New Agents and Strategies in the Management of Colorectal Cancer

A Review of Key Clinical Questions Regarding the Integration of Novel Therapies into Oncology Practice

Faculty

Axel Grothey, MD
Eric Van Cutsem, MD, PhD

Editor

Neil Love, MD

CME Certified

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OVERVIEW OF ACTIVITY

The pace of oncology drug development has accelerated in recent years to previously unmatched levels. Fueled by an increased understanding of the biologic underpinnings of tumor development and progression, clinical research platforms largely focused on evaluating the potential benefits of novel targeted therapeutics possessing unique mechanisms of action and safety profiles have led to improved outcomes across many different tumor types. The successes yielded by this rational approach to the design and evaluation of new therapies has in turn provided medical oncologists and patients with many additional and beneficial FDA-endorsed treatment options.

Although it is indisputable that new and effective treatments are good for all, it is interesting to note that minimal publicly accessible information exists regarding how, if at all, new therapies are being incorporated into practice and what factors may affect this dynamic. Even more, it is poorly documented whether the influx of new agents and the accompanying informational burden are affecting community-based medical oncologists and their need for additional resources. As such, additional strategies and resources are needed to help clinicians overcome the difficulties they are now facing as they attempt to stay up to date and informed. To bridge the gap between research and patient care, this CME activity uses the input of cancer experts to frame a relevant discussion of recent research advances and newly approved agents in colorectal cancer (CRC) that can be applied to routine clinical practice. This information will help medical oncologists formulate up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Recognize the FDA approvals of regorafenib and ziv-aflibercept, and identify clinical situations for which these agents may be appropriate therapeutic options.

- Effectively counsel patients regarding the expected efficacy and tolerability of newly approved therapeutics for the management of CRC.

- Develop practical strategies to prevent and/or ameliorate the toxicities associated with recently approved therapies for patients with CRC.

- Understand practical considerations in the use of these newly approved agents in order to ensure appropriate administration and patient safety.

- Recall the design of ongoing research efforts attempting to further define the role of recently approved therapies, and counsel and/or consent appropriate patients with CRC regarding potential clinical trial participation.

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Axel Grothey, MD
Professor of Oncology
Department of Medical Oncology
Mayo Clinic
Rochester, Minnesota

Contracted Research: Bayer HealthCare Pharmaceuticals, Eisai Inc, Genentech BioOncology, Lilly.

Eric Van Cutsem, MD, PhD
Professor of Medicine
Digestive Oncology
University Hospital Gasthuisberg/Leuven
Leuven, Belgium

Contracted Research: Amgen Inc, Bayer HealthCare Pharmaceuticals, Merck, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc, Sanofi.

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Apple iPad 1, 2 or the New iPad
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iTunes 10.5.3

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Regorafenib

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Editor's Introduction

Regorafenib is a multikinase inhibitor that received approval by the United States Food and Drug Administration (FDA) on September 27, 2012 for the treatment of metastatic colorectal cancer (mCRC) in patients who have previously received fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy and, if KRAS wild-type disease, an anti-EGFR therapy. To provide insight into how regorafenib may be optimally integrated into the treatment of mCRC, Dr Axel Grothey discusses a number of practical issues regarding the agent's clinical development, efficacy, safety and administration. Additional commentary is also provided by Prof Eric Van Cutsem.

Mechanism of Action

DR LOVE: Would you discuss the mechanism of action of regorafenib?
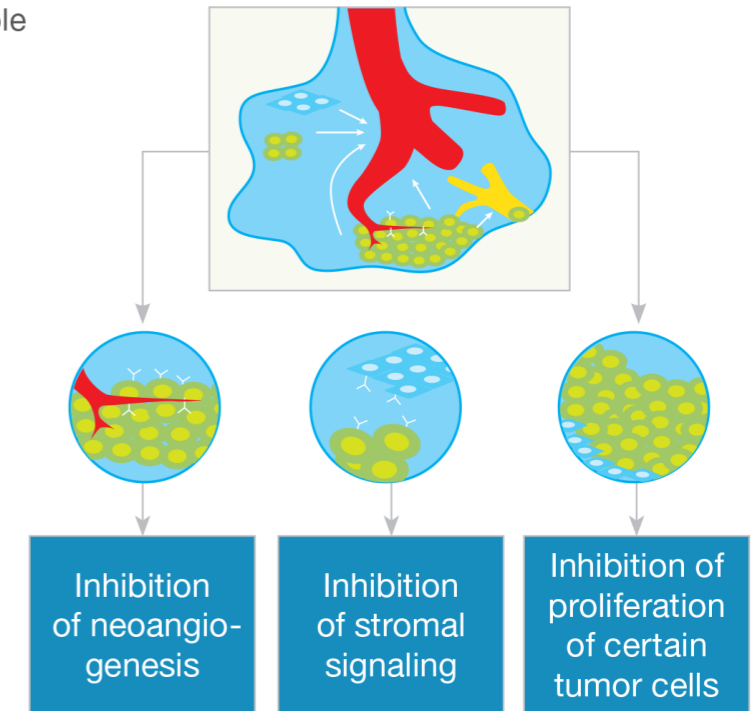
DR GROTHEY: Regorafenib is a broad-spectrum oral tyrosine kinase inhibitor (TKI) that affects multiple kinases we consider important for certain biologic features of the microenvironment of tumor cells (Figure 1). One of the unique properties of regorafenib that is not necessarily mirrored in other multikinase inhibitors is that angiogenesis inhibition occurs through VEGFR inhibition and through inhibition of tyrosine kinase with immunoglobulin and EGF homology domain (TIE2). TIE2 is one of many pro-angiogenic factors that are emergent redundant mechanisms tumor cells use to overcome VEGF blockade.

The best data we have so far for a biomarker to regorafenib relate to TIE expression levels (Lenz 2013).

1   MODE OF ACTION OF REGORAFENIB

Regorafenib inhibits multiple cell-signaling kinases:
- Angiogenic
    - VEGFR1-3, TIE2
- Stromal
    - PDGFR-ß, FGFR
- Oncogenic
    - KIT, B-RAF, RET

Inhibition of neoangio-genesis

Inhibition of stromal signaling

Inhibition of proliferation of certain tumor cells

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

DR LOVE: Would you talk a little more about that?

DR GROTHEY: In the early days of development of regorafenib the agent was believed to be a good BRAF inhibitor. However, we now know that it is not necessarily the best BRAF inhibitor. But along the way TIE2 was implicated in some of the mechanisms that mediate resistance to VEGF therapy.

When you delve a bit deeper into this, VEGF expression is important to develop immature blood vessels and TIE2 is important in the development of the more mature blood vessels. So that is something that can destroy

existing vasculature. The bottom line is it's a dual approach toward anti-angiogenesis therapy.

That being said, however, I believe it's naïve to think that every patient has the same factors upregulated. It's an interaction between the microenvironment and the specifics of this tumor behavior, et cetera. For example, it could be that in one patient it's a combination of basic fibroblast growth factor and placental growth factor, or another patient has TIE2 activation. Each individual patient may have a different signature. So that makes it more difficult to develop a biomarker.
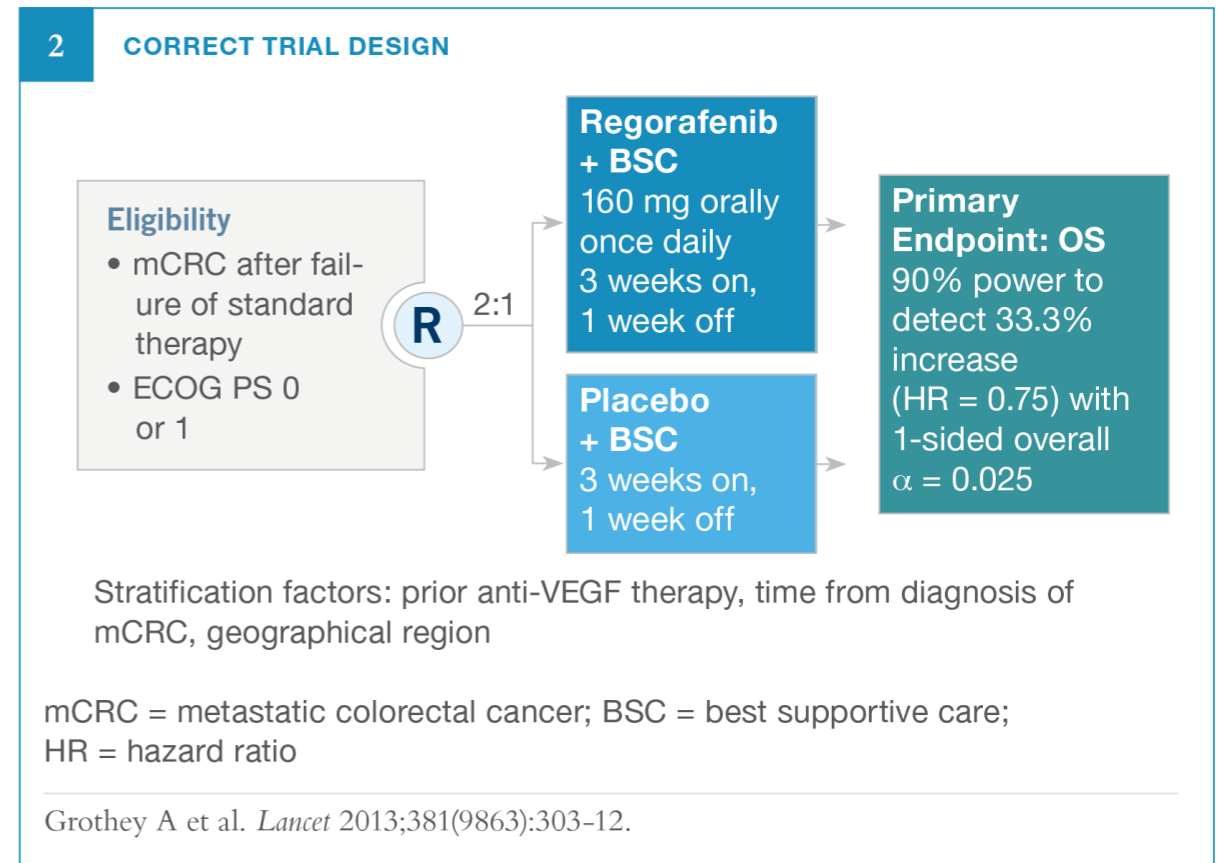
DR LOVE: How do you conceptualize the mechanism of action of regorafenib in colorectal cancer versus GIST?

