

New Agents and Strategies in the Management of Noncolorectal Gastrointestinal Cancers

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

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From the publishers of:

Gastrointestinal
Cancer™

U P D A T E



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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 in many large and rigorous clinical trials across many different cancers. 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.

Importantly, this influx of new agents brings with it an accompanying informational burden that is challenging community-based medical oncologists to stay up to date and informed. As such, additional strategies and resources are needed to help clinicians overcome the difficulties they are now facing as they attempt to learn about new therapies and appropriately employ them in the clinic. 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 noncolorectal gastrointestinal (GI) cancers. This information will help medical oncologists formulate up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Recognize the recent FDA approvals of ramucirumab and regorafenib, 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 gastrointestinal stromal tumors (GIST) and gastric or gastroesophageal junction (GEJ) adenocarcinoma.

- Develop practical strategies to prevent and/or ameliorate the toxicities associated with these recently approved therapies.
- 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 GI cancers regarding potential clinical trial participation.

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EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, Exelixis Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals, an Amgen subsidiary, Pharmacyclics Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc, Teva Oncology and VisionGate Inc.

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This activity is supported by educational grants from Bayer HealthCare Pharmaceuticals and Lilly.

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Regorafenib in the Management of Gastrointestinal Stromal Tumors





Editor's Introduction

Regorafenib is a multikinase inhibitor that received expanded approval by the United States Food and Drug Administration (FDA) on February 25, 2013 to treat advanced gastrointestinal stromal tumors (GIST) that cannot be surgically removed and no longer respond to imatinib and sunitinib. This approval was based on results of the pivotal Phase III GRID trial. To provide insight into how regorafenib may be optimally integrated into the treatment of this challenging disease, Dr George Demetri reviews the agent's development and gives an overview of a multitude of key issues associated with its use in the clinic.

Importance of Continuous Kinase Inhibition in Metastatic GIST

DR LOVE: What is the average duration of response to imatinib in patients with metastatic GIST? Would you discuss the rationale for continuous kinase suppression in GIST and how this ties into the importance of developing new agents, such as regorafenib?

DR DEMETRI: Recently, a clinically relevant summary was published of important new strategies for treating GIST. It's clear that the use of kinase inhibitors in an oncogene-addicted disease such as GIST is important. This article emphasizes that keeping that oncogenic kinase under control with effective tyrosine kinase inhibitor (TKI) therapy is an important part of treatment (Le Cesne 2013).

We also presented long-term follow-up of the Phase III NCI-supported Intergroup SWOG-S0033 study at ASCO 2014 on which patients with metastatic GIST were randomly assigned to 2 different doses of continuous imatinib (Demetri 2014). At the end of the day what was

important about this study was that 13 years later, almost 23% of the patients remain alive. These are people who we would have expected to pass away a year or two into the course of their metastatic disease.

An interesting aspect is that most of these patients experienced progressive disease somewhere around 18 to 24 months into therapy. So how is it that, on average, patients experienced disease progression 2 years into a new therapy but one quarter are still alive more than 10 years later? That is why continuous kinase inhibition is important. This shows us that management of GIST is not simply a drug management question.

A number of those patients who experienced progression of disease had 1 clone growing somewhere in their body, which was excised by a surgeon, and the patient remained on the kinase inhibitor. And they often got many more years out of that before another clone arose. They might have undergone another surgery or they had more clones than surgery could manage, and then they received a different kinase inhibitor.

So I believe that sets a different paradigm in how we manage our agents in patients with metastatic disease — keeping the oncogenic kinase under control with continuous kinase inhibitors is the “new world order” — and that's true for virtually all of the oncogene-addicted tumors that are driven by mutations.

Regorafenib — Mechanism of Action

DR LOVE: How do you conceptualize the way the 3 approved agents work, how that ties into the various types of mutations and where regorafenib fits in?

DR DEMETRI: I would ask whether a drug is relatively selective or relatively

promiscuous. The term for “relatively promiscuous” these days is multitargeted, but that’s a terminology issue. It’s important to lump them into these 2 categories. Imatinib is a relatively selective inhibitor that targets KIT and BCR-ABL (Figure 1), which is why it’s a terrific drug for leukemia. It also inhibits the platelet-derived growth factor (PDGF) receptor. So it’s not perfectly specific, but it’s relatively selective.

This relative selectivity is the underlying reason that imatinib is an extremely well tolerated drug. It does not target the vascular endothelial growth factor (VEGF) receptor, so you don’t generally observe the kind of hypertension that we expect as a class effect from a VEGF receptor inhibitor. Imatinib does inhibit the PDGF receptor, however, and unopposed inhibition of the PDGF receptor leads to some third spacing of fluid and swelling in the body. Patients receiving imatinib can develop edema and their weight can increase because of some degree of third spacing.

Then we have the multikinase inhibitors sunitinib and regorafenib, both of which not only inhibit KIT but also inhibit the VEGF receptor in addition to a number of other factors (Figure 1). We don’t see the edema and weight gain associated with imatinib as much with the multikinase inhibitors because even though they do inhibit the activity of the PDGF receptor, they do so by blocking the VEGF receptor, which is a vascular permeability factor.

Imatinib was the first of these agents to be approved by the FDA. When patients developed resistance to imatinib, it was usually because of certain mutations in the oncogenic KIT kinase that prevented imatinib from binding to the ATP-binding pocket. This led to the development of sunitinib, which is a smaller molecule that can get around the ATP-binding pocket mutations that limit imatinib from binding.

Sunitinib, because it’s a smaller molecule, hits a lot more kinases, including the VEGF receptor. Even so, eventually the tumor cell winds up getting around sunitinib in a further iteration of resistance, and that’s why we

1	COMPARISON OF IMATINIB, SUNITINIB AND REGORAFENIB		
	Imatinib ¹	Sunitinib ²	Regorafenib ³
Mode of action	Tyrosine kinase inhibitor	Multikinase inhibitor	Multikinase inhibitor
Type	Small molecule	Small molecule	Small molecule
Targets	KIT PDGFR BCR-ABL	KIT PDGFR-β FLT3 VEGFR2	Include: KIT PDGFR VEGFR-1, 2, 3 FGFR-1, 2 ABL
Route of administration	Oral	Oral	Oral
Possible side effects	Fever, chills, shortness of breath, bleeding, diarrhea	Hypertension, diarrhea, HFS, bleeding, tumor lysis syndrome, ONJ	Bleeding, liver damage, hypertension, HFS, skin rash
FDA approval	GIST, ALL, CML, MDS	GIST, PNETs, kidney cancer	GIST, CRC
HFS = hand-foot syndrome; ONJ = osteonecrosis of the jaw			
¹ Marcucci G et al. <i>Clin Cancer Res</i> 2003;9(4):1248-52; ² Mena AC et al. <i>Anticancer Drugs</i> 2010;21(Suppl 1):3-11; ³ Grothey A. <i>Lancet</i> 2013;381(9863):303-12.			

developed regorafenib. Regorafenib shuts down many of the mutations that neither imatinib nor sunitinib can inhibit.

In fact, we’ve been pleasantly surprised because when we started the clinical testing of regorafenib we thought it would be a little different, but it turns out that more basic science and a lot of clinical experience have confirmed that regorafenib was better than we expected it to be for some of the most difficult-to-treat mutations in the activation loop of the intracellular KIT oncogenic kinase (Serrano-Garcia 2013).

Even so, tumors do eventually develop resistance to regorafenib also.

What’s been most enlightening for us is understanding the mechanisms of resistance to regorafenib. How does the GIST cell become resistant to regorafenib? The answer lies within the ATP-binding pocket, which sits in exon 13 and exon 14 of KIT. It turns out that regorafenib does not fit into that pocket very well. That’s the pocket that sunitinib fits into perfectly.

Sunitinib fails because it cannot bind to exons 17 and 18 kinase activation loop mutations, and regorafenib binds there beautifully. So it turns out that sunitinib and regorafenib are quite complementary. That concept is the basis for a study on which patients with metastatic and/or unresectable GIST will alternate between regorafenib and sunitinib with the idea being that regorafenib will inhibit one set of clones and, while the drug binding pocket clones are starting to come out, a month later you basically knock those down with a month of sunitinib and then you go back to targeting the kinase activation loop mutations by going with a month of regorafenib (Figure 11, page 19).

Early Clinical Trial Data with Regorafenib in GIST

DR LOVE: Would you comment on the early research and development of regorafenib in GIST?

DR DEMETRI: The history of our involvement with regorafenib and its development goes back to when we were completing the development of sunitinib. Sunitinib had more activity than we’d anticipated, and we tried to figure out exactly how it was working. We collaborated with a number of scientists and evaluated the structural biology and ascertained that the tumor cells that were resistant to imatinib had generally developed a resistance mutation that essentially threw a molecular elbow out into the ATP-binding pocket, and imatinib couldn’t get around that elbow. But sunitinib, a smaller molecule, could fit under the elbow and still inhibit the kinase.

2 EFFICACY RESULTS SUMMARY OF A PHASE II TRIAL OF REGORAFENIB FOR METASTATIC AND/OR UNRESECTABLE GIST AFTER DISEASE PROGRESSION ON IMATINIB AND SUNITINIB	
Efficacy	n = 33
Clinical benefit rate	79%
Partial responses	12%
Stable disease (for ≤16 weeks)	67%
Median progression-free survival	10 months
George S et al. <i>J Clin Oncol</i> 2012;30(19):2401-7.	

When the tumor cells were exposed to continuous sunitinib and became resistant, we knew that was a problem of the enzymatic activation loop, which was deeper within the structure of the kinase, and neither sunitinib nor imatinib could inhibit that. We performed other structural and functional biology studies on a number of other chemicals and found different binding kinetics for the class of drugs that is represented by regorafenib, which can shut down those activation loop mutants.

A Phase II trial was undertaken to evaluate regorafenib and reported terrific activity with the agent, much more than we had come to expect from other agents evaluated in the third-line setting after disease progression on imatinib and sunitinib (George 2012; [Figure 2]).

This 34-patient Phase II trial reported an impressive result in this rare disease. What’s a big effect in this setting? It means that the disease could be controlled without progression for at least 6 months (Figure 6, page 14). Our experience with all sorts of other kinase inhibitors after disease progression on imatinib and sunitinib is that it’s easy to control the disease with almost any agent for about 2 months, 3 months or even 4 months, but it’s difficult to control it for 6 months.

We were impressed with the results reported on this Phase II study of regorafenib — the median progression-free survival of 10 months was

extraordinary. When we evaluated across the different types of KIT mutations, median progression-free survival was a little shorter for patients with exon 9 and exon 11 mutations, and the median progression-free survival for patients with wild-type tumors was somewhere in the middle. So it varied, but it didn't vary much. These data led us to believe that regorafenib was a different agent from several of the other drugs we had been testing.

