ASCO-GI 2018

CME Webcast on the Conference Highlights of the ASCO-GI 2018 Symposium on the Management of Patients with Colorectal Cancer

John Marshall: Welcome to the CME webcast on the conference highlights of the ASCO-GI 2018 symposium on the management of patients with colorectal cancer.

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Faculty

I am Dr John Marshall, Professor and Division Chief at the Department of Hematology Oncology at the Lombardi Comprehensive Cancer Center in Washington DC, and I am joined today by my very good friends, Dr Johanna Bendell, the Director of the GI Cancer Research Program and Chief Development Officer at the Sarah Cannon Research Institute in Nashville, Tennessee, and Dr Tanios Bekaii-Saab, Professor at the Mayo Clinical Cancer Center in Scottsdale, Arizona.

Prevalence/Management of Colorectal Cancer

We all know that colorectal cancer (CRC) is a very common cancer, affecting many of our patients around the world. In fact, in the United States, it is the fourth most commonly diagnosed cancer, with more than a million new cases worldwide and a very high mortality rate, around 700,000 deaths just in 2012 alone. We know that this will increase over time. In the United States, there were 140,000 new cases of colon and rectal cancers, with as many as 50,000 people dying in 2018, so this is a major public health problem. It is increasing over time. We are also seeing a shift in younger patients getting the disease; it was a disease of only the elderly, and now increasingly we are seeing it in younger patients.

We are learning about better diagnostics and better prognostic and predictive molecular markers, and much of what we are going to talk about today is understanding those better, so that we can apply that information to our patients going forward.

Current Treatment Options in CRC

The treatment of metastatic CRC, of course, involves many agents and lines of therapy. I think when we first assess a patient with metastatic CRC, the question really is, is the patient ever resectable for cure? It is one of the few cancers where surgery is an option, removing metastatic lesions does cure some patients, so we are always categorizing patients in our own minds as in is this patient ever potentially resectable for cure, or in fact,

are there too many metastases, and our only treatment choices are going to be systemic chemotherapy?

Unfortunately, the majority of patients fall into the latter category, so we have lots of data, lots of medicines that are applied to these patients, and, we have a concept that the more medicines that we are able to give our patients, the longer they live. It becomes a chess game where we play a first-line move, a first-line regimen. We often have a maintenance time period; we then have second-line regimens, and then of course we have subsequent third- and fourth-line regimens.

For the most part in first-line therapy for metastatic disease, we use fluorouracil (5-FU)-based treatment, whether oral capecitabine or infusion 5-FU with leucovorin. They are essentially equivalent. We start all of our regimens with 5-FU, and then we either add chemotherapy such as oxaliplatin or irinotecan; I think you can use either – sometimes it depends on patient preference and toxicity. Sometimes it is the investigator preference. We also have a regimen where you combine both; a FOLFOXIRI [leucovorin, 5-FU, oxaliplatin, and irinotecan]-type regimen can be used in first-line metastatic CRC therapy with data to support a more heavy-handed initial line of therapy if required, based on the patient in front of us.

We then can add a biologic; this is usually either bevacizumab, a vascular endothelial growth factor inhibitor, or one of the two epidermal growth factor receptor (EGFR)-targeted drugs in first line. That latter group has actually narrowed, to where now we have fewer patients eligible, if you will, for EGFR-targeted therapy, as we understand more about molecular testing, the RAS/BRAF story, but also we are going to discuss today “sidedness,” whether the tumor is on the right side or the left side, which predicts whether the patient will be responsive or resistant to the EGFR-targeted therapies.

For about 80% of patients, bevacizumab would be a first-line choice; about 20% of patients, the EGFR-targeted therapies would be a choice in first-line treatment of metastatic disease.

Our response rates are pretty good in early metastatic disease; 50%, to 70% of patients will have a nice response, others will have significant stable disease. We then back off on chemotherapy and typically recommend a maintenance-like strategy, where we lighten up on the chemotherapy to try to reduce the toxicity while maintaining the benefit rate. Eventually somewhere around 1 year, the patient will begin to progress again and will need to switch to second-line therapy.