DR GROTHEY: GIST is a molecularly simple tumor. We understand driving mutations and even mechanisms of resistance that don't allow imatinib, for instance, to enter the binding pocket of c-KIT kinase. So regorafenib is easy to understand in GIST because it targets c-KIT and it targets PDGFR — the exact mutations we find commonly in GIST.

In colon cancer, regorafenib's mechanism of action probably differs from patient to patient. Patients have different ways in which they've arrived to this last-line setting. They have different tumor biology, different genetic makeup and different tumor/host interactions, so it will be difficult to identify one biomarker that covers every patient population. It's more or less the sum of all of the above. I believe the reason regorafenib works in this setting is because it's so promiscuous in its activity.

Key Clinical Trials Leading to FDA Approval

DR LOVE: Would you discuss the background and rationale surrounding the design of the Phase III CORRECT trial in mCRC that led to the approval of regorafenib?

2 CORRECT TRIAL DESIGN

Eligibility
- mCRC after failure of standard therapy
- ECOG PS 0 or 1

R 2:1

Regorafenib + BSC
160 mg orally once daily
3 weeks on, 1 week off

Placebo + BSC
3 weeks on, 1 week off

Primary Endpoint: OS
90% power to detect 33.3% increase (HR = 0.75) with 1-sided overall $\alpha = 0.025$

Stratification factors: prior anti-VEGF therapy, time from diagnosis of mCRC, geographical region

mCRC = metastatic colorectal cancer; BSC = best supportive care; HR = hazard ratio

Grothey A et al. *Lancet* 2013;381(9863):303–12.

DR GROTHEY: We did not have data initially that regorafenib worked in patients with colon cancer, so it was considered ethical to have a placebo-controlled trial without crossover. That's not an easy sell, so to make this more acceptable for patients we introduced a 2-to-1 randomization (Figure 2). When we talked to a patient about potentially entering this trial we were able to say, "You have a 2 out of 3 chance of receiving this agent," and I believe this aspect helped patients commit to the trial. Something happens as soon as you go above a 50% chance. We never had a problem with patient accrual based on the placebo. Everyone said, "Maybe I will be the lucky one because it's a 2 out of 3 chance. I'm going to be 1 of those 2."

The primary endpoint was overall survival. The initial benchmark we wanted when we designed the study was about a 25% reduction in death events. The study was meant to accrue 690 patients around the world, and we selected these countries carefully in order for the study to be

representative of how we typically treat a Western patient population, which I believe helped to make these data quite clean.

CORRECT was projected to accrue for 26 months, and it accrued in 10 months. Have you ever heard of a study that accrued 16 months ahead of schedule, if it was supposed to enroll, let's say for 2 1/2 years, and it was done in less than a year? It was initially thought that if the trial was positive the agent would be submitted for approval in 2017, but obviously it was approved much earlier.

The trial had 1 interim analysis for futility, and there was none. Then the first interim analysis of superiority stopped the study. The *p*-value we had to meet was quite stringent. It was not simply 0.05, it was 0.0092, and the study met those criteria. The data monitoring committee said, "We need to allow patients who are on placebo to cross over to regorafenib."

DR LOVE: Would you talk more specifically about the eligibility and efficacy results of the trial?

DR GROTHEY: To be eligible patients had to have received all agents approved for the management of mCRC in their respective countries. At that time bevacizumab was not approved in China, but CORRECT was formulated in a way that allowed for Chinese patients to be eligible for the trial. We had a stratification factor for prior bevacizumab or not. Eventually, all the patients who came on study from China, which turned out to be less than 5, had all received bevacizumab previously so the stratification factor "went away."

Thus every patient on the study had received prior bevacizumab and had access to fluoropyrimidine, oxaliplatin and irinotecan. If they had KRAS wild-type disease, they also had access to cetuximab or panitumumab.

Median lines of therapy were 3 or 4, so clearly it was a more refractory patient population. Performance status of zero or 1 was mandated. The

3   CORRECT: SUMMARY OF EFFICACY RESULTS

Efficacy	Regorafenib + BSC (n = 505)	Placebo + BSC (n = 255)	Hazard ratio	*p*-value
Median overall survival	6.4 mo	5.0 mo	0.77	0.0052
Median progression-free survival	1.9 mo	1.7 mo	0.49	<0.0001
Disease control rate	41.0%	15%	—	<0.0001

BSC = best supportive care

Grothey A et al. *Lancet* 2013;381(9863):303-12.

median age was comparable to what you see in other colon cancer trials. Interestingly, we had more patients with KRAS mutation-positive disease — approximately 55% — than we did with KRAS wild-type disease. The reason for that is it takes the patient to the point of having refractory disease 1 line earlier because patients with KRAS mutations do not have the option of receiving cetuximab or panitumumab. A few patients also had BRAF mutations on the trial — about 2% to 4%.

CORRECT met its primary endpoint of overall survival. The hazard ratio was 0.77, so a 23% reduction in deaths, and the median overall survival with placebo was 5 months versus 6.4 months with regorafenib (Grothey 2013; Figure 3).

The hazard ratio was stronger at 0.49 for the secondary progression-free survival endpoint. However, the median progression-free survival was not different because of the shape of the curve, which overlapped until about the point of the median time for progression and then it spread. This means at the time point of 8 weeks when the first scan was conducted, it appeared that 50% of patients experienced no benefit whatsoever.

When I first saw that overlap of the progression-free survival curves, I

thought there must be a biomarker similar to a KRAS-like effect. We evaluated for traditional biomarkers such as TIE2, et cetera, but we've never been able to separate these curves.

I went through the clinical study report line by line and the population who had the most chance to benefit included the patients who had less tumor volume, had better performance status, were not debilitated as much with, let's say, 4, 5 or 6 lines of therapy, to whom the physicians said, "Oh, we have this clinical trial for you, let's enroll you on it."

I believe this is one of the key points. The CORRECT study only allowed patients with PS 0 and 1 disease. Now, that's an assessment a physician makes. You have a patient in front of you and you've promised this patient, "We'll enroll you on this clinical trial," and then it takes time to enroll the patient on study and the patient moves from PS1 to PS1.99 before you can administer the drug, and then it doesn't work. That's the problem with a lot of these last-line trials. Many patients are at the point of no return. They have no chance to respond, regardless of what approach you take. You could throw the best agent in the world at the disease, especially an agent that induces responses, but it won't be able to turn the tumor dynamics around. Whatever happens, it doesn't matter. Patients will experience disease progression. It's simply a biologic phenomenon.

The critical point I make to physicians when discussing practical management is this: When patients have their first scan at 8 weeks, that's when we see whether the patient has benefited from regorafenib because if they have not experienced disease progression by this point, then they have a fairly good chance of benefit in the long term.

We need to make sure that patients have a chance to reach 8 weeks on therapy because — and we will talk more in depth about this later — the side effects of this agent come early, within the first 2 weeks. We must

monitor our patients closely for the first cycle of therapy. This is something we've learned from regorafenib more than from any other kinase inhibitor.

DR LOVE: What about responses?

DR GROTHEY: We reported few responses on the CORRECT trial — the response rate was 1% with regorafenib and 0.4% with placebo. Approximately 42% of patients who received regorafenib had stable disease at 8 weeks as best response. So regorafenib is not an agent that can induce an anatomical shrinkage per the RECIST criteria.

We have seen a number of patients whose tumors have cavitations and a hollow rim that persists. The tumor doesn't change in size but has become empty. This phenomenon has previously been reported in patients receiving bevacizumab. You don't see the shape and size of the lesions change, but they appear more cystic. It's fibrotic transformation, and we see tumor marker decline. Patients experience benefit — there is some antitumor efficacy — but not to the extent that tumor shrinkage can be measured.

We didn't mandate PET scans on the CORRECT study, but in clinical practice now once in a while we perform PET scans to see what's happening. I've observed PET responses in patients receiving regorafenib before we see tumor shrinkage.

Tolerability and Management of Side Effects

DR LOVE: Would you discuss what was observed in the CORRECT trial and, for that matter, prior studies in terms of side effects and toxicity with regorafenib?

DR GROTHEY: I wouldn't say regorafenib introduces a new side-effect profile compared to other kinase inhibitors because we typically observe

the same laundry list of issues — hand-foot skin reaction, diarrhea, hypertension, et cetera (Grothey 2013; Figure 4). Where the side-effect profile does differ with regorafenib compared to other TKIs is that there is rapid onset of these toxicities with the drug, at least at the dose quoted in the package insert (160 mg). We presented data at both the Gastrointestinal Cancers Symposium and ASCO 2013 evaluating the timing of treatment-emergent adverse events on the CORRECT trial, and it is clear that the side effects peak in the first 2 to 3 weeks (Grothey 2013; Figure 6). That is especially the case with the 2 critical side effects, hand-foot skin reaction and fatigue.

When we first initiated the CORRECT study, we saw the patient before we began the treatment, administered the drug and followed up after 2 weeks, which was often too late. Patients had experienced toxicities by that point, which jeopardized their continuation on study.

Our approach now is to either see patients back after 1 week or contact them after 1 week to titrate doses. We see them back in clinic after 2 weeks because the package insert rightly mandates a liver enzyme check every 2 weeks during the first 2 months of treatment.

DR LOVE: Would you comment on the black-box warning regarding hepatotoxicity that is included in the regorafenib package insert?

DR GROTHEY: The black-box warning regarding hepatotoxicity in the package insert for regorafenib (Figure 5) is based on 5 fatalities on the CORRECT study, one of which was clearly an overdose in a Japanese patient who ultimately passed away due to liver insufficiency. The 4 other cases were attributed to other reasons such as liver metastasis. So we do see elevated liver enzymes and we do hold doses and subsequently lower doses.