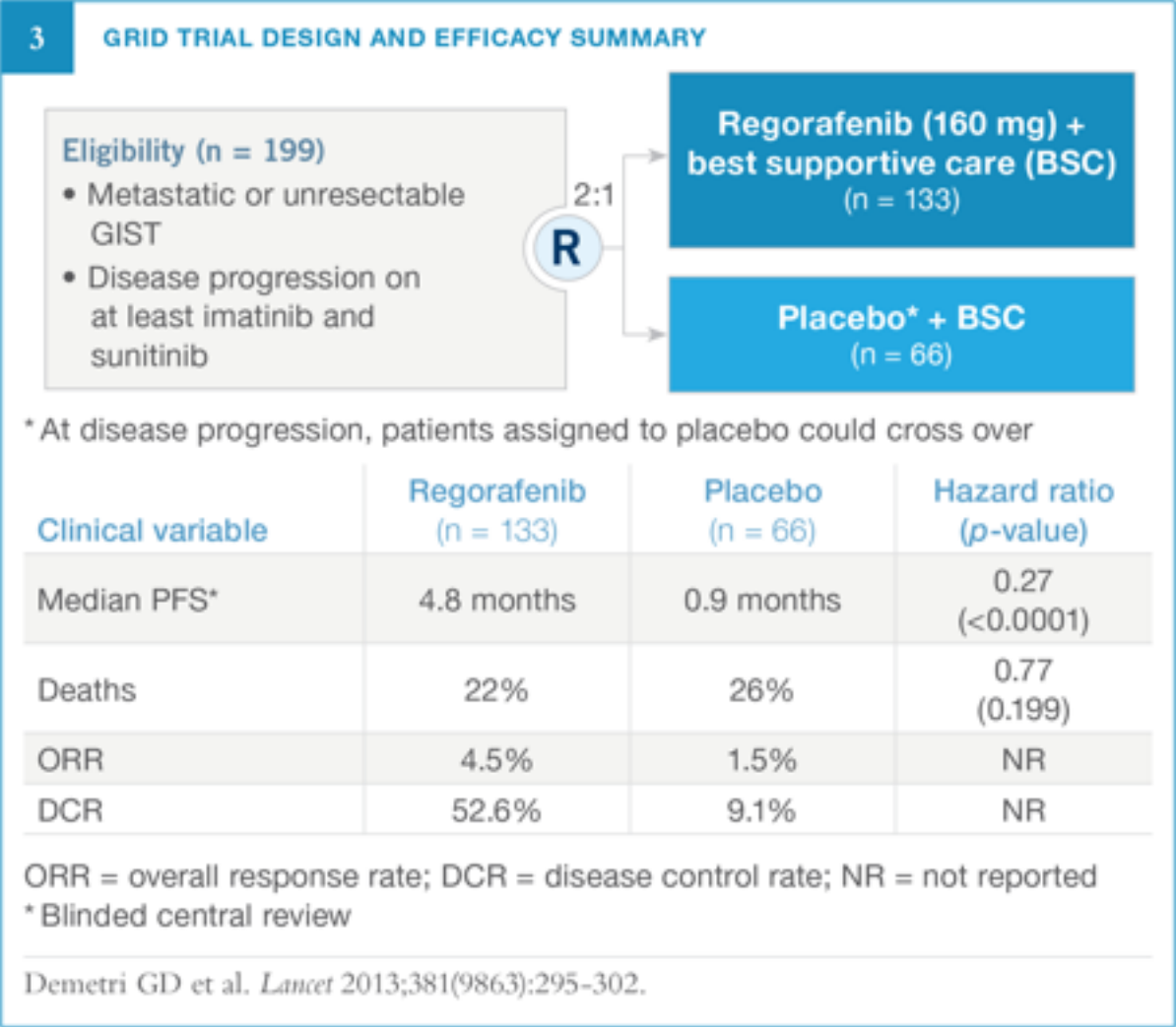
Key Clinical Trials Leading to FDA Approval

DR LOVE: Would you discuss the Phase III GRID clinical trial data that led to the approval of regorafenib in GIST?

DR DEMETRI: The timeline here was exciting because the Phase II trial led by Dr Suzanne George entered the first patient with GIST to receive regorafenib in February 2010, and we completed the study in the fall of 2010. Then the GRID study opened in January 2011 and closed to accrual a scant 7 months later in July 2011. The results of the study were published in *The Lancet* in January 2013, and by February 2013 the FDA had approved regorafenib in this setting. So from the first patient with this disease to receive treatment to FDA approval was about 3 years.

I believe that's a measure of how well the agent worked, how obvious it was that it was working and how functional our GIST and sarcoma community worldwide was. Now the question is, how do we explain to doctors why we're excited about it because a lot of people could view this and say, "It's a third-line drug. Who cares about third-line?"

The important aspect is that regorafenib works reasonably well in a number of people. We've had many people who go well beyond the median 6- or 8-month benefit period into several years. That's one of the points that Drs Waddell and Cunningham focused on in the *Lancet* editorial they authored on the GRID publication (Waddell 2013). Here's an agent that's



approved in the United States for both colorectal cancer and this “oddball” oncogene-addicted disease called GIST, but the data are so much more powerful in GIST than they were in colorectal cancer, even though the colorectal study reported a survival benefit because of the way it was designed without a crossover. The GRID study for patients with GIST did not yield a survival benefit because we planned for it not to have a survival benefit (Demetri 2013; [Figure 3]). As soon as patients experienced disease progression, they were unblinded and if they were on placebo they were allowed to cross over to regorafenib.

Most patients receiving placebo experienced disease progression in less than a month, and obviously that's a short time. So, of course, no survival

benefit was achieved by limiting these patients to placebo for less than a month before they could receive regorafenib. All of us involved in that study feel good about the fact that no statistically significant survival benefit was observed because that means we did our job well. We didn't make people die to prove that the drug worked. The regulatory authorities should be praised for saying, "Yes, we agree with you. This agent works, and we'll approve it."

We designed the GRID study very much like we designed the sunitinib registration trial. We did not molecularly select for any subtype of GIST. The entry criterion was simply that patients had to have received and experienced disease progression on imatinib and sunitinib as a minimum. Patients could have received imatinib, sunitinib and 5 other drugs. In fact, only about half the patients had received only imatinib and sunitinib. About half had received several other agents also.

But the good news is that it didn't matter. By not selecting, we were still seeing the same efficacy across the board. We performed all sorts of subset analyses to ascertain if one group of patients did not benefit from the agent, and we couldn't identify such a group, which is good.

In the end, we enrolled 199 patients to this study in a 2-to-1 randomization fashion, so patients had 2 chances to receive active regorafenib versus placebo. We reported a hazard ratio of 0.27 for patients receiving regorafenib, so a 73% reduction in the risk of disease progression. In many ways, this result was driven by the fact that in this setting of multiply resistant GIST many patients on the placebo arm experienced disease progression rather consistently and rapidly in less than a month. So this is aggressive disease.

With regorafenib on board, approximately half of the patients reached almost 6 months. And now we're more than several years into this study and we still have approximately 15% of patients who are still on study. So

the median numbers of any kind of a large clinical trial only tell part of the story. Some patients who receive the drug experience disease progression earlier — and we're trying to figure out what to do for them and why it's happening — and then other patients experience extraordinarily long, prolonged responses and benefit.

When I say "responses" in GIST, let me add that generally what we're talking about is control of the disease. The objective response rate in this study was quite low — 4.5% with regorafenib versus 1.5% with placebo.

DR LOVE: Was that low response rate also observed in the Phase II study?

DR DEMETRI: It was, in fact (Figure 2, page 8). The Phase II study was a little higher, at 12%, but certainly it was within the margin of error of small studies. That's typically the case for all agents administered after disease progression on imatinib. Imatinib invokes this enormous response upwards of 66% after a couple of years, but what does that say about GIST? It says that first-line GIST is generally a single-clone disease. The dominant clone is virtually all one type of cell with one mutation before patients are subjected to TKI selection pressure. Once you attack that with one good kinase inhibitor of any kind, you obtain a massive response rate.

By the time the patient develops resistance to that first-line therapy, you have polyclonal disease popping up, which is exactly what you see in standard colorectal cancer when patients first present. Carcinomas tend to be polyclonal when you first discover them. They're clonal, but they've had time to evolve a polyclonal nature within themselves, and that's what GIST proves. By the time you get to third-line therapy, you're dealing with polyclonal disease that starts with a clonal origin but then is heterogeneous because other mutations have come in on top of that.

DR LOVE: Would you elaborate on that concept and discuss the reported response rates across these 3 agents in their respective settings?

DR DEMETRI: Sure, and let’s start with the easiest one, which is imatinib. First-line imatinib therapy is remarkably effective for patients with GIST. About two thirds of patients experience objective responses, and another 20% of patients experience disease control, for an overall disease control rate of about 86% (Figure 4).

Once you develop resistance to imatinib and now you’re in the second-line setting, sunitinib only provides a response rate of 12% to 14%. But now you have the disease control rate of 50% to 60% for a certain period, and that’s an important factor. Anybody can attain stable disease for 2 weeks, but stable disease for 4 to 6 months is important.

In many ways, that’s why progression-free survival is a better metric. It’s a measure of how long the disease remains stable in 100 patients, for example. How long would it take 50 of them to have their disease worsen? Although the progression-free survival benefit of sunitinib compared to placebo is not bad, it’s certainly not the 24 months that we’ve come to expect from imatinib. Does that mean sunitinib is less potent than imatinib? That is absolutely not the case because if anything sunitinib is more potent. It means that resistant GIST is more difficult to treat than TKI-naïve GIST in the first-line setting.

So even though imatinib has this terrific response rate and sunitinib has a less impressive response rate, the disease control rate is also important. Now we come to third-line therapy, where the disease is even more aggressive and more heterogeneous. What do we observe in terms of a response rate with regorafenib? We don’t see a good response rate, objectively. We see a lower response rate, but the progression-free survival is still approximately 5 months.

If you evaluate a waterfall plot — which in many ways is simply another way of assessing how stable or responsive a disease is — it supports what we see in the progression-free survival curve. It indicates that a number of

4 FIRST-LINE IMATINIB VERSUS SECOND-LINE SUNITINIB VERSUS THIRD-LINE REGORAFENIB IN ADVANCED GIST			
Clinical outcome	First-line imatinib ¹	Second-line sunitinib ²	Third-line regorafenib ³
ORR	44.4%-71.7%	12%	4.5%
SD	21.1%-44.4%	67%*	48.1%†
Median PFS	12.8-24.7 mo	10 mo	4.8 mo
Median OS	38.4-60.0 mo	Not yet reached	Not yet reached
ORR = overall response rate; SD = stable disease; PFS = progression-free survival; OS = overall survival			
* SD ≥ 16 weeks; † SD ≥ 12 weeks			
¹ Heinrich MC et al. <i>J Clin Oncol</i> 2008;26(33):5360-7; ² George S et al. <i>J Clin Oncol</i> 2012;30(19):2401-7; ³ Demetri GD et al. <i>Lancet</i> 2013;381(9863):295-302.			

patients are having stability or modest minor shrinkage of their tumor as their best response, and it confirms what the progression-free survival curve shows. All of us would like to induce the kind of high objective responses that we observe with first-line imatinib in GIST in the later-line settings, but I believe that will necessitate combination therapies. That’s a big focus of our research program here. We can’t do it with the currently available approved agents yet.

DR LOVE: Why can’t you do it with the currently approved drugs?