The chemotherapy you gave first line might dictate what you give second line, and the biologic you gave in first line might change in second-line. Of course, all of this is

contingent on what is going on with that patient, how much tumor burden he or she has, how many symptoms are present, what are the personal goals?

Usually 6 to 9 months after that, patients will have progressed on second-line therapy and that moves us into third line, where we have new oral agents with a nice survival advantage that has been demonstrated. Re-challenging with chemotherapy is also an option as well as many investigational options.

By using these lines of therapy, we are trying to keep control over the cancer, maintain quality of life, and, most important, increase survival for our patients through these lines of therapy.

Targeted Therapies in CRC: Mechanism of Action

We know, more or less, how targeted agents work. We have had angiogenesis inhibitors longer, there are three of them – bevacizumab, aflibercept, and ramucirumab. They actually work slightly differently in terms of mechanism of action. They are very similar, however, when you use them in a clinical setting. They have very similar clinical benefit; they have different toxicity profiles; aflibercept and ramucirumab tend to have a higher toxicity profile than bevacizumab, but they are all three approved in second-line therapy for patients with metastatic CRC.

The EGFR therapies have become increasingly interesting because we are beginning to understand who the right patient is at the right time. We realized the EGFR receptor was important, but we have clearly learned that is not the whole story; in fact, it is not even part of the story. We now know that you need to have normal *RAS* genes, normal *BRAF* genes.

Added to that, as I mentioned earlier, you need to have the sidedness story correct, that left-sided CRCs seemed to be the ones that respond, right-sided CRCs seemed not to respond, at least in early lines of therapy.

We have CRCs with *BRAF* mutations that are causing us some trouble, and although EGFR therapies don't work as well on them, there are some newer, phase 2 data that adding a BRAF inhibitor, vemurafenib, to the EGFR-targeted therapy increased the benefit rate. A very small phase 2 study actually supported a change in the National Comprehensive Cancer Network (NCCN) guidelines to bring this targeted therapy into these earlier stages.

Finally, we are going to discuss regorafenib, a multitargeted tyrosine kinase inhibitor, I call a kind of dirty bomb – it hits lots of targets. We are not 100% sure which targets are the

most important for this drug, but we do have new data that support activity with this agent, even in earlier lines of therapy. We have also new data around dosing.

Discussion Outline

There is a lot we know, more than we knew before, and our goal for this session is to review nine abstracts from ASCO-GI held in January 2018 in San Francisco. These abstracts are important to us and help fill in some gaps in knowledge, to help make us better clinicians, to better understand the medicines that are available, and to use them to treat our patients.

Just to give you a broad overview, I am going to review abstracts that focus on EGFR-targeted therapy and some of the newer data. Dr Saab is going to discuss regorafenib and two key studies that he led; these studies have really changed my practice and thinking about this medicine. We will talk a little bit about genomic profiling. Dr Bendell will focus on tumor sidedness and how that plays into the clinical scenario. We will wrap up with a discussion and overview of how this information affects our practice and provides recommendations for your practice going forward.

Anti-EGFR Therapy

I am going to do is focus on three abstracts that report results of trials of the drug panitumumab compared with cetuximab. I think these three abstracts help us in shaping our understanding of optimum use and strategy when using EGFR-targeted therapies.

Abstract 745: Panitumumab versus cetuximab in patients with wild-type *KRAS* exon 2 metastatic colorectal cancer who received prior bevacizumab therapy: a combined analysis of individual patient data from ASPECCT and WJOG6510G

Abstract 745, titled “Panitumumab versus cetuximab in patients with wild-type KRAS exon 2 metastatic CRC, who received prior bevacizumab therapy.” This was a combination analysis of the ASPECCT trial, which been presented previously, with another study, the WJOG6510G trial. This study was an additional study looking at essentially the same thing of a head-to-head comparison between these two compounds, of cetuximab and panitumumab, as the single agents in wild-type *KRAS* exon 2 metastatic CRC colon.