This is one of the aspects of administering regorafenib that we're learning how to manage over time now that it's being used in clinical practice in

4   CORRECT TRIAL: SUMMARY OF SIDE EFFECTS

Grothey A et al. *Lancet* 2013;381(9863):303–12.
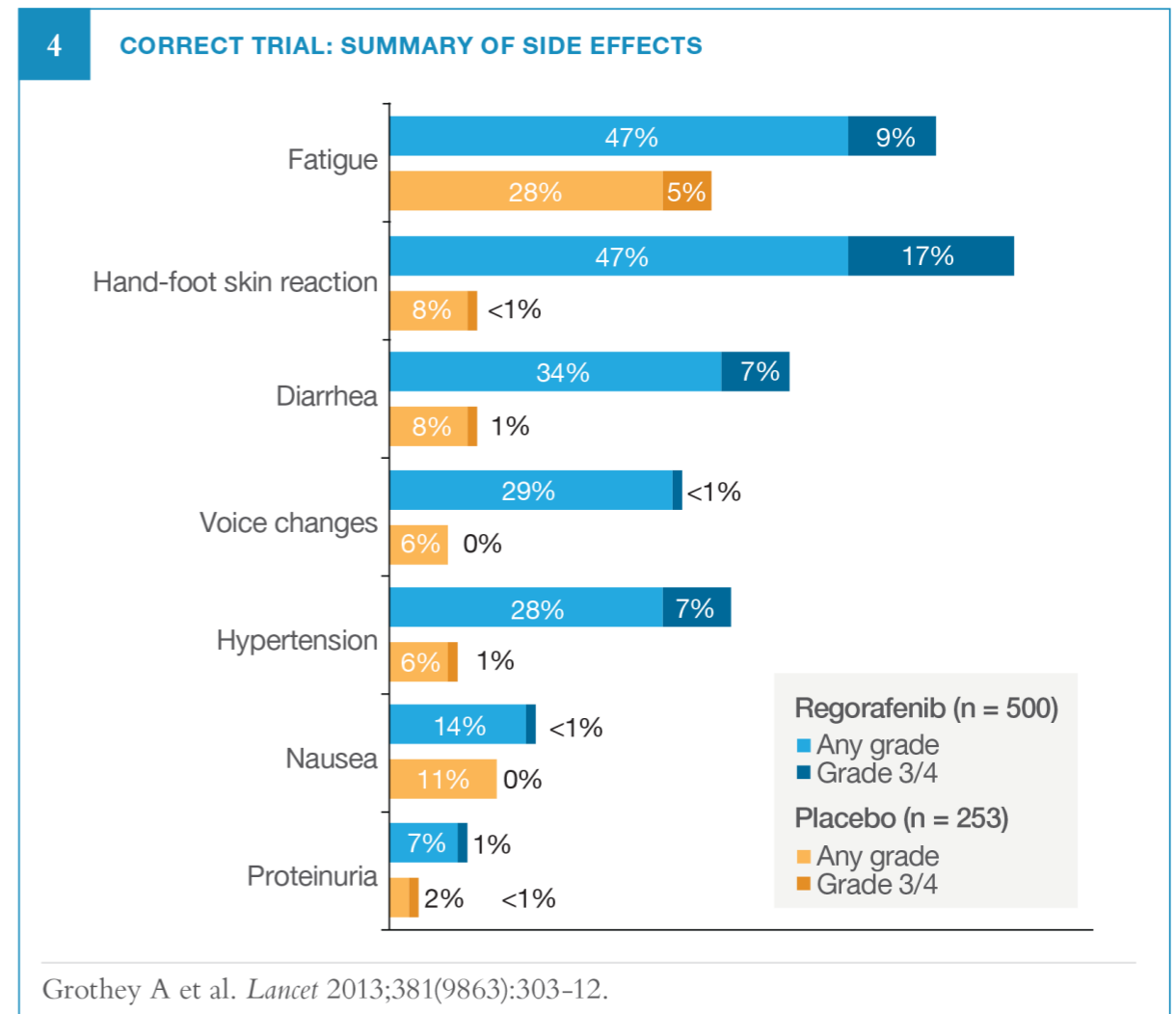
different patient populations than those studied within the clinical trials. We will need to monitor for this issue. The majority of patients do not experience liver dysfunction, but a sizeable minority may.

DR LOVE: How does the hand-foot skin reaction with regorafenib compare to what's observed with sorafenib or with capecitabine, for that matter?

DR GROTHEY: I would say it's similar, although I observe more foot problems with regorafenib compared to sorafenib. I've noted a shift in where this toxicity occurs. The actual reaction itself once it occurs is similar because it's not only the scaling and reddening that is typically associated with capecitabine. An inflammatory component arises that we

do not see with capecitabine. It's much more of a violent skin reaction. A number of patients on capecitabine do not experience any problems within the first cycle. It's more of a cumulative effect with time. With regorafenib the onset is early.

It's important for community oncologists who may have not had experience with regorafenib to be aware of early monitoring, management of side effects and prophylaxis. If they administer 160 mg of regorafenib and then don't see the patient back for 2 or 4 weeks, that's a disaster waiting to happen.

Let's say for argument's sake that the patient is extremely fit, perhaps an athlete, and the oncologist believes he or she could tolerate anything. If hit hard right out of the gate by these toxicities, the oncologist might think, "This is a drug I can never use" and have the perception, "If the first cycle is already that bad, what would happen if I continue the treatment?"

What we now know, however, is that you can reduce the dose and patients seem to better tolerate the agent, or even if you maintain the dose, patients will get used to that.

DR LOVE: What approaches have been evaluated to prevent hand-foot skin reaction?

DR GROTHEY: We use the same approach whether we are initiating treatment with sorafenib or regorafenib. Patients receive a handy little supply package with creams and information on how to soften calluses. Patients are instructed preemptively to apply moisturizing lotions to their hands and feet and then put gloves and socks on right from the get-go on the day they start regorafenib. They are instructed to also wear them at night. These practices have been shown to help patients taking sorafenib.

DR LOVE: What is your approach once hand-foot syndrome occurs?

| 5 | **RISK OF HEPATOTOXICITY WITH REGORAFENIB** |

- Severe and sometimes fatal hepatotoxicity has been observed in clinical trials.
- Obtain liver function tests (ALT, AST and bilirubin) before initiation of regorafenib and monitor at least every 2 weeks during the first 2 months of treatment. Thereafter, monitor monthly or more frequently as clinically indicated. Monitor liver function tests weekly in patients experiencing elevated liver function tests until improvement to less than 3 times the upper limit of normal or baseline.
- Interrupt and then reduce or permanently discontinue regorafenib for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis, depending on severity and persistence.

Regorafenib package insert

| 6 | **CORRECT TRIAL: FREQUENCY (%) OF TREATMENT-EMERGENT ADVERSE EVENTS OVER TIME IN PATIENTS WITH METASTATIC COLORECTAL CANCER TREATED WITH REGORAFENIB** |

Adverse event	Cycle of therapy							
	1 (n = 500)	2 (n = 417)	3 (n = 229)	4 (n = 193)	5 (n = 119)	6 (n = 91)	7 (n = 55)	8 (n = 43)
HFSR	32	26	24	24	26	25	15	5
Fatigue	45	23	16	24	17	22	11	9
Hypertension	21	11	3	4	4	2	0	5
Rash/ desquamation	24	7	3	4	5	1	0	0

HFSR = hand-foot skin reaction

Conclusion: In the CORRECT trial, the incidences of the most common adverse events in the regorafenib group peaked early during treatment and no evidence was apparent for cumulative toxicity with regorafenib.

Grothey A et al. Gastrointestinal Cancers Symposium 2013; **Abstract 467**.

DR GROTHEY: Patients eventually do not remove all of their calluses. Sometimes they are not religious enough in their use of the recommended urea-based creams. We need to look at some patients' nails to ensure they don't have issues. One of the critical issues I'm becoming more and more

aware of is the need to evaluate patients' feet. This sounds trivial, but people are willing to expose themselves almost everywhere, but looking at patients' feet is almost like going through a rectal exam. Having them take their shoes off is important, even if you're in Minnesota and they have boots on. Ask them to take them off. Don't simply rely on the patient saying, "My feet are fine."

With regard to blisters, for instance, you need to open the blisters under sterile conditions because they can lead to situations in which the patients can't walk anymore. Thus, we send our patients to dermatology, where they carefully open and drain the blisters.

DR LOVE: What other side effects have you observed with regorafenib?

DR GROTHEY: The second-line toxicities were quite mild. There's not a lot to talk about.

Hypertension has been observed, which is probably a class effect, but you must keep in mind that all of these patients have received bevacizumab before. So they have likely already undergone management for VEGF-related hypertension. It didn't stand out as an important side effect. The frequency of proteinuria was low, similar to what has been reported with bevacizumab. Patients hardly ever experienced any problems with it.

Fatigue is a bit of an issue. On the CORRECT trial, any-grade fatigue was 47% with regorafenib and 28% with placebo. Rates of severe fatigue were 9% and 5%, respectively. Some of that fatigue can be attributed to the stage of disease. It's cancer-related fatigue to some degree, but it's there and it tends to present early. Loss of appetite also comes early.

I would estimate that for 1 or 2 out of every 8 patients, we need to do something for the fatigue. If you talk about dose modification or interventions such as stopping the drug (Khan 2014; Figure 7), the

7	RECOMMENDED DOSE MODIFICATIONS FOR REGORAFENIB
Action	**Adverse event/issue**
Interrupt dose	• Grade 2 HFSR that is recurrent or does not improve within 7 days despite dose reduction • Grade 3 HFSR (interrupt therapy for a minimum of 7 days) • Symptomatic Grade 2 hypertension • Any Grade 3 or 4 AE
Reduce dose to 120 mg	• First occurrence of Grade 2 HFSR of any duration • After recovery of any Grade 3 or 4 AE • Grade 3 AST/ALT elevation
Reduce dose to 80 mg	• Recurrence of Grade 2 HFSR at the 120-mg dose • After recovery of any Grade 3 or 4 AE at the 120-mg dose (except hepatotoxicity)
Discontinue permanently	• Failure to tolerate 80-mg dose • Any occurrence of AST/ALT >20 x ULN • Any occurrence of AST/ALT >3 x ULN with concurrent bilirubin >2 x ULN • Recurrence of AST/ALT >5 ULN despite dose reduction to 120 mg • Any Grade 4 adverse reaction; resume only if the potential benefit outweighs the risks

HFSR = hand-foot skin reaction; AE = adverse event; AST = aspartate transaminase; ALT = alanine transaminase; ULN = upper limit of normal

Khan G et al. *Cancer Manag Res* 2014:6;93–103.

number 1 reason why you do that is hand-foot skin reaction. The number 2 reason is fatigue.

DR LOVE: Other than dose reduction, can anything be done for the fatigue?