DR DEMETRI: That’s the \$64 million question we’re researching. What is it that keeps these tumors alive? Is it that enough sleeper cells are stunned by even sunitinib and regorafenib, so they don’t grow but they’re not quite hit hard enough to induce apoptotic cell death? Or is it that some other signaling pathway keeps them alive? Is some antiapoptotic signal they’re receiving from something else keeping them alive, but the kinase inhibitors are doing all they can to keep them from growing? None of us know the answer to these questions as of yet. So this is a big part of our current SPORE research initiative and many other research initiatives here.

We also have not been able to identify a type of patient who, having experienced disease progression on imatinib and sunitinib, should not receive regorafenib. We’ve observed benefits across the board in virtually all of the genomic types of GIST — exon 9 KIT mutants, exon 11 KIT mutants, the so-called no mutation or wild type. It’s as if regorafenib has a differential activity across the board in GIST. That’s what the Phase III trial has indicated.

By way of example, I will refer to a patient who I cared for on the SWOG-S0033 trial who was receiving imatinib for about 10 years along with the judicious use of radiofrequency ablation for a few small metastases.

Once the patient's disease became resistant to imatinib, she received sunitinib and experienced about a year’s worth of benefit on sunitinib before again developing disease progression. She then received regorafenib and had a terrible experience with that before being referred here to Dana-Farber, at which point we said, “You should give regorafenib another try,” because at that point we did not have any other real clinical options for her. Thankfully, she did, and the regorafenib has delivered good activity for her.

DR LOVE: Would you expand on the correlative analyses that were performed on the GRID study?

DR DEMETRI: We performed all sorts of correlative analyses on this study (Figure 5), including a technique called BEAMing technology, which is a way of taking a blood sample and expanding out the mutations in the free DNA component that floats around in the blood outside of tumor cells. That’s how we performed the final analyses to determine whether a group of patients with mutations didn’t benefit the same way as everyone else with regorafenib because, if we could identify such a genomically defined patient population, it would allow us to not administer an ineffective drug to such patients.

5 GRID TRIAL OF REGORAFENIB: PROGRESSION-FREE SURVIVAL ANALYSIS BY SUBGROUP		
Subgroup	n	Hazard ratio (HR)
Anticancer line		
Third line	113	0.23
≥4 lines	86	0.31
Duration of imatinib Tx		
<6 mo	22	0.50
≥6 to <18 mo	33	0.19
≥18 mo	144	0.24
Mutation status		
KIT exon 11	51	0.21
KIT exon 9	15	0.24
HR < 1.0 favors regorafenib compared to placebo.		
Demetri GD et al. <i>Lancet</i> 2013;381(9863):295-302.		

In our BEAMing correlative science analysis, we observed the same efficacy across the board, regardless of the mutational burden in the patients.

DR LOVE: Has the mutational burden of patients with newly diagnosed GIST who have not yet received imatinib ever been evaluated to see how that might differ from the patient who’s out to third-line therapy and is receiving regorafenib? Would you expect to observe differences there?

DR DEMETRI: We are interested in this type of analysis, and a wonderful study out of Germany was published in *Cancer Research* last year that performed such an evaluation (Simon 2013). They wanted to ascertain what the spectrum of mutations look like and how they change with time. When these diseases present for the first time, they’re essentially monoclonal with 1 mutation. You don’t see the rare 1 in 10 million cells hiding in the background. But under the selection pressure of treatment with any of the kinase inhibitors, those first cells are generally destroyed through apoptosis.

Then the resistant clones come up. It usually takes them months or years to grow because they're evolutionarily unfit. But eventually the selection pressure of the kinase inhibitor allows them the chance to expand their niche. By the time a patient reaches second-line or third-line therapy, you are dealing with a different disease from first-line GIST.

DR LOVE: Is that why you see a different trajectory in a patient with chronic myeloid leukemia (CML) who can have long-term responses to these agents versus those with GIST?

DR DEMETRI: That is exactly right. GIST is more like a lower-key version of CML in blast crisis. If you consider CML in blast crisis, none of the kinase inhibitors work that well.

So by the time you get to third-, fourth- or fifth-line therapy for patients with GIST, it's similar to dealing with CML in blast crisis as opposed to first-line GIST. You might ask, why isn't first-line GIST as well controlled as first-line CML, which can respond to first-line therapy for a decade or more?

But in fact approximately one quarter of our patients with GIST can respond to first-line therapy for a decade or more. So it's more a matter of what the patient is like when they first start therapy. Another interesting aspect about the GIST world is that many of the key papers from when we started treating this disease back in 2000 are already outdated because those patients, thankfully, don't exist anymore.

In terms of the patients who went on the first studies of imatinib and sunitinib, the bulk of their disease was large because, in general, doctors weren't screening for recurrence of GIST the way they do now. So those patients had enormous tumor burdens and awful bulk of disease. Nowadays we would expect patients to fare even better than they did in the early days of imatinib because the bulk of disease in most patients is generally smaller.

Practical Guidelines, Dosing and Method of Administration

DR LOVE: Would you review some of the key issues related to personalized dosing to support the care of patients receiving regorafenib?

DR DEMETRI: Our experience is that close follow-up in the first month of starting any patient on regorafenib is the key to better patient and provider satisfaction. Frankly, our nurses have liked staying in touch with patients in that first month to avoid any kind of more time-consuming problems for the patients and, frankly, for themselves and the medical staff down the line.

DR LOVE: When you're initiating a patient on regorafenib therapy, do you preemptively adjust the dose, depending on performance status or hypertension levels, et cetera?

DR DEMETRI: This is an interesting question. This is something that all 5 of the investigators in our group approach slightly differently but with one similarity. We personalize treatment to the risk the disease is placing on the patient.

If you have a patient with "rip-roaring" GIST that's extremely bulky and you have 1 shot to get it right and the patient's reasonably fit, we would probably start with the higher dose with an extraordinarily low threshold to quickly dose modify if needed.

However, if the disease is moderate, we might start low and work up. I don't believe in only 1 approach, and the patients and the tumors they harbor are all so different that we do wind up customizing management.

We typically go from 160 to 120 mg and 120 to 80 mg. But what's interesting and different about regorafenib — and we saw this in our Phase II and Phase III studies and now are observing it in clinical practice — is that, in a patient who may need a dose interruption and then

reintroduction of the drug at a lower dose, we stop the dose for a day and the next day we reintroduce it at 120 mg. That patient may get used to the drug and 2 months later may be perfectly fine. Then we'll reconsider possibly escalating the dose back to 160 mg. The goal is to make sure you have enough of the active moiety in the bloodstream, and we have that discussion with the patient.

We saw the same phenomenon even in our Phase II study — patients who started at 160 mg but then went down to 120 mg and again to 80 mg, as long as their disease was still in check, could then a couple months later escalate the dose all the way back to 160 mg without any tolerability problems. That means some sort of a tachyphylaxis is taking place. The body adapts to this agent, and the patients tolerate it much better after their system has had a month or 2 to reset.

DR LOVE: Do oncologists need to keep any special considerations in mind when administering regorafenib — time of day, with or without food, et cetera?

DR DEMETRI: We don't find such considerations to be all that important. We typically instruct the patients to take all of their regorafenib at once, although some patients prefer to split it up. I must say we haven't studied that rigorously. Most of our trials have said one shot, and we've had good compliance with that. One of the questions in any clinical trial and certainly in practice is, if you have to take 4 pills, are people really splitting them and telling you they're taking them all at once? But the studies have been written with all 4 pills, 40 mg times four, taken once a day for the first 21 days of each 28-day cycle.

DR LOVE: What would be your rough estimate of the percent of your patients receiving regorafenib who end up requiring dose reductions or holding the drug?

6 COMPARISON OF RESPONSE ASSESSMENT CRITERIA IN THE ASSESSMENT OF REGORAFENIB ACTIVITY IN 20 PATIENTS WITH ADVANCED GIST ENROLLED IN A PHASE II TRIAL				
Tumor response criteria	RECIST 1.1 number	RECIST 1.0 number	WHO number	Choi number
Best response				
Complete response	0	0	0	0
Partial response	4	4	4	18
Stable disease	15	15	14	1
Progressive disease	1	1	2	1
Time to best response, weeks, median (inter-quartile range [IQR])	16 (8-33)	12 (8-24)	15 (8-24)	9 (8-16)
Clinical benefit	18 (90%)	18 (90%)	17 (85%)	17 (85%)
Clinical benefit rate 95% confidence interval	70%-97%	70%-97%	64%-95%	64%-95%
Progression-free survival, weeks, median (IQR)	66 (41-93)	44 (33-88)	34 (17-58)	24 (17-33)

Shinagare AB et al. *Eur J Cancer* 2014;50(5):981-6.

DR DEMETRI: I believe that the clinical trials are clear on this. I would say approximately one third of patients will require some sort of a dose modification. It's a significant number.

DR LOVE: Have you had any patients in whom you've had to flat out discontinue regorafenib?

DR DEMETRI: We have not, and the interesting thing is that we had patients like that referred in from outside doctors. I have 1 patient in particular who comes to mind. She had been receiving regorafenib for about 10 days and then immediately went off it and went on to some other agent. When she came in for a consultation for resistant GIST, I said, "What happened? Did the regorafenib fail that quickly?" And she said, "No. I just had such terrible side effects — skin reactions, diarrhea, everything. I would never touch that

drug again.” To which my response was “We have no other options. The drug didn’t fail, but you didn’t tolerate it. We have other ways of dosing it that might still make this a tolerable drug for you.”

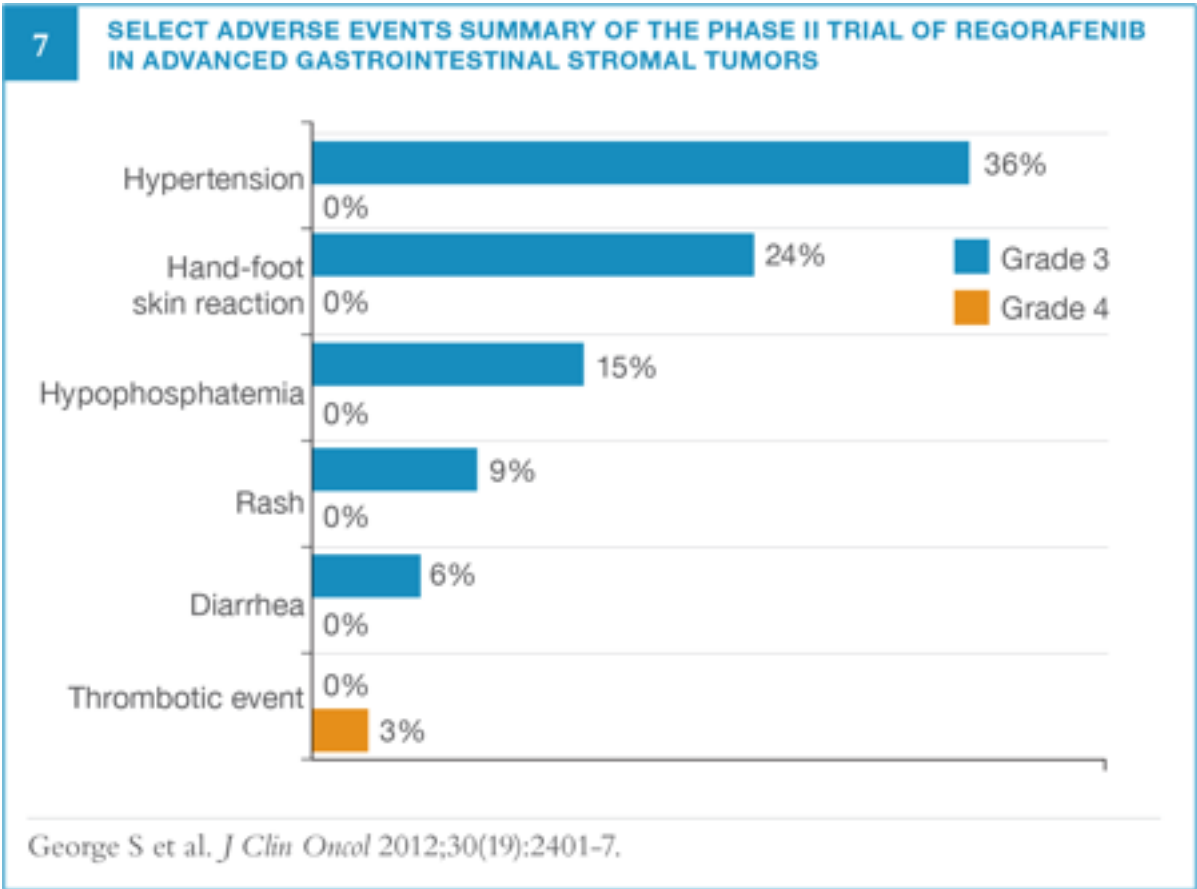
At the end of the day, she decided, “Okay. I’ll trust you. But if I get sick again, I won’t like you very much.” So she went back on regorafenib and has been successfully receiving it for about 18 months. We had to dose it gradually, take her up to a certain level and modify the dose here and there, but this woman is receiving therapeutic doses of regorafenib with reasonable tolerability. This is a single case, but it proves the rule I’m trying to emphasize, which is that if you customize the dosing to an individual, the patients don’t have to experience terrible toxicities.