Study Design

The majority of patients, 1000 patients, came from the ASPECCT study; another 120 were being brought forward from the WJOG6510G clinical trial, and they were merged for this analysis. This is a very pure kind of study: Is one drug different from the other?

We know that panitumumab, for example, is a fully human monoclonal; cetuximab has a little mouse in it. There tend to be infusion reactions more in one than the other, the

schedules are a little different, but clinically we think of these medicines as being very similar. This was just a head-to-head to see if there were any differences between the two medicines.

Combined Analysis of OS and PFS

The combination analysis confirmed what we already knew from the ASPECCT study.

We observe similar toxicity around the skin reaction between the two treatments; cetuximab, because it has a little mouse in it, has more infusion reactions. hypomagnesemia seems to be more of a problem with panitumumab, so there are subtle differences with their toxicity profile. Although I don't want to make too much out of this, the panitumumab performs at least as well, if not a nose better than the cetuximab.

This analysis demonstrates that either medicine can be used, with slight differences in dosing schedules and side effect profiles, but clinically, they perform very much the same way.

Author Conclusions

The author has concluded that panitumumab had a good prolonged overall survival (OS) and progression-free survival (PFS) compared with cetuximab. I am not sure I would agree that there is a dramatic difference in how they perform. If you look at the curves, panitumumab performs slightly better with a different toxicity profile This is just in *KRAS* exon 2. This study has not been sub analyzed for all RAS or right versus left sidedness.

Abstract 624: Analysis of *RAS*/*BRAF* mutations in a randomized phase II WJOG6510G study of panitumumab plus irinotecan versus cetuximab plus irinotecan on chemo refractory metastatic colorectal cancer

Abstract 624 is an analysis of *RAS/BRAF* mutations in a phase 2 study of panitumumab plus irinotecan versus cetuximab plus irinotecan. I don't know about Dr Saab or Dr Bendell, but I tend to add irinotecan when I am delivering EGFR therapy in refractory lines. So I was most interested in the results of this study. They have conducted an exploratory analysis around the *RAS* mutations.

Study Design

There were about 120 patients equally randomized between cetuximab and CPT-11, irinotecan, versus panitumumab—full doses of the EGFR-targeted therapy but reduced doses of irinotecan. This comports with how I give it. So, patients had to be *RAS* or *KRAS* wild type, already receiving irinotecan and oxaliplatin, but with no prior EGFR therapy. The endpoint of PFS is the primary goal here.

Results

This study has been stratified by the PFS and OS for the different subgroups. The top curve is the overall population; panitumumab is performing a little bit better in terms of OS, but the curves are very similar. Remember, there are only some 50 patients per arm, so we don't want to make too much out of the deltas in the curves.

The next graph shows mutational status. The *RAS* wild-type group is doing better, and the RAS mutated, or the *BRAF*-mutated group tends to perform less well, adding more support for "You should know *RAS* status going forward."

The last graph shows PFS/OS by that *RAS* wild-type subgroup. There are smaller numbers in this subgroup analysis, about 30 patients in each arm, and these curves sit on top of each other, with the panitumumab maybe a little better than the cetuximab.

Author Conclusions

This supports what I do in clinical practice; the authors concluded that there was a modest survival benefit associated with the panitumumab compared with cetuximab; I am not sure I would go that far. If anything, panitumumab is tending toward better result, but again, the sample size is too small.

I don't think it is an absolute contraindication to give EGFR-targeted therapy to a *BRAF*-mutated tumor, but I am less excited about it. I bring in vemurafenib if I can. Even more important, the clinical trials that currently ongoing should get patients with *BRAF* mutation on combination studies.

Abstract 729: SAPPHIRE: a randomized phase II study of mFOLFOX6 + panitumumab versus 5-FU/LV + panitumumab after 6 cycles of frontline mFOLFOX6 + panitumumab in patients with colorectal cancer

Abstract 729 reports results from the phase 2 SAPPHIRE study, posing the question, if we are going to give first-line panitumumab, what do we do about maintenance? I discussed earlier the concept of maintenance, which is usually with a bevacizumab front-line strategy. If we start with panitumumab or other EGFR therapies, how do we handle maintenance?