DR GROTHEY: One option is holding the drug. Probably the best data we have on dealing with fatigue relates to dexamethasone. That's not

something you use on a long-term basis. So we typically perform dose reductions or hold the agent, perhaps for a couple of days.

Additionally, some patients talk about voice alterations. They become a little hoarse. I've heard that this may be related to PDGF inhibition. I've not found any reference to that, so I would put some caveats around that.

Dosing and Method of Administration

DR LOVE: How is regorafenib administered, and are any specific issues related to the time of day it's taken, with and without food, et cetera? The package insert specifies that it should be taken with a low-fat (less than 30%) breakfast.

DR GROTHEY: We normally instruct patients to take regorafenib with a light meal, right after breakfast. Because it has a long half-life, it is not dependent on the time of the day. We tell patients to take all 4 tablets at once on a 3-week on, 1-week off schedule if we are using the package insert dose, so it's not spread out. Is this the best way to administer it? I don't know.

DR LOVE: Do we have any information, or do you have any insight on the minimal dose needed to benefit a patient?

DR GROTHEY: That remains an unanswered question, in part. I have a number of patients now who have benefited from 120 mg. We do not have additional published data, however, to say that the "sweet spot" for dosing is 120 mg.

Now, another point relates to the beauty and the detriment of a flat dose. Do we believe that different shapes and sizes of people require the same dose? Consider the distribution of regorafenib in the body of, say, a college football linebacker compared to a tiny Japanese woman. Do they both need 160 mg? Is this matched?

DR LOVE: What was the rationale for using a flat dose?

DR GROTHEY: A number of the kinase inhibitors — sorafenib, sunitinib and now regorafenib — eventually went to flat-rate dosing for a variety of reasons, such as compliance and development of tablet size, because in the end you must commit to a tablet size.

DR LOVE: Would you ever consider "dosing up" in a much larger patient who was tolerating the 160 mg with zero issues?

DR GROTHEY: That's a good question, Neil, but I wouldn't, because then we'd be in uncharted waters. Patients can become miserable if you overdose. One of my "star patients" who had been receiving the agent the longest initially received 160 mg on the CORRECT trial and came in after 2 weeks of therapy in the fetal position, miserable, with elevated liver enzymes. Her platelets were down to 15,000/mm^3, so it was a toxic effect. She recovered and went back on study, and within the first day of receiving 120 mg she experienced a skin reaction. Once we reduced her dose to 80 mg she was perfectly fine and we were able to escalate back up to 120 mg.

DR LOVE: Are there any situations in which you would start with the full dose — for example, in a younger patient in good condition with PS 0 who has only received a couple of lines of treatment?

DR GROTHEY: I'm not religiously linked to the 120-mg dose. I could see myself using the 160-mg dose, and in clinical trials we're still doing it. We're still using 160 mg of regorafenib on clinical trials because that's the approved dose. But you must monitor the side effects early on.

DR LOVE: Eric, what has been your experience with the optimal dosing of regorafenib for your patients?

PROF VAN CUTSEM: It is correct that the 160 mg used in the CORRECT trial is too high for some patients. What some American physicians tell us

is that they start with 120 mg and then increase to 160 mg if the patient does not experience toxicity.

If we use the example of capecitabine at the point when its dose was established and it was first brought to market about 15 years ago, a number of patients experienced profound toxicity with the agent. We did not know whether that was its optimal dose, and no major efforts improved on its dosing. It may have been that continuous administration at a lower dose would have been better tolerated.

A post hoc analysis by Dr Dan Haller some years ago in the *JCO* evaluating geographic differences seemed to suggest that perhaps the diet of American patients could explain the increased toxicity they experienced with capecitabine (Haller 2008). Projects are now under way to evaluate whether another dose of regorafenib would be optimal.

For now, my personal approach in the late-line setting is to initiate therapy at 160 mg and follow the patient carefully for the first 2 weeks and the first cycle. One of my nurses calls patients around day 8 to see whether they have experienced any problems, and we bring the patient back into the clinic on day 15. If the patient experiences toxicity, we decrease quickly to 120 mg. Dose reduction schemes and preventive measures for hand-foot skin reaction are important in this setting.

If we were administering regorafenib in the third- or fourth-line setting in patients in good condition, then it would probably be a little better tolerated.

Practical Guidance for Use in Clinical Practice

DR LOVE: Axel, you touched on this before, but specifically, when you initiate treatment with regorafenib, how do you approach patient follow-up?

DR GROTHEY: For the first cycle, I see patients when I can on a weekly basis. That is sometimes difficult to do, however, in Minnesota because many patients come from far away. If so, we see them on an every other-week basis. We contact them after 1 week. We perform liver function tests every 2 weeks for the first 2 cycles. I believe that the package insert is correct in how that needs to be done. I see patients after they've completed the first 2 months of therapy, and we order their first scan to ascertain if they are benefiting from therapy.

When we feel more comfortable about the dosing and if they have not experienced any liver toxicity, then I see them back every 4 weeks.

DR LOVE: Would you discuss the patients in your practice to whom you've administered regorafenib who represent typical scenarios you might see?

DR GROTHEY: The typical scenario is that patients come after 2 weeks, when we see them back or they report in and say, "I feel more fatigued. I don't know whether I can continue on this dose, but I'm willing to give it another try." So we maintain the dose for another week, then they get a week off. You see them back, and they say, "My week off was good. I might want to start with a lower dose this time." So we decrease to 80 mg, and then we see them back after 2 weeks. We see them back after every 2 weeks in the first 2 cycles. Then they might say, "I think I can try 120 mg again." So we bounce around between 80 and 120, and then we go through the first scan. We try to carry patients through to the first scan.

One patient who comes to mind is a small-framed young man who experienced a large benefit with regorafenib. He experienced no side effects after 2 weeks on an initial dose of 120 mg. I suggested that we escalate the dose to 160 mg, and he still has not experienced any problems whatsoever. He said it's the best treatment he's ever received, so a huge variability exists among patients.

In conversations I've had with my colleague Dr Tanios Bekaii-Saab, he has conveyed to me that he typically dose reduces for smaller-framed patients. He's more comfortable now that he's committed to this approach of adjusting dose based on body shape/body size than ever before.

DR LOVE: What percent of patients are able to receive regorafenib and have a reasonable quality of life without major problems? Maybe they run into a problem for which you have to dose adjust, but ultimately you're able to successfully administer treatment?

DR GROTHEY: We are eventually able to successfully treat and find the correct titrated dose for the majority of patients. If you do everything right and you carry patients through the first month of therapy and identify the right dose, I'd say that 3 out of 4 patients can tolerate regorafenib but it takes time and effort to find the right dose. It's active management.
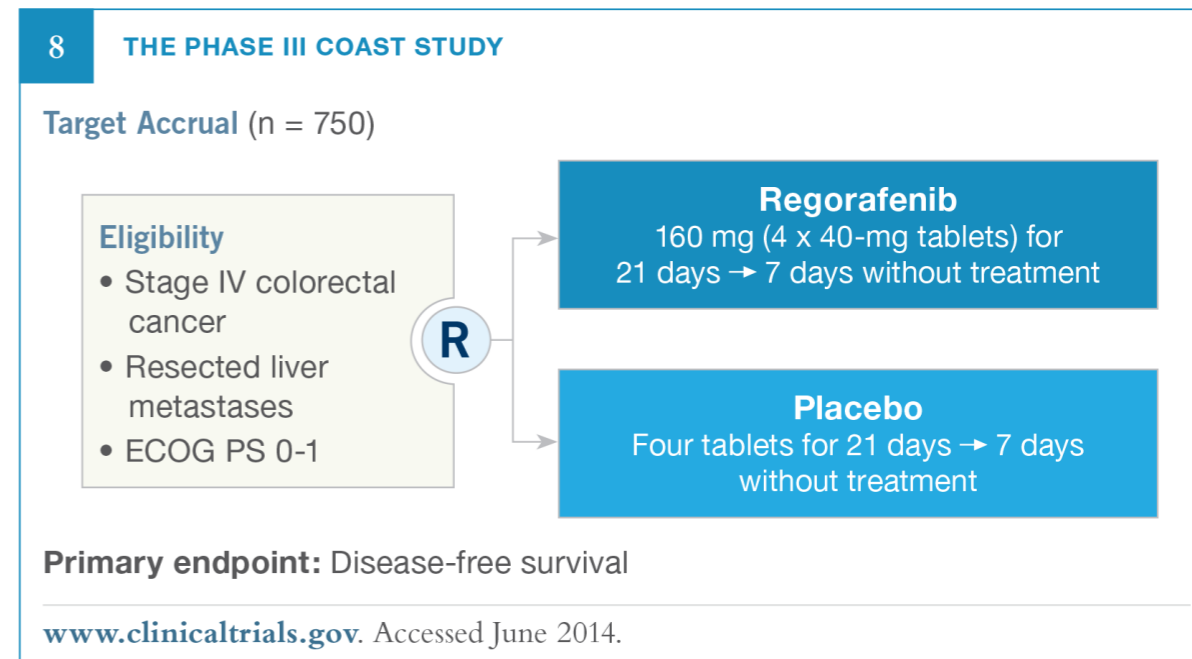
DR LOVE: What fraction of patients benefit from receiving the drug?

DR GROTHEY: Not every patient with colon cancer needs regorafenib because some might have too poor of a performance status to have the chance to benefit. If you select the right patient population, PS 0 and 1, as were the patients on the CORRECT trial, I believe the chance that patients experience benefit is 50-50.

Future Directions

DR LOVE: What are some of the large ongoing trials evaluating regorafenib in colorectal cancer?

DR GROTHEY: A large ongoing registrational trial called COAST is evaluating regorafenib as adjuvant therapy for patients with resected Stage IV disease (Figure 8). Obviously this is a population whose disease is considered to be at high risk of recurrence. We inform such patients that they have a chance of cure, but realistically that rate is only about 25% for

8   THE PHASE III COAST STUDY

Target Accrual (n = 750)

Eligibility
- Stage IV colorectal cancer
- Resected liver metastases
- ECOG PS 0-1

R

Regorafenib
160 mg (4 x 40-mg tablets) for 21 days ➛ 7 days without treatment

Placebo
Four tablets for 21 days ➛ 7 days without treatment

Primary endpoint: Disease-free survival

www.clinicaltrials.gov. Accessed June 2014.

patients who have undergone resection of liver metastases.

This trial, which opened in December 2013, randomly assigns patients after curative resection of liver metastases and completion of all planned chemotherapy to regorafenib or placebo for 2 years or until disease progression.