DR LOVE: How do you generally approach the clinical application of these 3 approved kinase inhibitors?

DR DEMETRI: These 3 inhibitors — imatinib, sunitinib and regorafenib — were registered by the FDA and regulatory authorities in that order, and, believe it or not, it makes sense to use them in that order. You start with imatinib because it’s usually the best tolerated. It will also be the cheapest when it goes off patent in the United States in about a year, so it has everything going for it to stay as front-line therapy.

If and when the disease progresses on imatinib and surgery cannot take out 1 or 2 little clones, then you move to sunitinib, which inhibits the most common resistance mutation that prevents imatinib from working — a mutation in the ATP-binding pocket. Then, eventually, when the disease progresses on sunitinib, you move to regorafenib because it inhibits a type of mutation that neither sunitinib nor imatinib can hit, and it targets virtually everything the other 2 can inhibit also.

DR LOVE: Could you envision a clinical scenario in which you’d want to use regorafenib before sunitinib?



DR DEMETRI: We strongly encourage people to use sunitinib first. I don’t see a benefit to jumping over sunitinib and going to regorafenib first.

Tolerability and Management of Side Effects

DR LOVE: Would you review the safety profile of the Phase II trial of regorafenib we discussed previously (Figure 2, page 8)?

DR DEMETRI: The most common Grade 3 or Grade 4 side effects on the trial were high blood pressure and hand-foot skin reaction (Figure 7). The high blood pressure is clearly a class effect with VEGF receptor inhibitors, and we can deal with that.

Hand-foot skin reaction is an important side effect because, even though we saw it with sunitinib, we observed it a little more with regorafenib. But

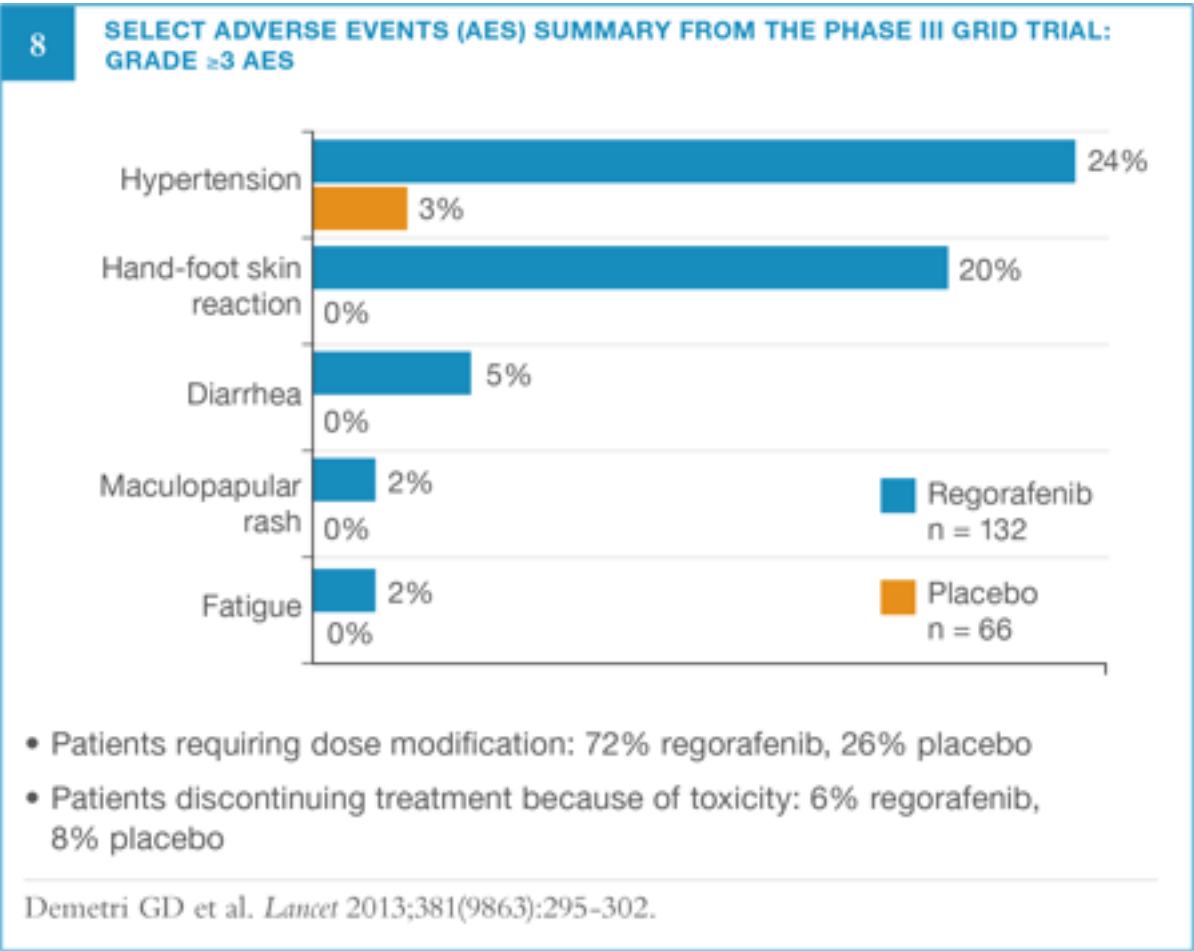
we knew what to look for, and we worked closely with our nurses to say, “The important thing about this is to recognize it early, to not let it get bad so that the patients are blistering and the awful toxicity means that the patient will have to stop the drug for a week or 10 days before it could be reasonably restarted.”

Our collaborative research team and I discussed quite a bit how we should design the Phase III study, considering that we were seeing almost one quarter of the patients experiencing Grade 3 hand-foot skin reaction in the Phase II study. Was that too high a dose, or was that the right dose?

We wanted to ensure that patients received an adequate dose of regorafenib. All of the preclinical experiments have indicated that you need an adequate dose of these kinase inhibitors to shut down the highly multiply mutated oncogenic kinase. So, rather than risk underdosing, what we decided to do, based on our Phase II experience, was to tell doctors, “Start with this high dose, but monitor the patients carefully, especially in the first 2 to 3 weeks, because that’s when you’re most likely to hear something from the patient that their hands and feet are tingling or they’re having a bit of pain. That’s the time to modify the dose.” That’s the golden window of opportunity to personalize the dose for that individual patient so that you don’t wind up continuing to administer too high of a dose to a patient and end up with awful toxicity so that neither the doctor nor the patient wants to keep the agent going.

And that’s what we did in the Phase III study. I have great respect for all the colleagues all over the world who were able to dose this agent without hurting patients. It was a remarkable skill set from everyone involved.

DR LOVE: Data published by Dr Axel Grothey and colleagues on the time course of developing hand-foot syndrome in patients with metastatic colorectal cancer revealed that it is quite rapid, as you’ve observed in GIST (Grothey 2013). Do you see any difference in the time course and the types



of symptoms in patients who’ve received sunitinib, which is presumably the majority?

DR DEMETRI: We can see rapid onset of hand-foot syndrome when patients first receive regorafenib, but because we’re trained to look for it we’ve been able to modify the dose. So if a patient experienced hand-foot syndrome with sunitinib and now that they are receiving regorafenib they report a little tingling, we discontinue the regorafenib for a day, and the next day when the tingling goes away we reintroduce the drug at a reduced dose to avoid the hand-foot skin reaction.

It’s completely about expecting this and having the nurse check in with the patient 5 to 10 days into treatment to ask, “How’re you doing? I want to make sure you’re not experiencing any problems.” Do not wait for the

patient to call in distress. This is an important aspect about administering this drug successfully. And I would emphasize that for us it's more like 5 to 7 days. By the time you get to 10 days, you're already far in. If toxicity on the skin is going to occur, it will happen then.

DR LOVE: What typical toxicities did you observe on the GRID study? Did they differ from those reported on the Phase II trial, and what have you observed in your own experience?

DR DEMETRI: The important aspect of the Phase III GRID study is that we essentially confirmed what we observed from the Phase II study, which was that about 20% of patients experienced hand-foot skin reaction or high blood pressure that was severe enough to be called either Grade 3 or Grade 4 (Figure 8). Luckily, at that point our doctors and collaborators caring for patients on study were both well trained and intelligent about how to modify the dose of regorafenib so that almost no one had to be taken off study because of toxicity. I believe only 5% or 6% of patients had to discontinue regorafenib because of toxicity, which was exactly the same response if not lower than on the placebo arm.

A number of patients — more than 30% — had their dosing regimen adjusted in some way. So customizing the dose of regorafenib for a patient with GIST is an important part of clinical practice. That's different than many other drugs we use, and that's an important message to get out to the general community oncologists. I believe few doctors have heard that this agent can be well tolerated if you're careful about staying in touch with patients and customizing both schedule and dose in the first month of treatment.

If you only administer regorafenib at the FDA-labeled dose and don't pay attention in that first month, the risk is high that the patient will develop severe skin toxicity, severe hypertension, diarrhea or some other kinase inhibitor-related toxicity and not want to go back on treatment.

DR LOVE: Would you discuss the paper your group published on regorafenib and hypertension?

