)	**FOLFIRI + cet** (n = 72)	HR	*p*-value
Median OS	35.2 mo	32.0 mo	1.1	0.7
Median PFS	11.9 mo	12.7 mo	1.1	0.7

HR = hazard ratio; OS = overall survival; PFS = progression-free survival; ORR = overall response rate; NR = not reported; mt = mutation; wt = wild type

* Findings may not apply to KRAS mutations in codons 12 and 13.

Venook A et al. *Proc ASCO* 2014;**Abstract LBA3**; Lenz H et al. *Proc ESMO* 2014;**Abstract 501O**.

first-line oxaliplatin and bevacizumab to most of my patients, regardless of RAS status. The anti-EGFR antibody is administered in the second or third line.

Track 7

DR LOVE: You were involved in the Phase III RECOURSE trial of the novel fluoropyrimidine TAS-102 for patients with refractory mCRC. Would you discuss the results of the study (Yoshino 2014; [2.2])?

PROF VAN CUTSEM: TAS-102 is a new fluoropyrimidine with a different mechanism of action from classic 5-FU. It combines cytotoxic pyrimidine analog trifluridine and a thymidine phosphorylase inhibitor. A placebo-controlled Phase II trial for patients with pretreated mCRC reported an overall survival benefit and limited toxicity (Yoshino 2012).

The Phase III RECOURSE trial randomly assigned 800 patients who had received at least 2 prior lines of standard therapy including fluoropyrimidines, irinotecan and oxaliplatin. Most of the patients' disease was refractory to fluoropyrimidines. Surprisingly, we found a statistically and clinically significant benefit in overall survival. Progression-free survival was improved, but no improvement in response rate was recorded. Of interest, toxicity associated with TAS-102 was limited. The most frequent toxicity was neutropenia, but only about 4% of patients experienced febrile neutropenia. ■

2.2

RECOURSE: Efficacy and Safety Results of a Phase III Trial of TAS-102 or Placebo and Best Supportive Care (BSC) for Patients with Metastatic Colorectal Cancer Refractory to Standard Therapies

Outcome	TAS-102/BSC (n = 534)	Placebo/BSC (n = 266)	HR	*p*-value
Median OS	7.1 mo	5.3 mo	0.68	<0.0001
Median PFS	2.0 mo	1.7 mo	0.48	<0.0001
ORR	1.6%	0.4%	NR	NS
DCR	44.0%	16.3%	NR	<0.0001
Grade ≥3 AEs	**TAS-102/BSC**		**Placebo/BSC**	
Neutropenia	37.9%		0%	
Anemia	18.2%		3.0%	
Febrile neutropenia	3.8%		0%	

HR = hazard ratio; OS = overall survival; PFS = progression-free survival; ORR = overall response rate; NR = not reported; NS = not significant; DCR = disease control rate; AEs = adverse events

Yoshino T et al. *Proc ESMO WCGC* 2014;**Abstract O-0022**.

SELECT PUBLICATIONS

Douillard JY et al. **Panitumumab–FOLFOX4 treatment and RAS mutations in colorectal cancer.** *N Engl J Med* 2013;369(1):1023-34.

Heinemann V et al. **FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): A randomised, open-label, phase 3 trial.** *Lancet Oncol* 2014;15(10):1065-75.

Yoshino T et al. **TAS-102 monotherapy for pretreated metastatic colorectal cancer: A double-blind, randomised, placebo-controlled phase 2 trial.** *Lancet Oncol* 2012;13(10):993-1001.