This is a randomized phase 2 study that looks at keeping 5-FU plus panitumumab treatment going and dropping oxaliplatin, like we would do in an OPTIMOX-like schedule when bevacizumab is used.

Study Design

The study schema includes six cycles of FOLFOX (leucovorin, 5-FU, and oxaliplatin) plus panitumumab in first-line therapy. Patients are then randomized to oxaliplatin (Group A) or no oxaliplatin (Group B) Primary endpoint was PFS rate at 9 months after randomization.

Results

The results showed they were about the same. Again, 50 patients or so per arm, so I don't think we can write new laws based on this result, but it is a nice signal that we can back off on oxaliplatin as we do in a bevacizumab-containing regimen.

Because panitumumab and the EGFR drugs are single-agent active, we might even be able to drop the 5-FU as well and just give single-agent panitumumab. I think that would have been another interesting arm to put into this study

Author Conclusions

The authors essentially conclude that reducing or eliminating oxaliplatin is a legitimate choice. That way we can reduce your peripheral neuropathy, which is a primary goal.

Discussion: Clinical Practice Implications

Dr Saab, how do you interpret these head-to-head strategies around *RAS* mutation and EGFR therapies, and how does this affect you in your practice in Arizona?

Tony Bekaii-Saab: I think these studies are interesting in terms of our clinical practice. In all frankness, they won't change our clinical practice, they just consolidate our thoughts about how we practice. One, panitumumab and cetuximab, as you alluded to, continue to be considered as similar, with somewhat of a slightly different toxicity profile in terms of infusion reactions, but the whole conundrum about the skin toxicities may be worse with panitumumab versus cetuximab which, frankly, I never bought into. It gets confirmed again and again in studies that there is not much difference between the skin toxicities of panitumumab versus cetuximab. They have similar efficacy, very similar toxicity profile other than the infusion reactions, maybe slightly increased hypomagnesemia, so we can choose one or the other for whatever reason.

In the southeast United States, we probably want to go with panitumumab because of the infusion site reactions; in the rest of the country, we can choose. Clinical trials inform us on what we do, but my preference has been primarily to use panitumumab because we've established every other week dosing.

When we think again about whether we give them single agent versus a combination, I agree with you – I think giving EGFR inhibitors with irinotecan, and more often than not I

throw in the 5-FU at least in the first 4 months of treatment, so FOLFIRI (leucovorin, 5-FU, and irinotecan) plus panitumumab or cetuximab. Even when FOLFIRI plus bevacizumab fails, we can still use the irinotecan plus the EGFR inhibitor, which extends one line of therapy. This approach has actually been proven beneficial.

John Marshall: I am old enough to remember the BOND1 data, which randomized patients between single agent and combination, and the combination with irinotecan won in terms of response rate. That was before we knew about *RAS* mutation.

Discussion: Choice of Anti-EGFR Therapy

Dr Bendell lives and practices in the South. Does your choice of EGFR-targeted therapy really vary based on this infusion rate reaction in Tennessee?

Johanna Bendell: I think Dr Saab said it very well: we have this allergy belt that seems to run through the South. It was originally described in North Carolina and in Nashville, Tennessee, where we saw a much higher rate of infusion reaction with cetuximab. We all know that when you have an infusion reaction with cetuximab, they can be pretty intense. Our patients get hypoxic, some of them need to be intubated, and for this reason, with this increased risk of reaction in the South, we tend to be panitumumab users, just because we see a much lower incidence with panitumumab as opposed to cetuximab. We do use cetuximab in the setting mostly of clinical trials, and where we do we have a nurse standing by the patient when the infusion begins and through most of the infusion, just to make sure we are there to handle a reaction immediately if it happens.