9 HYPERTENSION ASSOCIATED WITH REGORAFENIB FOR GIST IN A PHASE II TRIAL	
Outcome	n = 32
Patients who developed regorafenib-induced hypertension	20 (63%)
Two weeks after initiating regorafenib therapy	
Plasma ET-1 increase*	25% (p < 0.05)
Plasma NO suppression*	20% (p < 0.05)
After restarting regorafenib therapy after washout	
Plasma ET-1 increase	30% (p < 0.05)
Plasma NO suppression	50% (p < 0.05)
ET-1 = endothelin-1; NO = nitric oxide	
* Normalized after 1-week washout	
De Jesus-Gonzalez N et al. <i>Am J Hypertens</i> 2012;25(10):1118-23.	

DR DEMETRI: A number of people have asked the question, what's the mechanism of the hypertension with VEGF receptor inhibitors? Is it something to do with the nitric oxide pathway? Is it something to do with endothelin?

Our colleague Dr Ben Humphreys has helped us understand exactly what kind of mechanism we might be seeing that could account for the hypertension, at least induced by regorafenib. The data are clear with regorafenib that you see this incredible coordinated and reversible suppression of nitric oxide and a stimulation of endothelin 1 levels (de Jesus-Gonzalez 2012; [Figure 9]). These are probably markers of drug exposure. It's not so much a measure of whether someone will respond to the agent or experience a benefit. I believe it's simply a pharmacologic marker of whether the patient has enough of the agent in their system.

Another factor that needs to be taken into account is that individuals metabolize the oral kinase inhibitors differently. If you take 10 patients, line them up and administer the same dose of any of the oral kinase inhibitors — whether it be imatinib, sunitinib or regorafenib — you will observe an order-

of-magnitude difference among those 10 patients in how they metabolize the drug. So, even though we have 1 FDA-approved dose and schedule, we still have a lot of room to customize dosing, especially when dealing with the potent multikinase inhibitors like sunitinib and regorafenib.

DR LOVE: Do you observe any hepatotoxicity in your patients receiving regorafenib?

DR DEMETRI: Hepatotoxicity is common with all of the kinase inhibitors. It is a bit unusual to see it in patients receiving regorafenib for GIST, however. I can say, though, that the numbers of times we’ve dose reduced regorafenib for hepatotoxicity is low — I would say easily less than 10%.

I don’t remember one instance of hepatotoxicity that has not been reversible. These are issues that, if you then reintroduce the drug at a lower dose, don’t arise again.

Other extremely unusual phenomena with regorafenib are noted in the package insert, such as reversible pulmonary or leukoencephalopathy syndrome. This is typically associated with hypertension and some sort of profusion syndrome, and I don’t believe we’ve observed any instances of those.

DR LOVE: What about the risk of intratumoral bleeding with regorafenib?

DR DEMETRI: The problem with that is that patients with advanced GIST are at risk of bleeding anyway. Bleeding can develop in a tumor. You never know if that’s the natural history of the tumor or a failed therapeutic attempt of the drug. We observed some bleeding in some of our early patients who were receiving imatinib for advanced GIST, and we also observed a little of it with sunitinib. We see that at a low frequency with regorafenib also. Again, I believe that’s the setting and the disease more than anything else.

DR LOVE: How do you tend to approach bleeding when it does occur?

DR DEMETRI: We basically customize our approach based on where the

10 RECOMMENDED REGORAFENIB MODIFICATIONS TO MANAGE HAND-FOOT SYNDROME (HFS)	
HFS Grade (occurrence)	Dose modification (considerations)
0 (prophylaxis)	Urea (10%)-based creams
1 (any)	None
2 (first)	Decrease medication by 1 dose level If toxicity resolves to Grade ≤1, dose escalate up to 160 mg/d If no improvement, interrupt Tx for ≥7 d (stop Tx permanently for pts requiring interruption for 4 wk)
2 (second/no improvement ≤7 d of first or at third occurrence)	Interrupt Tx until toxicity resolves to Grade ≤1 Stop Tx permanently for pts requiring interruption for 4 wk When resuming Tx, dose reduce by 1 level or by a further dose level at third occurrence If toxicity resolves to Grade ≤1, dose escalate up to 160 mg/d Those requiring >2 dose reductions must permanently stop Tx
2 (fourth)	Discontinue Tx permanently
3 (first or second)	Interrupt Tx for ≥7 d until toxicity resolves to Grade ≤1 Stop Tx permanently for pts requiring interruption for 4 wk When resuming Tx, dose reduce by 1 level or by a further dose level at second occurrence If toxicity resolves to Grade ≤1, dose escalate up to 160 mg/d
3 (third)	Discontinue Tx permanently

Grothey A et al. *Oncologist* 2014;19(6):669–80.

bleeding is. If it’s intratumoral bleeding, then typically the patient will have abdominal pain. Sometimes those can stop by themselves. The pressure will stop the bleeding internally. Sometimes they need emergency surgery. It varies. Because this is a VEGF receptor inhibitor, I believe the more interesting question is, if someone needs surgery, how long do you wait between discontinuing regorafenib and performing surgery? Our experience is good in this area. Most of the time for elective surgeries we have been able to stop

the regorafenib about a week beforehand, perform the surgery and resume the agent when the GI tract is back to normal, often a week after surgery.

We typically haven't observed any undue bleeding complications when we use this approach. So regorafenib is not like bevacizumab, which sticks around for weeks at a time. Regorafenib is a small molecule. It leaves the system in about a week, and the tolerability for that approach has been good.

DR LOVE: Do you hear any questions from community oncologists specifically about using regorafenib?

DR DEMETRI: The biggest concern we hear from the community is that doctors have had more experience with regorafenib in colorectal cancer than they have with GIST because the former is a more common disease.

They say, "I don't see many patients with GIST, but I hear that it's not a bad drug in GIST. However, the last 3 times I've administered it for a patient with colorectal cancer, it's knocked the wind out of their sails." And they want to know, what's the difference? I believe the answer to that question is 2-fold. One answer may be that patients with GIST are simply different from patients with colorectal cancer. It's possible that because GIST is driven by these oncogenic kinases, the tumors themselves may be soaking up the regorafenib differently, which, in turn, could lead to a different tolerability profile.

The more likely possibility is that all of these patients with GIST have received sunitinib already, so their bodies and minds have grown accustomed to one multikinase inhibitor and they know what to expect.

Future Directions

DR LOVE: What new trial concepts are under way in general and with regorafenib in GIST?

DR DEMETRI: In terms of how do we obtain better results in the future, much of the focus is on combinations and orthogonal approaches. With

11

PHASE IB SURE STUDY

Protocol ID: NCT02164240

Target Accrual: 35

Eligibility

- Metastatic and/or unresectable GIST
- Prior failure of at least imatinib, sunitinib and regorafenib (fourth line and beyond)
- ECOG PS 0-1
- No intolerance to sunitinib and/or regorafenib

Treatment

Sunitinib alternating with regorafenib

- Treatment cycle is defined as 28 days.
- Treatment consists of 3 days of once-daily sunitinib alternating with 4 days of once-daily regorafenib throughout each cycle.
- The starting dose level is sunitinib 37.5 mg/d and regorafenib 120 mg/d, and doses will be escalated in subsequent cohorts after a classical 3 + 3 design up to sunitinib 50 mg/d and regorafenib 160 mg/d or until maximum tolerable dose and recommended Phase II dose is determined.
- An alternative scheme of 4-week cycles of the same regimen but with 21 days of dosing followed by 7 days of rest will be studied in case of toxicities during days 22-28 of the starting 4-week continuous cycles.

www.clinicaltrials.gov. Accessed October 2014.

regard to combination therapies, should we be hitting something more upstream at the same level of a receptor tyrosine kinase, where targets like the fibroblast growth factor (FGF) receptors are always interesting targets? Should we also be focusing on targets on the tumor cell surface or something inside the cell deeper down than the signaling cascade, such as MEK? It is a popular approach to combine a MEK inhibitor with one of many upstream inhibitors. Such trial concepts include a KIT-directed inhibitor with a PI3 kinase inhibitor, a KIT-directed inhibitor with an FGF receptor inhibitor or a KIT-directed inhibitor with an mTOR inhibitor. Such trials are either in the design phase or are already active. Some of them have even met their accrual goal and closed.

Orthogonal approaches such as immune checkpoint inhibitors and some of the other immune-stimulating pathways are of great interest but remain understudied in the field of GIST research now. Those have been much better studied in the more common carcinomas than they have been in GIST.

DR LOVE: Would you discuss the Phase Ib SURE trial that recently opened at your institution?

DR DEMETRI: The aim of this trial is to expand on what we know about how these cells become resistant to regorafenib. The trial is evaluating short cycles of sunitinib alternating with regorafenib in patients with metastatic and/or unresectable GIST progressing after prior TKI therapy (Figure 11).

A logical question might be, why must you alternate these 2 agents? Why don't you administer them together? The answer to that question is that they have such overlapping side effects that you can't administer them together at the full doses.

What if you had different versions of each agent so that you could avoid the overlapping toxicities? Might that be the perfect combination? And the answer to that may be yes, but we'd probably require different agents to be able to do that. So I believe it's an interesting question as to how we can develop regimens going forward that are even better than the ones we have today.

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Ramucirumab in the Management of Gastric Cancer

2



Editor's Introduction

Ramucirumab is a fully human recombinant monoclonal antibody of the IgG1 class that binds to the VEGF receptor-2 (VEGFR-2), blocking activation of the receptor. On April 21, 2014, the FDA approved ramucirumab for use as a single agent for the treatment of advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma that has progressed during or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy, and on November 5, 2014, the FDA approved ramucirumab in combination with paclitaxel as treatment in the same setting. To provide insight into how this agent may be optimally integrated into the treatment of advanced or metastatic gastric or GEJ adenocarcinoma, Dr Jaffer A Ajani discusses its clinical development, efficacy, safety and administration.

Mechanism of Action

DR LOVE: How do you conceptualize the biology of gastric cancer? How dependent is the tumor on specific angiogenic signals compared to other solid tumors?

DR AJANI: I don't know if gastric cancer has a discriminatory molecular profile compared to other tumors. I don't view gastric cancer as a particularly hypervascular tumor compared to other tumor types.

Approximately one third of the patients with gastric cancer have a tumor with a diffuse-type histology. A lot of fibrous stroma is present because of the dysregulation of TGF beta. About half the patients with gastric cancer have tumors classified as intestinal type. Although gastric tumors are not particularly hypervascular, like other cancers they are probably dependent on growth factors.

DR LOVE: What are your thoughts on the mechanism of action of

ramucirumab? How does it compare to other anti-angiogenic agents, such as bevacizumab?

DR AJANI: Bevacizumab is an antibody against the ligand VEGF-A, so it is targeting a circulating molecule (Figure 12). Bevacizumab will deplete the level of VEGF-A, which is clearly an important molecule produced by the tumor. I believe ramucirumab is probably a better drug mechanistically than bevacizumab because it targets the receptor and not a ligand. Ramucirumab engages the VEGFR-2 receptor and disables its function. Its action is not dependent on the ligand. If you block the ligand, you worry that an alternate ligand exists that can still bind to the receptor and activate signaling. If you block or disable the receptor, you don't have to be concerned about this phenomenon.

DR LOVE: What about aflibercept?

DR AJANI: Aflibercept is a recombinant VEGFR antibody that binds to the ligands VEGF-A and VEGF-B. It also binds to PlGF, which is a molecule involved in resistance to anti-angiogenic therapy.

DR LOVE: Would you discuss how VEGF TKIs function?