PROF VAN CUTSEM: A large Phase IV program that is a continuation of the CORRECT study and for which Dr Grothey and I are co-principal investigators has recently completed accrual of more than 2,000 patients. This trial was running in many different countries and was undertaken as a postapproval commitment for the European authorities. The study was aimed more so at further evaluating safety, toxicity and side-effect management of regorafenib.

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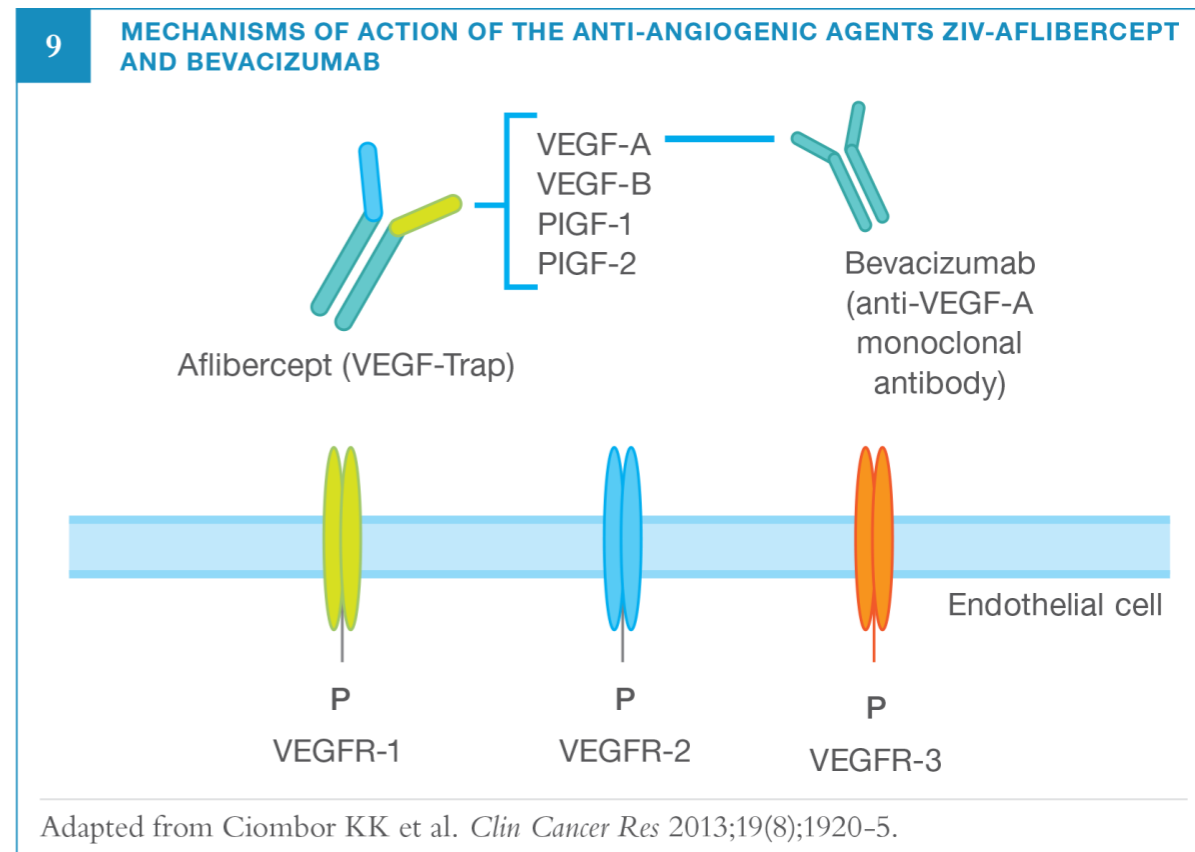
Ziv-Aflibercept

2

Editor's Introduction

On August 3, 2012, the FDA approved ziv-aflibercept injection for use in combination with 5-fluorouracil, leucovorin and irinotecan (FOLFIRI) for the treatment of mCRC that is resistant to or has progressed after treatment with an oxaliplatin-containing regimen. The designation *ziv-aflibercept* refers to the specific formulation of the agent used to treat mCRC as distinct from the formulation of aflibercept used in the treatment of wet age-related macular degeneration. This approval was based on the results of the randomized double-blind, placebo-controlled global multicenter VELOUR trial that enrolled patients with mCRC whose disease had progressed during or within 6 months of receiving oxaliplatin-based combination chemotherapy, with or without prior bevacizumab. To investigate how aflibercept may be optimally integrated into the treatment of mCRC, the study's lead author, Prof Eric Van Cutsem, discusses a number of practical issues regarding the agent's clinical development, efficacy, safety and administration. Additional commentary is also provided by Dr Axel Grothey.

Mechanism of Action

DR LOVE: Would you compare the mechanism of action of aflibercept to those of bevacizumab and other anti-angiogenic agents (Figure 9)?

PROF VAN CUTSEM: Aflibercept is a recombinant fusion protein that is unlike a traditional monoclonal antibody (Figure 10). It has a broader mechanism of action because it targets not only VEGF-A but also VEGF-B and placental growth factor (PlGF). Preclinical studies led by Dr Peter Carmeliet have suggested that the inhibition of PlGF plays an important role (Fischer 2007), but the relevance of PlGF inhibition has yet to be shown in the clinic.

9 MECHANISMS OF ACTION OF THE ANTI-ANGIOGENIC AGENTS ZIV-AFLIBERCEPT AND BEVACIZUMAB

Aflibercept (VEGF-Trap)

VEGF-A
VEGF-B
PlGF-1
PlGF-2

Bevacizumab (anti-VEGF-A monoclonal antibody)

Endothelial cell

P — VEGFR-1
P — VEGFR-2
P — VEGFR-3

Adapted from Ciombor KK et al. *Clin Cancer Res* 2013;19(8);1920–5.

At one point a specific antibody targeting PlGF was under development, but the decision was made not to continue moving that specific compound forward, probably because there were not enough hints of activity with the pure antibody in this setting. There's always a discussion of a broader mechanism of action with aflibercept but no one has yet elucidated the clinical role of inhibition of PlGF or VEGF-B. The clinical translation to higher activity may be correct, but we don't have any data. As you know, there are no head-to-head studies of aflibercept versus bevacizumab. We would need a head-to-head study to make that statement clear.

DR GROTHEY: Aflibercept is not an antibody. It is a remarkably designed molecule in which fragments of the VEGF receptors are linked to an antibody-like molecule. So we have a protein that is now able to bind

VEGF-A, similar to how bevacizumab acts, but aflibercept also binds VEGF-B and another pro-angiogenesis factor called PlGF. Thus, aflibercept inhibits 3 molecules, whereas bevacizumab only inhibits 1. It's soaking up factors produced by tumor cells that stimulate blood vessels. So it does what bevacizumab does in addition to something else beyond that. Now the question that we have is, how important are the other factors beyond VEGF-A for tumor biology in general? This is not completely conclusive right now.

## Early Clinical Trial Data with Ziv-Aflibercept

DR LOVE: Before we discuss the definitive Phase III trial of aflibercept, would you comment on some of the key earlier clinical research studies?

PROF VAN CUTSEM: A couple of Phase I studies were conducted, but there were no formal Phase II studies before the pivotal Phase III VELOUR study was designed. The first Phase I studies evaluated single-agent aflibercept (Lockhart 2010), and then there was a Phase I and IB study evaluating different dose levels of the drug with FOLFIRI. That trial evaluated a variety of different tumors, including cohorts of patients with colon cancer (Khayat 2013; Van Cutsem 2013).

This was a classic Phase I study with different dose levels of aflibercept followed by an expansion cohort of 20 to 30 patients with the recommended dose of aflibercept in combination with FOLFIRI. We performed this trial together with a center in Paris.

The goal was to establish a maximum tolerated and recommended dose, but some patients had colon cancer that was refractory to FOLFIRI or FOLFOX and later received FOLFIRI/aflibercept. Some received bevacizumab pretreatment, and some had bevacizumab-naïve disease at the time of this Phase I study. We completed that study, and signs of

10   ZIV-AFLIBERCEPT
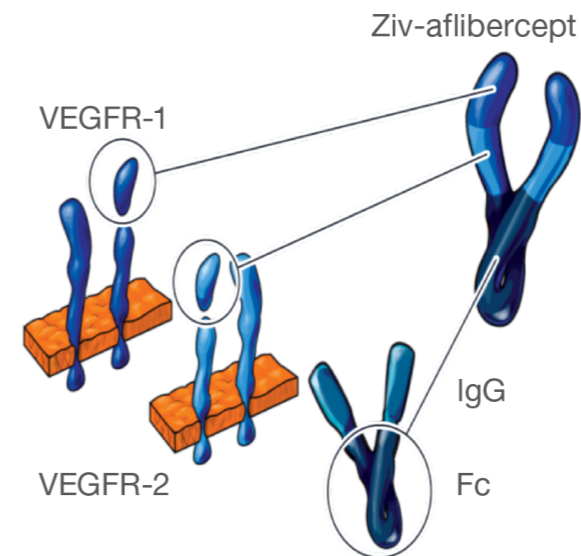
- Soluble fusion protein
- Consists of portion of extracellular domains of human VEGF receptors 1 and 2 fused to human IgG1 Fc portion
- Binds all VEGF-A isoforms, VEGF-B and PlGF
- High affinity: Binds VEGF-A and PlGF more tightly than native receptors
- Half-life in humans ~17 days

Courtesy of Prof Van Cutsem.

11   AFFIRM: A PHASE II STUDY FOR TREATMENT-NAÏVE METASTATIC COLORECTAL CANCER

	FOLFOX + ziv-aflibercept (n = 119)	FOLFOX (n = 117)
Median progression-free survival (PFS)	8.5 mo	8.8 mo
12-month PFS	25.8%	21.2%
Overall response rate	49.1%	45.9%

- Grade 3/4 adverse events, including hypertension, proteinuria, neutropenia, diarrhea and infections, were seen with >5% higher incidence in the ziv-aflibercept arm.

Patel A, Sun W. *Biologics* 2014;8:13–25.

activity were evident with aflibercept. The results were published in 2 papers back to back in the *European Journal of Cancer*.