Discussion: Pretreatment Testing

John Marshall: Dr Saab, what should we be measuring right now in patients before we give EGFR? Where are we with *BRAF* mutation?

Tanios Bekaii-Saab: I think there are essentials and there are less essentials. The essentials are the whole *RAS*-mutation profile: *RAS*, *KRAS*, *NRAS*, and the rare *HRAS*, and *HER2*. I am really focusing on all these and making sure we have these available to us before we take a treatment decision.

Because we are doing genomic sequencing on almost all patients, we are getting the "sugar on top" along with the "main cake". The main cake is *RAS*, *BRAF*, and *HER2*, and when I actually find a *BRAF* mutation, I am extremely reluctant to use an EGFR inhibitor. In fact, if anything, we try not to use it.

We have the BEACON trial, which is looking at the triplet in *BRAF*-mutated patients, and that is the study protocol patients go on preferentially if they do have *BRAF* mutations.

If they have *HER2* amplifications, again I am reluctant to use EGFR inhibitors, at least up-front, and I am pushing them down the line and preferentially move them to HER2-targeted strategy, on a clinical trial preferably.

Discussion: Anti-EGFR Therapy

John Marshall: Dr Bendell, you are going to talk a little bit later about right versus left sidedness, but maybe you can wax poetic about where you are using EGFR therapies? Is there a patient where you would use it first line for sure, and if you don't use it first line are there places later downstream where you absolutely would bring it in?

Johanna Bendell: I know in Europe there are a lot of data that talk about first-line EGFR antibodies in combination with chemotherapy, and there is probably a small population that will absolutely benefit from using these in the first-line therapy. I still don't think we know exactly who these people are. Sure, the *RAS* wild-type population, but are there more determinants that would help us lower down the group who needs to be treated with an EGFR inhibitor in the first line? The reason I ask this is that for patients with first-line colon cancer, this is the longest regimen they are going to be on – between 10 months and 12 months, so with the toxicity of the acneiform rash, which can be quite disfiguring, a lot of patients don't want to have that toxicity, especially for that period of time. We even have patients in the South—and call us vain—who don't want to ever have exposure to an EGFR inhibitor just because of that toxicity.

I tend to use them in my own practice later on down the line, just like you, Dr Marshall, sometimes in combination with irinotecan in the third line, if I need that response, or as a single agent, certainly in the *RAS* wild-type population, If we are checking *HER2* mutation, we definitely want those patients to be HER2 negative, because there is that thought that patients who have HER2 positivity are probably not going to respond to the EGFR antibodies. Then, for the *BRAF* population, like we have just discussed, to use an EGFR antibody mostly in the combination with a BRAF inhibitor, plus irinotecan in the second line, as is now part of the NCCN guidelines.

Regorafenib

Tanios Bekaii-Saab: I will proceed with discussing two abstracts, one related to regorafenib dosing, and the other one related to regorafenib sequence, both challenging our current practice.

Abstract 611: Regorafenib dose optimization study (ReDOS): randomized phase II trial to evaluate dosing strategies for regorafenib in refractory metastatic colorectal cancer (mCRC) – an ACCRU Network study

Abstract 611 is the ReDOS regorafenib dose-optimization study.

Study Design

This was a randomized phase 2 trial that assessed the dosing of regorafenib in patients with refractory CRC. The primary rationale for this study was that different dosing strategies were established in clinical practice based on no data. Some clinicians would start with dose escalation, others would go with standard dosing, which is 160 mg given orally and then de-escalate as needed; still others would choose 120 mg and stick to it. Some patients were dosed every other week. There were a lot of different practices around regorafenib which were unsubstantiated, and this study's intent was primarily to try to establish a dosing strategy.

We found from our clinical practices that, for 80% of patients, regorafenib is tough to initiate and maintain at 160 mg. In fact, only 20% are able to continue on 160 mg, so our dosing strategy, the experimental strategy—Arm A, was to stick with 80 mg on week 1 of cycle 1, in week 2 go up to 120 mg, and then week 3 to 160 mg, if there were no significant toxicities.