DR AJANI: The catalytic domains of tyrosine kinase receptors, particularly VEGFR2, are amenable to inhibition, but the problem we have with the TKIs is that we don't have very specific ones. These molecules have not been studied in a Phase III trial in gastric cancer, so we don't have data to show a benefit to the use of TKIs in this tumor type.

As we move forward, I believe we will see agents developed that target every step of the angiogenesis pathway, not just VEGF-A.

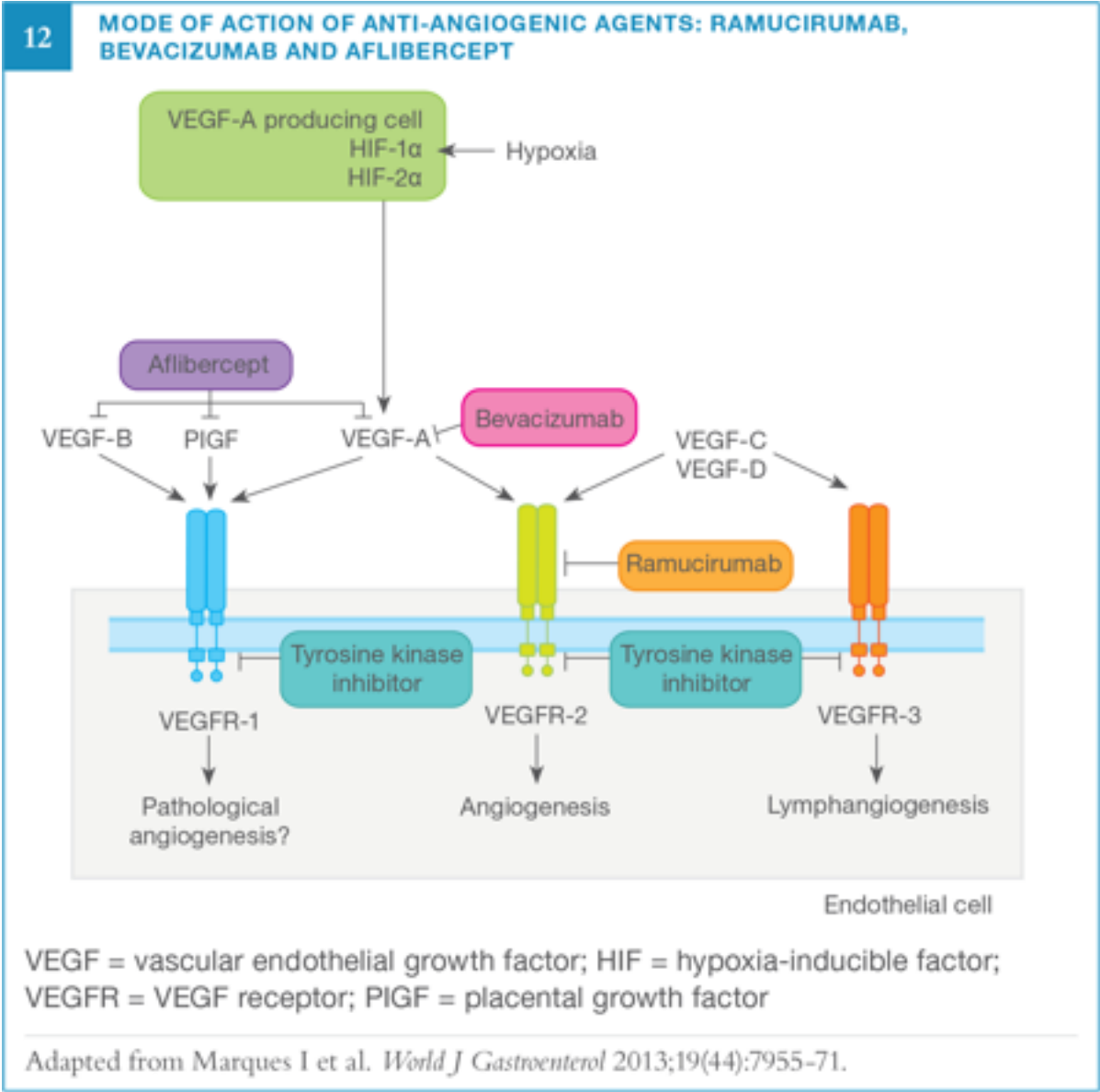
DR LOVE: What evidence existed indicating that targeted anti-angiogenic therapy had a role in the treatment of gastric cancer?

DR AJANI: Part of the background for investigating an anti-angiogenic approach came from data from the AVAGAST trial, which was designed based on the results from Phase II trials in the front-line setting that demonstrated high response rates and minimal side effects with the combination of bevacizumab and chemotherapy (Shah 2006, 2011). The AVAGAST study was a large, international, randomized Phase III trial in the front-line setting evaluating bevacizumab or placebo followed by standard chemotherapy — cisplatin and a fluoropyrimidine — for patients with advanced gastric cancer (Ohtsu 2011). The trial reported what at the time was considered a clinically meaningful median overall survival benefit of 2 months, but it was not statistically significant. Progression-free survival did statistically favor the bevacizumab arm (Figures 13, 14). The global nature of this trial may have been a potential downside. If we accept the fact that tumors are different in patients from different regions of the world because of genetics or somatic changes, then perhaps we should design trials by regional geography and not on a global scale.

Key Clinical Trials Leading to FDA Approval

DR LOVE: Would you please discuss the 2 major trials of ramucirumab, REGARD and RAINBOW? The REGARD trial was presented first and was the basis for the initial FDA approval. Would you review the details of this study and its findings?

DR AJANI: The REGARD trial was designed for patients who had previously received one treatment regimen, either a platinum-based therapy or a fluoropyrimidine-based therapy, for metastatic disease (Fuchs 2014; [Figure 15]). Patients were randomly assigned to either ramucirumab or placebo without any other anticancer agent. The randomization was 2 to 1 in favor of ramucirumab, so patients had a 2 out of 3 chance of receiving the drug. Despite this, the trial did have accrual difficulties because it is challenging to sit in front of a patient and discuss the possibility that they



will be receiving placebo. The decision was made to lower the target accrual for the trial, and we were able to complete the study.

The trial was considered positive, but I have some reservations. For overall survival, the hazard ratio was 0.77 and the *p*-value was 0.047. The expected hazard ratio of 0.69 was not achieved. The upper boundary value of the 95% confidence interval for the hazard ratio was 0.998, and this was almost at the point where the *p*-value would begin to become nonsignificant (Figure 15). The median duration of therapy with ramucirumab was 8 weeks, only 2 weeks longer than placebo. These results suggest to me that

the agent was not highly effective in the overall patient population in that trial. Ramucirumab is probably quite effective in certain patients, but we haven't yet identified who those patients are. In my experience with having patients on this trial, every patient came off the study because of disease progression at the time of their first response assessment 6 weeks after the start of treatment. This was a study-wide issue with the REGARD trial.

DR LOVE: What do you think globally about the efficacy of ramucirumab monotherapy?

DR AJANI: I know from my Asian colleagues that they are not going to use single-agent ramucirumab because they believe, as I do, that combining it with cytotoxics is better in this setting. For example, the taxanes are already approved for second-line therapy in Japan, and ramucirumab was not tested against taxanes. Also, because the efficacy of ramucirumab observed in the REGARD trial was not dramatic, I think one has to be cautious about using ramucirumab as a single agent.

I do believe that ramucirumab helps patients with advanced gastric cancer. The real challenge is that we don't know who those patients are, and we cannot enrich for that population currently. Hopefully in the future we will identify a biomarker that will allow ramucirumab to be administered to specific patients so that they will achieve the clinical benefit that we want to provide to them.

DR LOVE: What are your thoughts on the RAINBOW trial, which evaluated second-line ramucirumab in combination with paclitaxel?

DR AJANI: The design of the RAINBOW trial was similar to REGARD in that the same dose and schedule of ramucirumab was studied and the patient populations enrolled were the same (Wilke 2014a; [Figure 16]). In my opinion, RAINBOW was a better trial than REGARD in some ways. First, the number of patients evaluated was larger, with more than 660

13 AVAGAST: EFFICACY AND SELECT ADVERSE EVENTS SUMMARY

ITT population	Bev/FPr/cisplatin (n = 387)	Pbo/FPr/cisplatin (n = 387)	p-value
Median OS	12.1 mo	10.1 mo	0.1002
Median PFS	6.7 mo	5.3 mo	0.0037
ORR	46.0%	37.4%	0.0315
Grade 3-5 adverse events	n = 386	n = 381	
Hypertension	6%	<1%	—
Hemorrhage	2%	2%	—
Venous thromboembolic event	6%	9%	—
Arterial thromboembolic event	1%	2%	—

Bev = bevacizumab; FPr = fluoropyrimidine; Pbo = placebo; OS = overall survival; PFS = progression-free survival; ORR = overall response rate

Ohtsu A et al. *J Clin Oncol* 2011;29(30):3968-76.

14 AVAGAST: PROGRESSION-FREE AND OVERALL SURVIVAL BY GEOGRAPHIC REGION

OS by region	Bev/FPr/cisplatin	Pbo/FPr/cisplatin	HR
Asia (n = 188, 188)	13.9 mo	12.1 mo	0.97
Europe (n = 125, 124)	11.1 mo	8.6 mo	0.85
Pan-America (n = 74, 75)	11.5 mo	6.8 mo	0.63
PFS by region	Bev/FPr/cisplatin	Pbo/FPr/cisplatin	HR
Asia (n = 188, 188)	6.7 mo	5.6 mo	0.92
Europe (n = 125, 124)	6.9 mo	4.4 mo	0.71
Pan-America (n = 74, 75)	5.9 mo	4.4 mo	0.65

OS = overall survival; Bev = bevacizumab; FPr = fluoropyrimidine; HR = hazard ratio; PFS = progression-free survival

Ohtsu A et al. *J Clin Oncol* 2011;29(30):3968-76.