An important Phase II study called AFFIRM (Pericay 2012; Figure 11), which opened after VELOUR was designed, was presented later. The study

evaluated FOLFOX with or without aflibercept as first-line therapy for patients with mCRC. This was a rather small randomized study conducted in countries where the use of bevacizumab was not as well implemented at the time. AFFIRM did not seem to show increased activity with the addition of aflibercept to FOLFOX.

Was that because the sample size was small? Was that due to the fact that there were issues with patient selection? Was that because the investigators were not as experienced? Was that because of some specific design endpoints? Or was this related to the backbone of oxaliplatin? It may well be that irinotecan is a slightly better partner for these targeted agents.
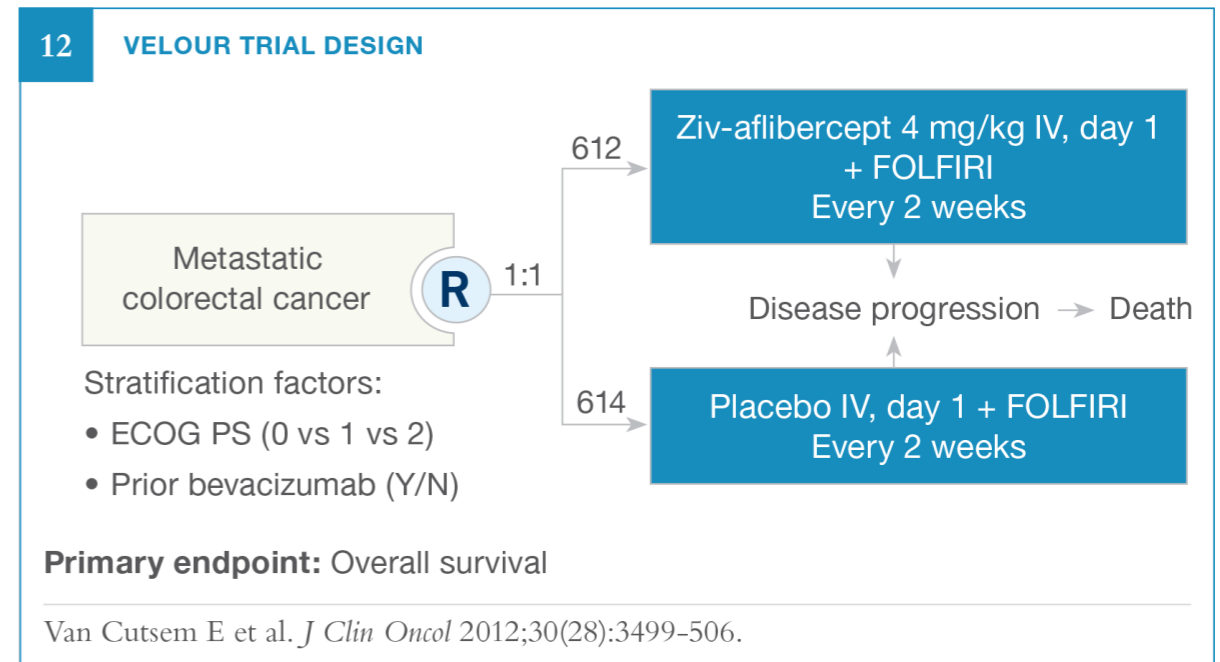
Key Phase III Trial Leading to FDA Approval

DR LOVE: Would you discuss the pivotal Phase III VELOUR trial that led to the approval of aflibercept in combination with FOLFIRI for patients with mCRC?

PROF VAN CUTSEM: This study had a straightforward design in which patients were randomly assigned to FOLFIRI or FOLFIRI/aflibercept (Van Cutsem; Figure 12). All 1,226 patients had disease that was refractory to oxaliplatin, and there were no imbalances with regard to patient distribution.

The vast majority of patients had an ECOG performance status of 0 or 1. A low percentage of patients — approximately 2% — had an ECOG performance status of 2. Slightly more men than women were on the trial. An important aspect of the patient characteristics is that approximately one third of the patients had disease pretreated with bevacizumab. The last crucial point is that approximately 10% of patients on each arm had received adjuvant treatment only, and approximately 20% of patients received adjuvant therapy and then first-line therapy for metastatic disease.

So that means that between 70% and 75% of the patients received 1 line of

12 VELOUR TRIAL DESIGN

Metastatic colorectal cancer — R 1:1 →
- 612 → Ziv-aflibercept 4 mg/kg IV, day 1 + FOLFIRI, Every 2 weeks
- 614 → Placebo IV, day 1 + FOLFIRI, Every 2 weeks

→ Disease progression → Death

Stratification factors:
- ECOG PS (0 vs 1 vs 2)
- Prior bevacizumab (Y/N)

Primary endpoint: Overall survival

Van Cutsem E et al. *J Clin Oncol* 2012;30(28):3499-506.

treatment for metastatic disease only, no prior adjuvant treatment. The good thing is that there was no imbalance in either the aflibercept or placebo groups.

More patients had 2 or more involved sites, and the majority of patients — more than 70% — in both arms had liver metastases, which was consistent with what we see in other second-line trials. More than 40% of patients had lung metastases, and between 10% and 20% of the patients had peritoneal disease.

DR LOVE: It's also of note that more than 40% of the patients experienced prior hypertension. Does that mean they basically had hypertension coming into the study, or was this related to prior bevacizumab?

PROF VAN CUTSEM: In some of the patients it was related to bevacizumab. It was not in all patients, of course, because only 30% of the patients had previously received bevacizumab. Patients could have a history of hypertension based on the inclusion criteria, but at the moment they went on the protocol their blood pressures had to be controlled and medication for hypertension was allowed in the study.

The primary endpoint of the study was overall survival, which was met with a statistically significant hazard ratio of 0.817 (Van Cutsem 2012; Figure 13). Median overall survival improved from 12.1 months to 13.5 months, which is not spectacular but is similar to the overall survival benefit reported with regorafenib (Figure 3, page 8) and to the 1.4-month benefit reported on the TML study of bevacizumab beyond disease progression (Bennouna 2013). So all 3 of these studies of new options for continued anti-angiogenic treatment for mCRC after disease progression on first-line bevacizumab-based therapy produced the same overall survival benefit, though this is simply an interesting coincidence.

We would have loved to see a bigger benefit, but those are the numbers. In the VELOUR trial, both secondary endpoints — progression-free survival and response rate — were also met (Figure 13). The median progression-free survival was 6.9 months compared to 4.7 months, with a statistically significant hazard ratio of 0.758. It is interesting that the response rate almost doubled from 11% to 19% on the study.

If you evaluate the forest plots, this benefit was observed across the different subgroups. One of the important questions often asked is, what is the benefit in patients who previously received bevacizumab versus those who had bevacizumab-naïve disease? A benefit was observed in both groups, but because of the smaller sample size in both those subgroups it was not statistically significant (Van Cutsem 2012; Figure 14). We also performed formal tests for interaction, but we didn't find a significant interaction for pretreatment, yes or no, or no bevacizumab versus prior bevacizumab, et cetera.
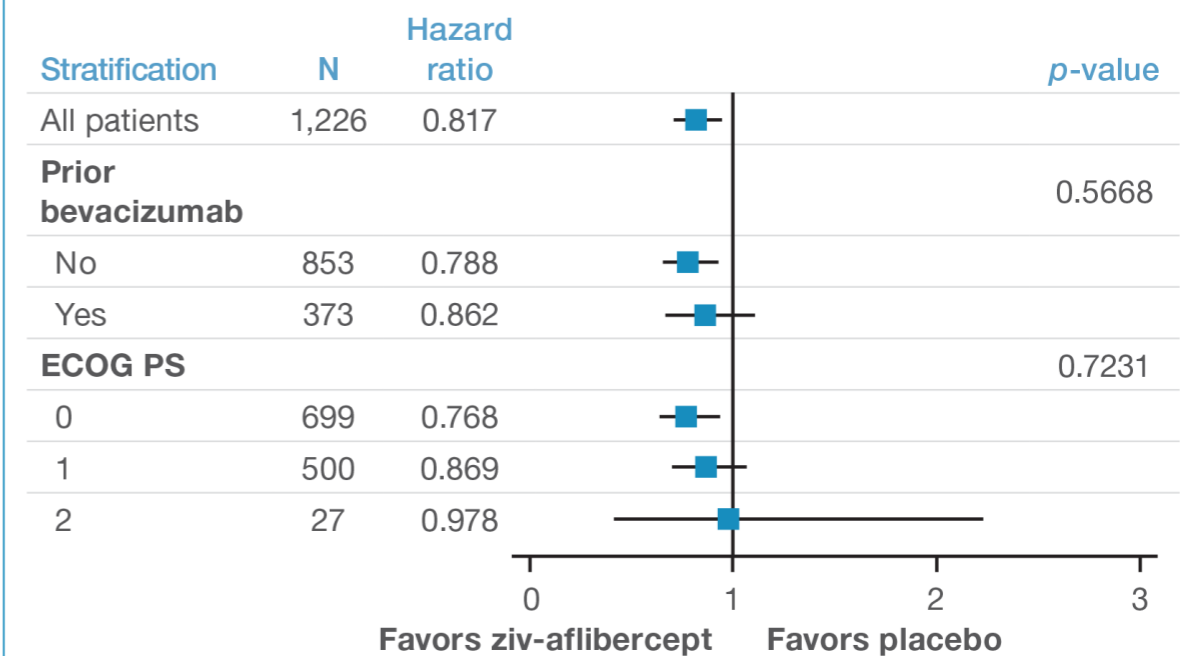
In other words, a benefit was observed with the addition of aflibercept to FOLFIRI regardless of whether patients had disease that was pretreated with bevacizumab, and that's consistent with the postprogression continuation theory of the TML study (Bennouna 2013).

13 VELOUR TRIAL: SUMMARY OF EFFICACY RESULTS

	FOLFIRI + ziv-aflibercept (n = 612)	FOLFIRI + placebo (n = 614)	Hazard ratio	p-value
Median overall survival	13.5 mo	12.1 mo	0.817	0.0032
Median progression-free survival	6.9 mo	4.7 mo	0.758	<0.0001
Overall response rate	19.8%	11.1%	—	0.0001

Van Cutsem E et al. *J Clin Oncol* 2012;30(28):3499–506.