Whatever the best dosing in cycle 1 was, we move with that dose to cycle 2, and that is what patients continued on.

Then Arm B was regorafenib 160 mg, so per standard protocol, per the correct trial. There was a secondary randomization looking at hand-foot syndrome reaction a pre-emptive versus reactive strategy with clobetasol, but we will not be discussing this today; we don't have the data available yet.

The primary endpoint of the study was essentially a composite of efficacy and toxicity, and it looked at the proportion of patients who complete two cycles and then initiate cycle 3 in both arms. Essentially, the patients who had significant toxicities did not continue through cycle 3 and would be accounted for, and those patients who actually had a relative response to stable disease or better would move on with minimal toxicities to cycle 3, so essentially, we capture both efficacy and toxicity with this primary endpoint.

Our goals were to improve the rate of moving to cycle 3 by 15% to consider this a positive study, and we have all the primary and the secondary endpoints of survival, PFS, and time to tumor progression.

Results

When we look at the results of the study, it was a positive study favoring the experimental arm, the dose-escalation arm, going from 80 to 120 to 160 mg and moving to cycle 3. Forty-three percent of patients were able to go through the escalating dose strategy

and get through cycle 3 and beyond. Only 24% of patients were able to proceed to cycle 3 on the standard dose. Although above the 15% goal, this was close to a 20% difference, which was statistically significant. By all means that was a positive study in terms of its outcomes.

When we looked at the secondary endpoint of OS, we found the result was intriguing. Survival with the dose-escalation strategy was superior versus Arm B, with 9 months versus 5.9 months, although this was not statistically significant. Progression-free survival was a little bit better, again with the dose-escalation strategy. Toxicities were also a little bit better with the dose-escalation strategy.

The overall quality of life was much better preserved with the escalating dose strategy versus the standard dose, where at 2 weeks you see a dip in the quality of life, which readjusts once we get to the adequate dose. Interestingly, this was a positive study across the board for patients with the dose-escalation strategy.

Author Conclusions

Our conclusion was a strategy with a weekly dose escalation from 80 to 120 to 160 was superior to 160 mg, and that there was a trend to improved OS, a little bit of improvement in PFS, maintained quality of life, improved the toxicity profile.

When we actually looked at the reason for patients not to move to cycle 3, there were almost double the percentage of progressors on Arm B, with the 150-mg dose versus Arm A, so the main reason for not moving forward to cycle 3 was progression, not toxicity. This result is interesting because it supports overall that not only did we improve the toxicity profile and make it easier on the patients, but we were also able to essentially optimize the strategy to perhaps improve efficacy as well. I say “perhaps” because this was a phase 2 randomized study, so we always have to take the results with a grain of salt. This has changed the NCCN guidelines already to include this dosing strategy as a strategy for regorafenib in metastatic CRC.

Abstract 557: REVERCE: randomized phase II study of regorafenib followed by cetuximab versus the reverse sequence for metastatic colorectal cancer patients previously treated with fluoropyrimidine, oxaliplatin, and irinotecan

The other study that was also interesting and intriguing was the REVERCE trial. This was a Japanese trial, so it did not include any non-Japanese patients. This study had the primary intent of looking at regorafenib followed by cetuximab versus the reverse sequence for patients with metastatic CRC previously treated with fluoropyrimidine, oxaliplatin, and irinotecan, based on the results of CONCUR. CONCUR was an Asian study that looked at regorafenib versus best supportive care in patients with refractory metastatic CRC.

CONCUR had fewer patients pretreated with cetuximab and bevacizumab, given that in that part of the world, there is less access to these biologics.

Historically, the results of CONCUR look much better than CORRECT historically, which suggested that perhaps if you move regorafenib a little bit up the line, you may see improvements in the deltas in OS and PFS that are more meaningful.

REVERCE: Study Design and Endpoints

The gist of the study is comparison of regorafenib before cetuximab or cetuximab followed by regorafenib in patients who failed 5-FU fluoropyrimidine, oxaliplatin and irinotecan.