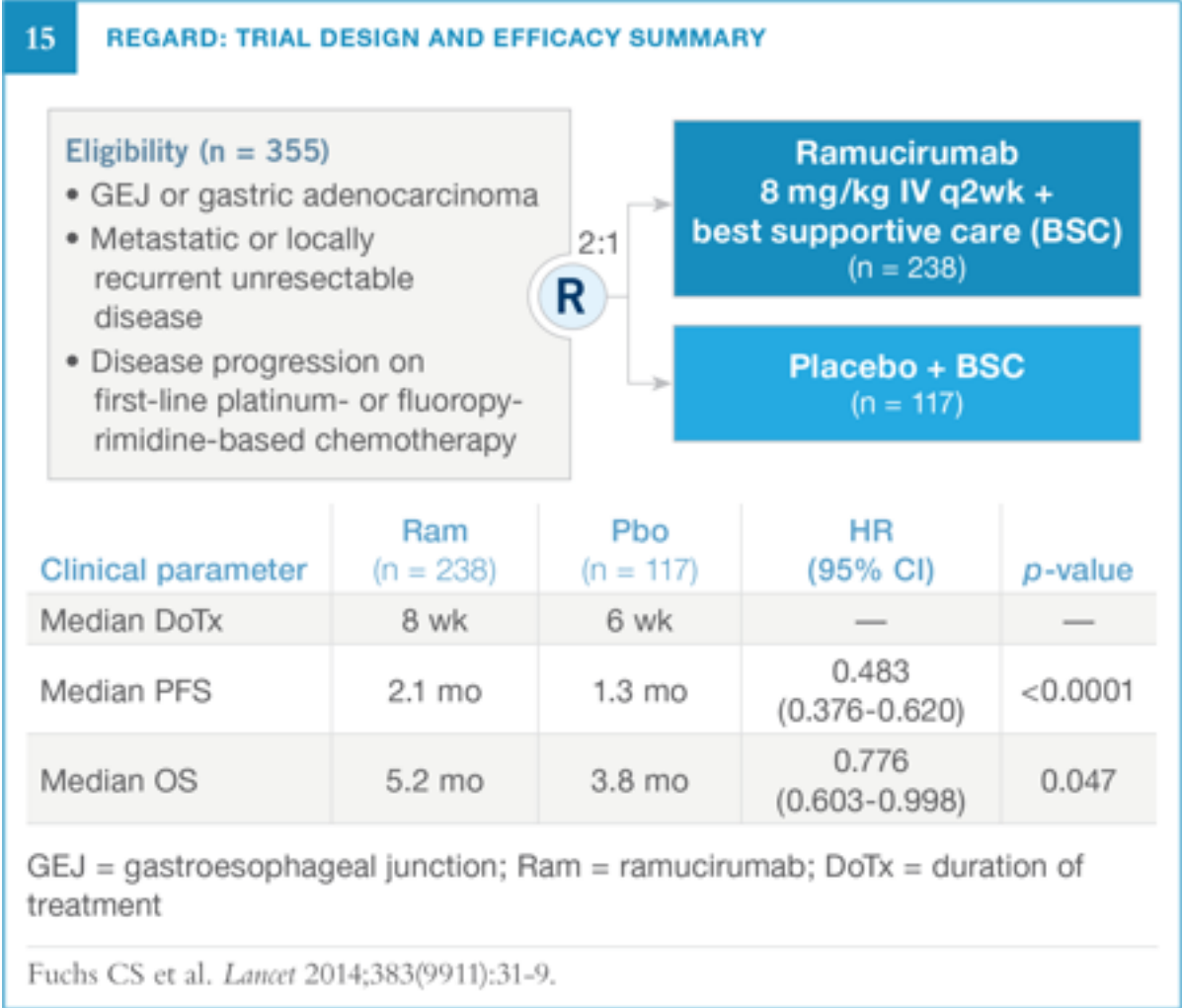
patients. Second, the randomization was 1 to 1 for ramucirumab to placebo. Paclitaxel was administered in both arms. Accrual for this study was easier than for the REGARD trial because it is a simpler discussion with the patient if you can say that on the RAINBOW trial they would be receiving what you would administer off trial anyway.

The primary endpoint was overall survival, and the assumed hazard ratio was 0.75. The actual hazard ratio for survival was 0.807 — a little worse than assumed — but the median difference was 2.2 months in the second-line setting (Figure 16). Although I don’t like medians, I believe it would be difficult to argue that this is not impressive.

“The geographical difference in the overall survival [in the RAINBOW trial] was remarkable, whereas that in the progression-free survival was small ... Since the geographical difference in the progression-free survival was much smaller than that in the overall survival, we cannot attribute the difference in survival time to differences in tumour biology in the two regions ... Wilke and colleagues speculated this regional difference might be due to the much higher use of post-study treatment in Asia (about 70%) than in other regions (about 40%).”
Sasako M. *Lancet Oncol* 2014;15(11):1182-4.

DR LOVE: Interestingly, the overall and progression-free survival benefits observed appeared to be different based on the primary tumor location (Figure 17). What about the response rates observed in the RAINBOW trial?

DR AJANI: That’s an important point because in the RAINBOW trial the response rates were fairly high. First of all, paclitaxel alone produced a very good response rate, 14% in the North/Central/South American population and 20% in the Asian population (Figure 16). When ramucirumab was added, however, the response rates increased further. The response rate to paclitaxel and ramucirumab was higher than what was observed with



ramucirumab itself in the REGARD trial. This is not only interesting but also important. These findings indicate that ramucirumab is facilitating tumor shrinkage when combined with chemotherapy.

DR LOVE: Of course we also know from analyses of both the REGARD and RAINBOW studies that the benefits of ramucirumab were similar in younger and older patients (Figure 18).

Tolerability and Management of Side Effects

DR LOVE: You participated in both the REGARD and RAINBOW trials. From your experiences, what can you tell us about the side effects and

toxicities associated with ramucirumab?

DR AJANI: I did participate in both trials, both of which were blinded. We observed 2 side effects that led us to believe that the patient was receiving ramucirumab: nosebleeds and hypertension (Figure 19). We administered ramucirumab to more than 18 patients on these trials, and I would say that about half of my patients who received ramucirumab experienced nosebleeds or hypertension. With regard to the hypertension, it is important to understand that patients who already have high blood pressure at baseline tend to be the ones who get into more trouble with ramucirumab. The more medications the patients are taking for hypertension, the more trouble they will experience at baseline. In fact, we have an internal medicine clinic that manages high blood pressure for us.

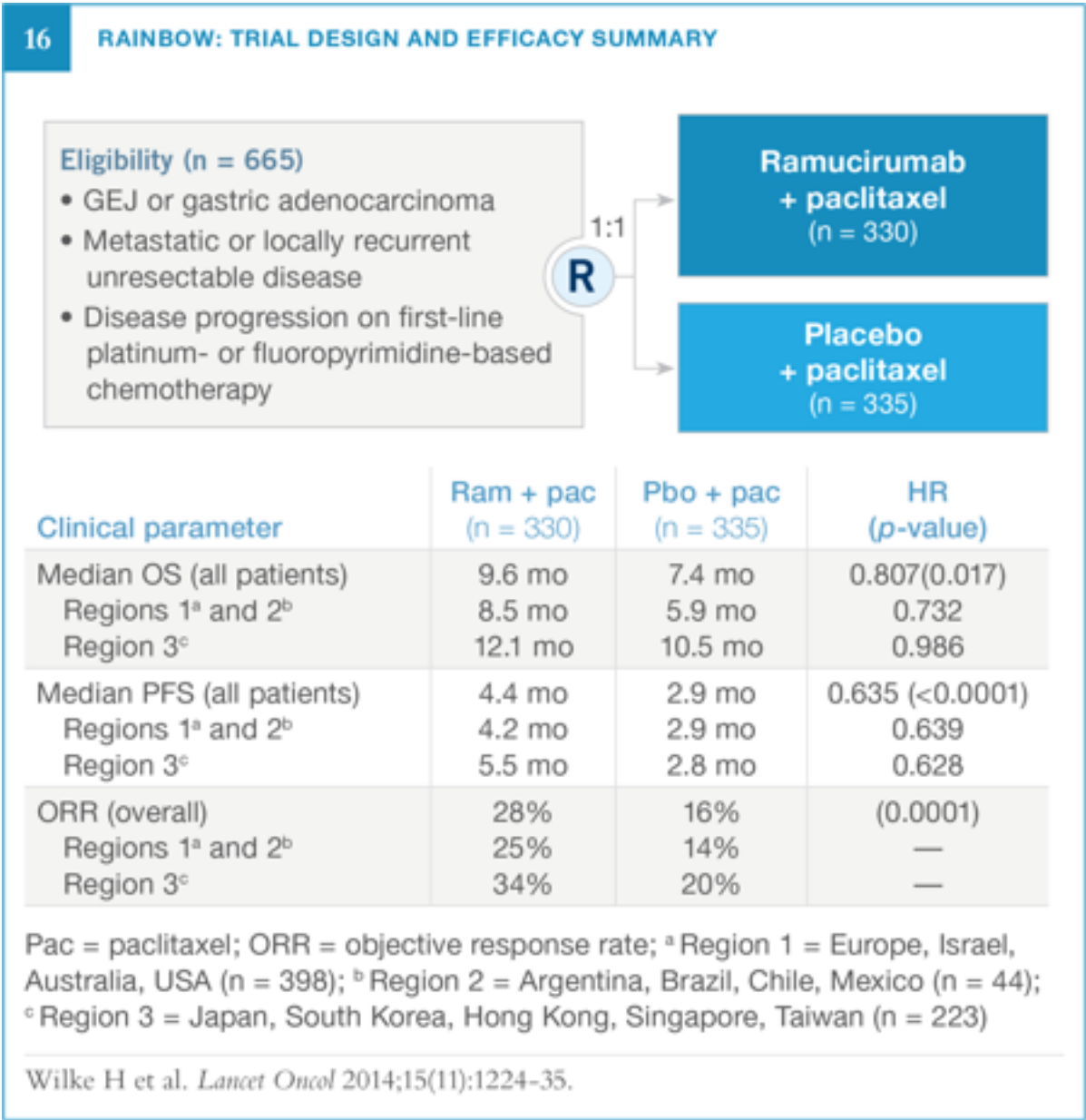
Curiously, I believe neutropenia is a little higher with ramucirumab. It is a real effect but is not highly meaningful.

DR LOVE: Are you aware of or have you observed any unusual or challenging side effects with ramucirumab?

DR AJANI: Overall, the toxicity profile of ramucirumab is not that different or unexpected from what we already know to be the case for this class of agents. I believe our benchmark for comparison would be bevacizumab, and in that context I have not observed anything unusual. All of the toxicity issues that I was already aware of with bevacizumab were less with ramucirumab.

DR LOVE: Does anything, theoretically, in terms of evaluating the different mechanisms of action of the anti-angiogenic agents, particularly comparing bevacizumab to ramucirumab, make you think their toxicity profiles would be different?

DR AJANI: This is a difficult question to answer. Ramucirumab is probably



a little less toxic than bevacizumab. The hypertension and thromboembolic events we observe with ramucirumab occur less frequently than what we observe with bevacizumab. Hypertension is similar in nature with both agents and is not commonly a major problem with ramucirumab. We have accumulated so much experience with the use of bevacizumab — I have treated more than 500 cases of gastric cancer with bevacizumab. In my experience with bevacizumab, the side effects

observed were minimal. I believe we observed 1 perforation, a few bleeds and a few people who experienced coagulation issues. Hypertension was common but manageable. Proteinuria and renal issues were rare.

DR AJANI: I have not encountered a single patient who has experienced arterial thrombosis. With bevacizumab my patients may not have stayed on the drug for long because patients with gastric cancer experience disease progression rapidly compared to patients with colon cancer, who may be receiving bevacizumab long term. The effect may be cumulative owing to prolonged exposure to bevacizumab. I also believe that, to some extent, as physicians we get used to the side-effect profile of an agent and can downplay toxicity.

Guidance for Use in Clinical Practice

DR LOVE: What are the NCCN recommendations regarding the use of ramucirumab for patients with gastric cancer?

DR AJANI: We in the NCCN state that the preferred treatment with ramucirumab will be in combination with chemotherapy as second-line therapy (NCCN 2014). Although the combination is preferred, single-agent ramucirumab is included as one of the recommended second-line treatment options (Figure 20).

DR LOVE: Would you consider administering ramucirumab as monotherapy in any clinical situations right now?

DR AJANI: I would not, although if a patient truly wants it I may consider it.