14 VELOUR TRIAL: FOREST PLOT FOR OVERALL SURVIVAL

Stratification	N	Hazard ratio		p-value
All patients	1,226	0.817		
Prior bevacizumab				0.5668
No	853	0.788		
Yes	373	0.862		
ECOG PS				0.7231
0	699	0.768		
1	500	0.869		
2	27	0.978		

Favors ziv-aflibercept   Favors placebo

Van Cutsem E et al. *J Clin Oncol* 2012;30(28):3499–506.

DR LOVE: How would you compare the findings from the TML study to those of VELOUR in terms of survival, progression-free survival and response rate?

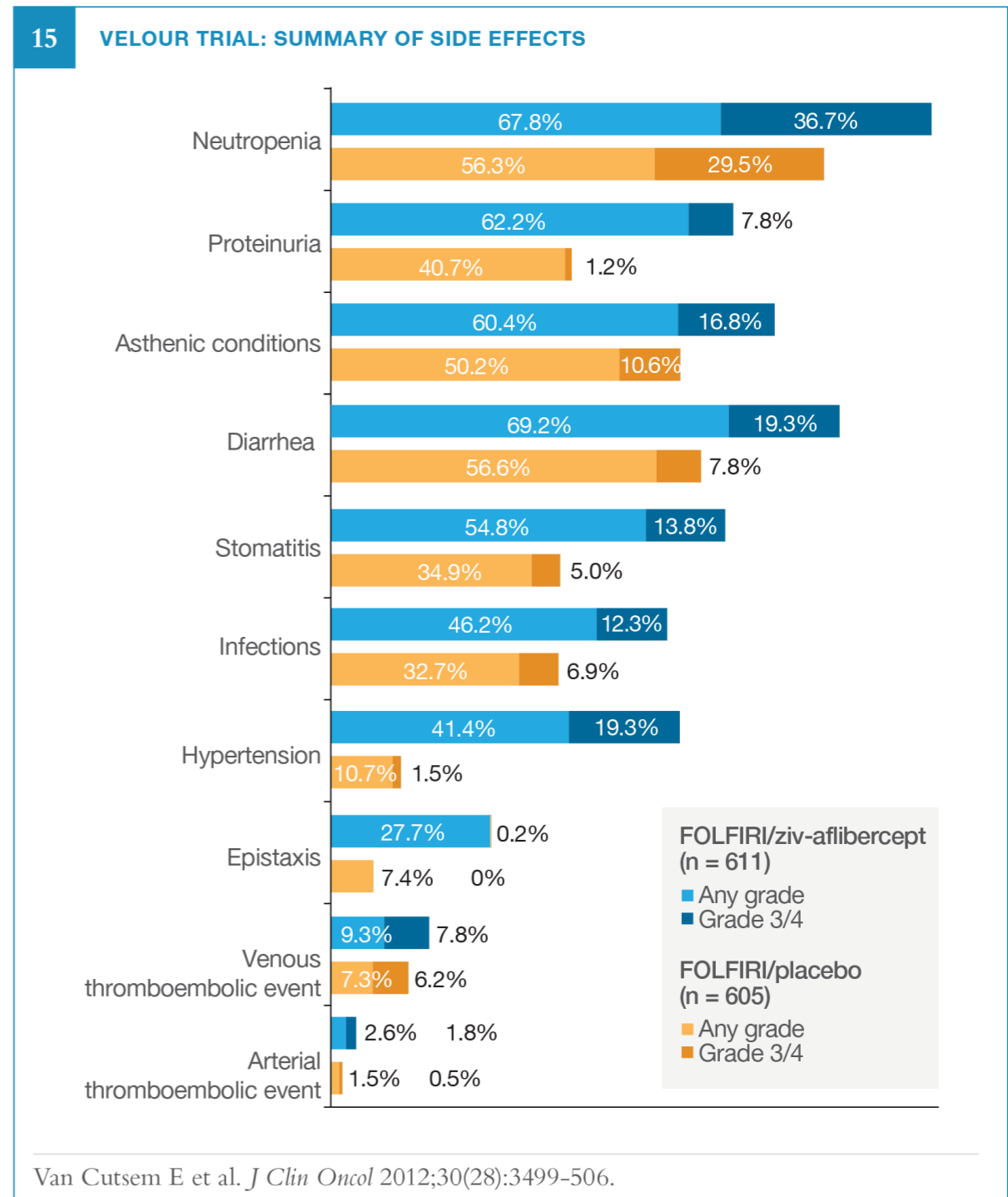**PROF VAN CUTSEM:** If you don't have head-to-head studies, it's always

difficult to perform cross-trial comparisons. The patient populations were different. We alluded already to pretreatment with bevacizumab or not. Another example is that in the VELOUR study, 10% of patients received only adjuvant treatment and then went on immediately to the study. That was not the case in the TML study, in which it was mandatory that patients receive a first-line chemotherapy doublet and bevacizumab. That's a slightly different type of patient. That helps us to say that we must be careful with cross-trial comparisons.

Tolerability and Management of Side Effects

DR LOVE: What common adverse events were reported on the VELOUR study, and do you typically see any of these now in clinical practice?

PROF VAN CUTSEM: The typical VEGF-related adverse events that you'd expect — hypertension, proteinuria, mucosal bleeding — were increased on the aflibercept arm (Van Cutsem 2012; Figure 15). A clear increase also occurred in chemotherapy-related adverse events on the FOLFIRI/aflibercept arm compared to the FOLFIRI/placebo arm. Patients experienced more diarrhea, neutropenia, neutropenic infections and stomatitis compared to patients who received FOLFIRI/placebo. This degree of increase of chemotherapy-related toxicities was not observed on the TML study of bevacizumab beyond disease progression.

We don't have a good explanation as to why this happens. Some theories exist based on controversial preclinical experiments. Some experiments suggest that the inhibition of PlGF may contribute to this increase in chemotherapy-related toxicities. Other preclinical "knock-out" experiments suggest that that's not the case, but the facts are there — we observed toxicity to a greater degree in the VELOUR trial. We don't have a good explanation whether that's due to the broader spectrum of activity of aflibercept or not.

15 VELOUR TRIAL: SUMMARY OF SIDE EFFECTS

Neutropenia — FOLFIRI/ziv-aflibercept: 67.8% any grade, 36.7% Grade 3/4; FOLFIRI/placebo: 56.3% any grade, 29.5% Grade 3/4

Proteinuria — FOLFIRI/ziv-aflibercept: 62.2% any grade, 7.8% Grade 3/4; FOLFIRI/placebo: 40.7% any grade, 1.2% Grade 3/4

Asthenic conditions — FOLFIRI/ziv-aflibercept: 60.4% any grade, 16.8% Grade 3/4; FOLFIRI/placebo: 50.2% any grade, 10.6% Grade 3/4

Diarrhea — FOLFIRI/ziv-aflibercept: 69.2% any grade, 19.3% Grade 3/4; FOLFIRI/placebo: 56.6% any grade, 7.8% Grade 3/4

Stomatitis — FOLFIRI/ziv-aflibercept: 54.8% any grade, 13.8% Grade 3/4; FOLFIRI/placebo: 34.9% any grade, 5.0% Grade 3/4

Infections — FOLFIRI/ziv-aflibercept: 46.2% any grade, 12.3% Grade 3/4; FOLFIRI/placebo: 32.7% any grade, 6.9% Grade 3/4

Hypertension — FOLFIRI/ziv-aflibercept: 41.4% any grade, 19.3% Grade 3/4; FOLFIRI/placebo: 10.7% any grade, 1.5% Grade 3/4

Epistaxis — FOLFIRI/ziv-aflibercept: 27.7% any grade, 0.2% Grade 3/4; FOLFIRI/placebo: 7.4% any grade, 0% Grade 3/4

Venous thromboembolic event — FOLFIRI/ziv-aflibercept: 9.3% any grade, 7.8% Grade 3/4; FOLFIRI/placebo: 7.3% any grade, 6.2% Grade 3/4

Arterial thromboembolic event — FOLFIRI/ziv-aflibercept: 2.6% any grade, 1.8% Grade 3/4; FOLFIRI/placebo: 1.5% any grade, 0.5% Grade 3/4

FOLFIRI/ziv-aflibercept (n = 611): Any grade, Grade 3/4

FOLFIRI/placebo (n = 605): Any grade, Grade 3/4

Van Cutsem E et al. *J Clin Oncol* 2012;30(28):3499-506.

Proteinuria was present but was in the expected range and did not strike us as concerning. This was similar to what has been observed with bevacizumab previously. We still monitor for proteinuria at our center, but it's not monitored so much if patients do not have hypertension.

A couple of cases of severe nephrotic syndrome have been described with aflibercept. There's a case report of a patient with a severe nephrotic syndrome with renal insufficiency. When a biopsy of the kidney was performed, they observed thrombosis in the renal vessels after aflibercept. We have also observed it in one of our patients. But that phenomenon was also described a number of years ago with bevacizumab (Wu 2010; Glusker 2006), so that's a class effect that is not specific to aflibercept.

Some people have said that it's more frequent with aflibercept, though the numbers don't support that claim. So that's not something we worry about.

DR LOVE: Does the magnitude of hypertension reported with aflibercept seem similar to that observed with bevacizumab?

PROF VAN CUTSEM: It was higher in the VELOUR study compared to the TML study, but as I mentioned, on the TML study there was a bias in patients who were sensitive for hypertension on bevacizumab in the first-line setting with disease that is not easily treatable. Such patients were not entered on the second-line study of bevacizumab postprogression continuation.

DR LOVE: How do you approach the issue of hypertension in patients receiving aflibercept both in terms of monitoring and management?

PROF VAN CUTSEM: My approach is similar to that for patients receiving bevacizumab. Blood pressure must be fine at the start of the first cycle of aflibercept, and then it is monitored during treatment with FOLFIRI and aflibercept. We recommend that patients normally measure their blood pressure at home because when they come in to the clinic their blood pressure will always be slightly elevated, whether it be from the tensions of traveling to the clinic or from "white coat syndrome." So the most reliable blood pressure measurement is taken at home.

Our nurses and physicians are diligent in reviewing the blood pressures the patients record at home. If they have an elevated blood pressure, we act the same way we would in patients receiving bevacizumab. We start the patient on a calcium blocker or an ACE inhibitor and, in some patients, a beta-blocker. You have to combine the different drugs in some patients.

DR LOVE: How do you approach the issue of growth factors?

PROF VAN CUTSEM: We don't administer prophylactic growth factors for patients with mCRC. In gastric cancer it is recommended to start with prophylactic growth factors when you use triplet regimens — a fluoropyrimidine, a platinum and docetaxel. That is not the case here. Of course, if a patient experiences severe neutropenia, then you may administer secondary prophylaxis.