The primary endpoint of this study was OS. So this was a Phase II randomized study that was powered for overall survival, sizeable in some ways, so a large Phase II – 180 patients. Those patients were *KRAS* wild type. And patients again, if you look at the schema, were randomized to regorafenib standard 160 versus cetuximab. There was the option for physicians to add irinotecan. When patients progressed they crossed over to the other arm. Secondary endpoint was the typical PFS, time to treatment failure, and overall response rate, among others.

Intriguingly, the study ended up meeting its primary endpoint with OS much better with regorafenib followed by cetuximab rather than cetuximab followed by regorafenib, 17.4 months versus 11.6 months, respectively, which translated to a hazard ratio of 0.61, and that was statistically significant. Progression-free survival results confirmed that cetuximab had its benefit preserved, whether given before regorafenib or after, whereby regorafenib had a much bigger effect if given prior to cetuximab rather than after cetuximab.

As with all phase 2 randomized studies, we have to be careful about overinterpreting the results, but it was intriguing enough that it did suggest that perhaps regorafenib could be considered, not “should be,” but could be considered prior to cetuximab in certain circumstances or instances, until we confirm this further.

Overall Survival

OS was incredibly intriguing, and PFS curves suggest that regorafenib may have a wider benefit if given a little bit earlier rather than later. The safety and quality of life were also comparable in both arms.

Author Conclusions

Overall, two studies suggesting that regorafenib does have a meaningful role in refractory metastatic CRC and perhaps should be considered in some instances to be moved a little bit up the line rather than be the last line of therapy.

John Marshall: Dr Saab, thank you very much. These two studies have significantly changed my thinking about regorafenib. First, it is not a drug that can catch a falling patient, but it is a medicine that, if patients are doing okay, can extend their outcomes well.

Discussion: Clinical Practice Implications

Clinical practice implications of these studies include how important it is to match the patients to the correct treatment. The second piece is determining the right dose of regorafenib. The ReDOS study is important to me, because I feel I can now use this medicine with more control over toxicity or without having a major problem with toxicity. I find myself using this medicine earlier, before I am recycling chemotherapy, and quite honestly sometimes even in the secondary maintenance phase with patients, so I am playing it earlier.

Dr Bendell, tell us what you think about these data and how they are affecting your practice?

Discussion: Clinical Practice Implications (cont.)

Johanna Bendell: I have to commend Tony and Axel and the rest of the investigators for this study, because I think it is showing us what we long thought. When regorafenib first came out, the 160-mg daily dose was really tough on our patients, and when we started them off at this high dose, sometimes they would have toxicity and would even refuse to take the treatment from that point on. Or we got patients who got really sick, so I think a lot of us were starting at lower doses, and then potentially ramping up. I love this study for actually showing us that is probably the right thing to do.

What I do in practice is start at 80 mg, or 120 mg in a younger, sturdier patient, and then I ramp up the dose, just as done in the ReDOS study.

Discussion: Regorafenib Before Anti-EGFR

John Marshall: Dr Saab, are you thinking about using this before an EGFR based on a phase 2 randomized trial?

Tanios Bekaii-Saab: The answer is yes and no, depending on the setting. We are talking about *RAS* wild-type tumors and assuming *BRAF* wild-type tumors, although *BRAF*-mutated tumors will probably never make it to regorafenib for most. There are about

15% to 20% of those patients who actually do, surprisingly, much better than expected, but overwhelmingly this is not the case.

In the *RAS* wild-type left-sided tumor, the answer is no, and I am moving those EGFR inhibitors to earlier lines, so if it is not first, it is definitely second.

For right-sided tumors, this is a different consideration. If we look at the EGFR inhibitors, specifically cetuximab, at least from CLGB80405, the way I interpret the data is that for tumors on the right side, there is no benefit from cetuximab, and perhaps even a slight detriment. The OS in CRC in the EGFR arm was less than what we have seen since 2000. For those patients, I may consider regorafenib before cetuximab, based again on individualized cases, but this could be, until confirmed in another study, the only instance where I may use regorafenib prior to cetuximab or panitumumab. In all other situations, I wouldn't.