DR LOVE: What about using ramucirumab as a single agent in a patient for whom you don’t want to administer second-line chemotherapy — let’s say an 85-year-old who’s in good condition and wants treatment?

17 HAZARDS FOR SURVIVAL BY PRIMARY TUMOR LOCATION IN THE RAINBOW TRIAL		
Primary tumor location	Overall survival	Progression-free survival
Gastric	0.899	0.694
Gastroesophageal junction	0.521	0.387

Wilke H et al; RAINBOW Study Group. *Lancet Oncol* 2014;15(11):1224–35.

18 HAZARDS FOR SURVIVAL BY AGE SUBGROUP IN THE REGARD AND RAINBOW TRIALS				
Age group	Overall survival	Progression-free survival	Overall survival	Progression-free survival
<65	0.85	0.45	0.75	0.57
≥65	0.72	0.49	0.86	0.67

¹ Fuchs CS et al. *Proc ASCO* 2014;Abstract 4057.
² Wilke H et al; RAINBOW Study Group. *Lancet Oncol* 2014;15(11):1224–35.

“In the preplanned subgroup analyses [in the RAINBOW trial] of both progression-free survival and overall survival, large differences were noted between gastric cancer and gastro-oesophageal junctional adenocarcinoma ... Such large differences in treatment effect were not noted in the AVAGAST trial, comparing chemotherapy with or without bevacizumab in the first-line treatment of advanced gastric and gastro-oesophageal junctional adenocarcinoma, which is another molecular targeting agent that blocks the VEGF signalling pathway. This difference might be due to chance or possibly to a difference between the VEGF-ligand antibody and VEGF-receptor antibody. There is an urgent need to investigate the molecular difference between the VEGF-ligand antibody and the VEGF-receptor antibody and between gastric cancer and gastro-oesophageal adenocarcinoma.”
Sasako M. *Lancet Oncol* 2014;15(11):1182–4.

“I would consider using ramucirumab monotherapy in a patient with a slightly impaired performance status, for whom I would be worried about adding in a taxane. Having said that, anecdotally, I have been treating a 92-year-old man with the combination of ramucirumab and paclitaxel and he is tolerating the regimen very well.”

Charles S Fuchs, MD, MPH, Dana-Farber Cancer Institute
September 20, 2014

DR AJANI: Perhaps I might consider it, but the issue is that the response rate is quite low as a single agent. The actual tumor shrinkage is only 2% to 3%. I view the efficacy of single-agent ramucirumab as being a little better than nothing but not as good as paclitaxel. It is difficult for me to be enthusiastic about administering ramucirumab alone.

Most patients with gastric cancer are actively symptomatic because this cancer is diagnosed based on the presence of symptoms. We don’t actively screen for gastric cancer. If we have a patient who is already symptomatic and has experienced disease progression on first-line therapy, administering single-agent ramucirumab that does not significantly alleviate patient symptoms as a second-line therapy doesn’t make sense. What makes sense is administering ramucirumab with chemotherapy because the combination can provide symptomatic relief (Al-Batran 2014; [Figure 21]). That’s the first approach you want to take because the survival prolongation from ramucirumab is miniscule.

“Since RAINBOW showed that second-line therapy can significantly improve survival of patients with advanced gastric cancer, ramucirumab plus paclitaxel could be regarded as a new standard second-line treatment for advanced gastric cancer. Our findings, combined with those of the REGARD trial, validate the role of VEGFR-2 signalling as an important therapeutic target in advanced gastric and gastro-oesophageal junction adenocarcinoma. Analyses are ongoing to identify potential predictive biomarkers for ramucirumab.”

Wilke H et al. *Lancet Oncol* 2014;15(11):1224-35.

19 REGARD AND RAINBOW: SELECT ADVERSE EVENTS SUMMARY

Adverse event (any grade)	REGARD ¹		RAINBOW ²	
	Ram (n = 236)	Pbo (n = 115)	Ram + pac (n = 327)	Pbo + pac (n = 329)
Bleeding/hemorrhage	13.0%	11.0%	43%	18%
Hypertension	16.0%	8.0%	25.1%	5.8%
Arterial thromboembolic event	2.0%	0%	1.8%	1.5%
Venous thromboembolic event	4.0%	7.0%	4.0%	5.5%

¹ Fuchs CS et al. *Lancet* 2014;383(9911):31-9; ² Wilke H et al. *Lancet Oncol* 2014;15:1224-35.

20 NCCN RECOMMENDATIONS FOR SECOND-LINE THERAPY FOR GASTRIC CANCER

Preferred regimens	Other regimens
Ramucirumab for GEJ and gastric adenocarcinoma	Irinotecan and cisplatin
Ramucirumab + paclitaxel for GEJ and gastric adenocarcinoma	Irinotecan and fluoropyrimidine
Docetaxel	Docetaxel and irinotecan
Paclitaxel	
Irinotecan	

“Ramucirumab produced better results when combined with paclitaxel (RAINBOW trial) than it did as a single agent (REGARD trial); therefore, ramucirumab in combination with paclitaxel is preferred.”

NCCN Guidelines Gastric Cancers, version 1.2014.

DR LOVE: With the ramucirumab/paclitaxel combination, is the idea to stop the paclitaxel at some point and keep the ramucirumab going?

DR AJANI: This is an interesting point, and I’m not sure if the trial protocols specified anything related to this. We didn’t have to do that in

any patient who received treatment on the trials. We do not have an algorithm for this, and I would approach it on an individual basis. I would like to administer paclitaxel for as long as possible with ramucirumab because I believe it works better with the biologic agent. A small percentage of patients, I would say around 10%, cannot tolerate therapy with taxanes, however, and they develop significant body aches and neuropathy.

DR LOVE: Given a patient with metastatic gastric cancer who required treatment, what are the treatment options you would commonly consider off protocol in the first- and second-line settings?

DR AJANI: We carry out HER2 testing for our patients with metastatic disease, and 6% to 7% of patients will demonstrate overexpression of the HER2 protein. In the first line, we use the same chemotherapy regimen for both HER2-positive and HER2-negative disease. We administer oxaliplatin as our preferred platinum with either 5-FU or capecitabine. In HER2-positive disease, I add trastuzumab and continue it for as long as I can after discontinuing chemotherapy. I have about 2 dozen patients who have been receiving trastuzumab for 5 years or more.

If the patient needs subsequent lines of therapy, I would continue the trastuzumab and first use irinotecan and later on a taxane, likely docetaxel. We prefer using irinotecan to using a taxane in the second-line setting because then we can recycle the fluoropyrimidine easily. If the patient received 5-FU in the first line, I would then administer capecitabine second line and vice versa. For HER2-negative disease, the approach would be the same with the exception of not including trastuzumab in the treatment plan.

In the second-line setting, I do want to use ramucirumab, but with chemotherapy. Again, the results of the RAINBOW trial indicate that this agent performs better when you combine it with chemotherapy.

21

RATES OF IMPROVEMENT/STABILIZATION OF GLOBAL QUALITY OF LIFE (QoL) WITH RAMUCIRUMAB

	REGARD ¹		RAINBOW ²	
	Ram (n = 238)	Pbo (n = 117)	Ram + pac (n = 330)	Pbo + pac (n = 335)
Global QoL at 6 weeks	34%*	13%*	53%	50%
Global QoL at 12 weeks	NA	NA	36%	27%

NA = not assessed; * $p = 0.23$

REGARD¹: "Of patients who provided 6 week data, a larger proportion of those in the ramucirumab group reported stable or improved quality of life than those in the placebo group; however, this difference was not significant."

RAINBOW²: "For patients with advanced gastric cancer, addition of ramucirumab to paclitaxel did not impair QoL. Compared with placebo + paclitaxel, QoL was maintained for a longer time and more patients reported stable or improved scores."

¹ Fuchs CS et al. *Lancet* 2014;383(9911):31-9; ² Al-Batran SE et al. *Proc ASCO* 2014;Abstract 4058.

DR LOVE: Could you envision yourself using ramucirumab in patients with HER2-positive disease?

DR AJANI: If I had an opportunity to use it with chemotherapy, I would use ramucirumab in all of those settings. In patients with HER2-positive disease, I don't know at this point how ramucirumab would fit in exactly because this population of patients fares well. If trastuzumab were to be denied, then I would consider ramucirumab with chemotherapy.

DR LOVE: What about using ramucirumab in earlier-line settings? Are any clinical trials evaluating this?

DR AJANI: A Phase II randomized trial evaluating this agent in the front-line setting for advanced gastric or esophageal adenocarcinoma was recently completed (Yoon 2014; [Figure 22]). I am not aware of any trials evaluating ramucirumab as adjuvant or neoadjuvant therapy, nor am I aware of any ongoing Phase III trials with this agent in gastric cancer.

“I do utilize ramucirumab in patients who have progressed on front-line HER2-directed therapy. We do not know directly about the role of ramucirumab in patients with HER2-positive gastric cancer, because many of the studies did not assess HER2 status. However, in the gastric cancer models, combining a HER2 antagonist with a VEGFR inhibitor has potential synergy. No study has yet been conducted to address this question, but in the second-line setting combining a HER2 antibody with ramucirumab seems like a logical approach. I am convinced that it would be well tolerated, even with the addition of chemotherapy.”

Charles S Fuchs, MD, MPH, Dana-Farber Cancer Institute
September 20, 2014

Dosing and Method of Administration

DR LOVE: What is the approved dose and administration schedule of ramucirumab? How would you administer it both as monotherapy and in combination with chemotherapy?

DR AJANI: The approved dose is 8 mg/kg, and it is administered as an infusion every 2 weeks. That schedule works out well for the patients with advanced gastric cancer because most other therapies used are administered every 2 weeks also. I would like to be able to use ramucirumab either with irinotecan or one of the taxanes. I administer irinotecan and docetaxel every 2 weeks, so ramucirumab fits in well. I do not use the schedule from the RAINBOW trial — in which the taxane was administered on days 1, 8 and 15 — because that would be inconvenient for my patients who travel far distances.

DR LOVE: Are any issues notable concerning the administration of ramucirumab? Have you observed any infusion reactions?

DR AJANI: I haven’t witnessed a single infusion reaction. We have only had to modify the dose in one patient because of hypertension. As I mentioned

22 PHASE II TRIAL OF FRONT-LINE RAMUCIRUMAB AND FOLFOX

Clinical parameter	Ram + FOLFOX (n = 84)	Pbo + FOLFOX (n = 84)	HR (p-value)
Median PFS	6.4 mo	6.7 mo	0.98 (0.89)
PFS rate at 3 months	89%	75%	— (0.020)
Median OS	11.7 mo	11.5 mo	1.08 (NR)
Disease control rate	85%	67%	— (0.008)
NR = not reported			
Yoon HH et al. <i>Proc ASCO</i> 2014;Abstract 4004.			

previously, patients who are taking 2 or 3 antihypertensive drugs are at high risk for complications with anti-angiogenic agents. We have not had to dose reduce or discontinue treatment because of bleeding or any other issue.

DR LOVE: Do you preemptively dose reduce or change the administration schedule of ramucirumab in certain clinical situations?

DR AJANI: I have only administered ramucirumab on protocol, so I have not had the occasion to consider such preemptive measures with dose and schedule. However, I believe that the approved dose of ramucirumab is well tolerated.

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