DR LOVE: What about the issue of aflibercept and wound healing, and how do you approach the issue of patients who require surgery?

PROF VAN CUTSEM: We don't know as much as we do with bevacizumab because the drug is newer, but I would say my approach is almost the same as with bevacizumab in the sense that the major mechanism of action of aflibercept is also inhibition of VEGF. We know that interfering with VEGF interferes with wound healing. So the general recommendation for elective surgery is to wait 6 weeks after the last administration of aflibercept.

The resection of liver metastases in these patients is a lesser issue than it is with bevacizumab or with other anti-VEGFR antibodies because aflibercept is not used in the first-line setting, which is where most of the patients have their disease converted from unresectable to resectable.

If patients have to undergo emergency surgery, of course, that's a different story. We know that wound healing will probably be slower in these patients and that there's an increased chance of wound-healing complications, as there is with bevacizumab.

DR LOVE: What's your current perception in terms of the risk of arteriovenous events with bevacizumab versus with aflibercept?

PROF VAN CUTSEM: With bevacizumab it's clear that there is a slightly higher incidence of arterial thromboembolism, especially in patients older than age 65 and in patients with a history of arterial thrombosis. And if you're older than age 65 and have a history of arterial thrombosis — be it transient ischemic attack, angina pectoris or myocardial infarctions — you further increase the risk with bevacizumab.

I believe that the risk is equivalent with aflibercept. Of course, there are much fewer studies with aflibercept than with bevacizumab. Regarding venous thromboembolism, that's slightly different. The data with bevacizumab are controversial. Some combined analyses, or meta analyses, indicate a slightly increased chance of venous thromboembolism (Nalluri 2008). Some studies indicate no increased risk with bevacizumab (Hurwitz 2011).

The clinical message is that if a patient had a venous thromboembolism, pulmonary embolism or a deep venous thrombosis in the legs, that's not a contraindication to placing them on bevacizumab or aflibercept. I would, however, administer low molecular weight heparin along with the anti-angiogenic agent.

If a patient has experienced a myocardial infarction 6 months prior, and especially if the patient is older or has angina pectoris, I would be reluctant to administer bevacizumab or aflibercept. I would discuss it with the patient, of course, but that's a risk factor with which I would not push to administer either of these agents.

DR LOVE: What about bleeding?

PROF VAN CUTSEM: We observed some mucosal bleeding on the VELOUR study. You see that with bevacizumab and with aflibercept. The most frequent bleeding is epistaxis, and that's most often Grade I and Grade II.

Occasionally you see some gastrointestinal (GI) bleeding, but that's not frequent. You don't often see other severe bleeds in this regard.

In the VELOUR study, we didn't observe any differences between the 2 arms with regard to GI perforations, but I believe that's simply by chance. If you review the data from the large combined analysis of bevacizumab published in *Lancet Oncology* a few years ago, the risk of GI perforation was 1.5% (Hapani 2009). I believe we have no reason to say that aflibercept is different. Perforations have also been reported in other studies in this regard, so it's probably similar.

DR LOVE: What about posterior encephalopathy?

PROF VAN CUTSEM: Yes, posterior encephalopathy was reported in the beginning with aflibercept. That came on later with bevacizumab and was added to the package insert. I've seen a few patients with this on aflibercept. I don't believe we can make a statement that it doesn't happen. Some of these patients have severe hypertension, but it's not always the case that you see hypertension along with posterior encephalopathy.

This is not the same as posterior leukoencephalopathy, or PRES syndrome as it is sometimes called, which is not only linked to bevacizumab but also sometimes observed in transplant patients who receive immunosuppressive agents.

Dosing and Method of Administration

DR LOVE: What's the FDA-approved dose and schedule of aflibercept? Is that what you are using? Can you use it every 3 weeks rather than every 2 weeks?

PROF VAN CUTSEM: The officially approved dose and regimen of aflibercept for colon cancer is the one that we used in the VELOUR study, which is every 2 weeks at 4 mg/kg in combination with FOLFIRI. In the

past, some studies used aflibercept every 3 weeks, which was also integrated in some of the larger studies later on, but that's not the approved regimen in colon cancer.

DR LOVE: Does your dosing strategy change for elderly patients or those with poor performance status?

PROF VAN CUTSEM: The dosing of aflibercept doesn't change in older patients or those with poor performance status. The vast majority of patients on the VELOUR trial — more than 95% — had a performance status of 0 or 1, so a small percentage of patients had a performance status of 2. Of course, if a patient has PS 2 disease, we must be careful that it's not a borderline 2 and not a 3 because then we should not treat with aflibercept.

DR LOVE: Would you alter the dose for patients with either hepatic or renal dysfunction?

PROF VAN CUTSEM: We don't change the dose of aflibercept for patients with hepatic or renal dysfunction. Of course, we have to account for hepatic dysfunction. The chemotherapy backbone accompanying aflibercept contains irinotecan, which is contraindicated in patients with clearly elevated bilirubin levels.

If the patient's bilirubin level is above 1.5 mg/deciliter (dL), and certainly if it is above 2 mg/dL, we are extremely cautious and do not administer irinotecan. And, as such, we would not administer aflibercept because it should not be administered as a single agent and should not be administered in combination with 5-FU only and, at the moment, it should not be administered in combination with oxaliplatin, either.

Practical Guidance for Use in Clinical Practice

DR LOVE: Would you discuss how you currently use aflibercept in clinical practice?

PROF VAN CUTSEM: We never use aflibercept in combination with oxaliplatin, only in combination with irinotecan, and we typically use it in patients who did not previously receive irinotecan. So one scenario in which we'd use it is in a patient who experienced rapid tumor progression on first-line FOLFOX/bevacizumab. We want to switch to FOLFIRI and add aflibercept as second-line therapy in this group of patients regardless of KRAS status because your question can then be, do you use the same approach in patients with KRAS wild-type disease as you do in those with KRAS mutation-positive disease? In this situation the answer is yes because aflibercept exhibits activity in both of these settings.

However, I would not switch to aflibercept for a patient who received first-line FOLFOX/bevacizumab but who did not experience disease progression until 1 year later. I would continue bevacizumab for such a patient.

As for the situation of what I would do after 4 months or 6 months, that's a bit more difficult. I'd still consider 4 months to be rapid disease progression, and I would probably change everything. Six months becomes more of a gray zone. I would analyze the toxicity the patient experienced in the first-line setting, knowing that aflibercept will be a bit more toxic than bevacizumab in this situation. Once we reach the 8-month mark or beyond, I would probably continue with bevacizumab postprogression.

DR LOVE: Axel, would you describe the type of patient to whom you would administer aflibercept?

DR GROTHEY: Let's assume you have no biologic treatment option second line for EGFR antibodies and you have a patient who has received first-line

FOLFOX/bevacizumab, and within the first 3 months on treatment the patient develops clear tumor progression. So more or less you immediately lock into an irinotecan-based regimen in the second line.

Then you question yourself, "What else can I do?" This would be a situation in which I would consider aflibercept as an option.

DR LOVE: Do you believe that aflibercept can be used after bevacizumab continuation — in other words, third line or beyond?

PROF VAN CUTSEM: I don't believe that aflibercept can be used in the "real" third-line setting. That's all a bit of semantics. So for a patient who received FOLFOX/bevacizumab and then FOLFIRI/bevacizumab, could you then suggest FOLFIRI/aflibercept? I don't believe it can be used in this situation because that's not what the data say and also because that's a patient whose disease is resistant to FOLFIRI.

We don't have any data in the literature that suggest that aflibercept can reverse resistance to irinotecan. It increases the activity of irinotecan in irinotecan-naïve patients, but that is different than reversing resistance to irinotecan.

Future Directions

DR LOVE: What new trial concepts are under way with aflibercept in colon cancer?

PROF VAN CUTSEM: One aspect we regret is that we do not have any biomarkers for aflibercept, as is the case with bevacizumab. Such evaluations were also not performed on the VELOUR study. However, there is now a follow-up study and we are collecting all the tumor blocks for patients on the VELOUR trial. We will perform exploratory analyses and translational research. Of course these may not produce an answer as to a

16 | **KEY ONGOING TRIALS OF ZIV-AFLIBERCEPT-BASED THERAPY FOR COLORECTAL CANCER**

Study identifier	Study endpoints	Phase	N	Setting	Treatment arms
AFLAME (NCT01661270)	Survival	III	330	2nd-line tx for metastatic CRC (mCRC)*	• FOLFIRI + ziv-aflibercept • FOLFIRI + placebo
NCT01571284	Safety, QoL	III	900	2nd-line tx for mCRC*	• FOLFIRI + ziv-aflibercept
AFEQT (NCT01670721)	AEs, QoL	III	200	2nd-line tx for mCRC*	• FOLFIRI + ziv-aflibercept
EORTC-1207, BOS3 (NCT01646554)	Survival, resection rate, safety	II/III	240	Neoadjuvant	• FOLFOX ➜ surgery • FOLFOX + ziv-aflibercept ➜ surgery
NSABP-FC-8 (NCT01889680)	TTP, safety	II	120	1st-line tx for mCRC	• mFOLFOX6 + ziv-aflibercept ➜ 5-FU/LV • mFOLFOX6 + ziv-aflibercept ➜ 5-FU/LV + ziv-aflibercept

QoL = quality of life; AEs = adverse events; TTP = time to progression; LV = leucovorin

* Only 1 prior chemotherapeutic regimen for metastatic disease, which must have been an oxaliplatin-containing regimen. Patients experiencing relapse within 6 months of completion of oxaliplatin adjuvant chemotherapy are also eligible.

www.clinicaltrials.gov. Accessed July 2014.

biomarker of benefit with aflibercept, but these analyses are what everyone wants right now.

Similar to the Phase IV program we discussed that is further evaluating the tolerability of regorafenib, a nonrandomized study is evaluating FOLFIRI/aflibercept with the goal of further describing safety aspects and some quality-of-life parameters in patient-reported outcomes.

Several studies are under way with aflibercept in colon cancer, either from the pharmaceutical industry or from cooperative groups in the United States or Europe. The EORTC is performing a randomized Phase II study evaluating aflibercept in addition to chemotherapy before surgery for resectable liver metastases (Figure 16). A large biomarker program and a whole spectrum of different Phase II trials are also ongoing.

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