Discussion: Regorafenib Before Anti-EGFR? (Cont.)

John Marshall: Dr Bendell, any comments on that sequence with regard to EGFR and regorafenib, given the new data?

Johanna Bendell: I think this is a very interesting study from Japan of cetuximab and regorafenib sequencing. It is a small study, so we have to take that into account. I think it is very hypothesis generating, with the thought that maybe the sturdier patient will do better on regorafenib, so provide it more benefit earlier on as opposed to receiving cetuximab-based treatment.

I hadn't really switched my practice at this point, because I more give cetuximab or an EGFR inhibitor in combination with irinotecan, but I think that it is not completely practice changing, but I think it is very reasonable to consider giving regorafenib first.

Discussion: Prescribing a Dose Escalation

John Marshall: Then one last point I would like to raise on this is this new strategy, starting somebody at 80 mg and then dose escalating depending on how they are doing—has created a new kind of issue for us. One is the prescription itself. Do you write for 80 mg, or do you write for 160 mg because the mechanics of prescription has become tricky? We also have to remember that a vial of regorafenib has about 40 days of stability once opened, so you may not be able to order stock and let it sit on the shelf.

The second issue is scheduling patient visits. I have been saying to them, "I want to see you in a week to do some chemistry panels and liver function tests, check your hands, and then I want to see you a week after that." I can be a little less tight in subsequent cycles. Has anybody found out a better way to do this? Dr Saab?

Tanios Bekaii-Saab: Unfortunately, at this point in time, at least for the first cycle, we are bringing patients in weekly to assess them, and the clinics are writing the script for 160 mg with instructions about how to take the pills. The prescription itself remains stable at 160 mg, so there will be no confusion. They will have enough pills, but we see them weekly. Occasionally, we have let some patients show up in 2 weeks, as long as the nurse, nurse practitioner, or my pharmacist checks on them and reminds them to escalate. That is less optimal.

The optimal way to do it if you can, is to see them on a weekly basis. The physician doesn't really need to see them; it is really the nurse practitioner. You can argue oncology nurses can do it as well, but that is only in the first cycle. You figure out the right dose for those patients and then they go on cruise control.

John Marshall: Dr Bendell, do you have any special way you have figured out how to do it in Nashville?

Johanna Bendell: I don't know that we have all the answers here in Nashville, but the way we do it is very similar to Dr Saab's. I tend to, in patients where I am not at all concerned about adherence, I do write for the 160-mg dose and then give them very specific instructions about starting at 80 mg for a week and having the nurses check in. I actually see patients after 1 week of treatment just to see how they are doing, give them very specific instructions on when to call in—significant fatigue, any signs of hand-foot syndrome—so we are ready to hold the dose if we need to. I find that most people who start at 80 mg don't need to hold the dose. We bump up to 120 mg the next week, and we give them a call or have them come in, depending on the patient. It is very patient-based

It is all a matter of close follow-up, close communication, and very good education with the patients.

Tumor Characteristics

Tanios Bekaii-Saab: As we start to apply comprehensive genomic profiling on almost all our patients with CRC, and in most cancers, the issue of tissue versus blood comes about.

Abstract 569: Comprehensive genomic profiling of ctDNA in patients with colon cancer and its fidelity to the genomics of the tumor biopsy

There is a significant interest in trying to move to profiling our patients through circulating tumor DNA, which certainly has its convenience, but also has its limitations.

Abstract 569 looked at comprehensive genomic profiling of circulating tumor DNA in patients with CRC and its fidelity to the genomics of the tumor biopsy.

Study Design

This study was designed to look at hybrid-capture–based genomic profiling in 62 genes on circulating tumor DNA. This was a small study— 91 patients—and the fraction of circulating tumor DNA in the blood was estimated using maximum somatic allele frequency. The frequency of the alterations were compared with those from tumor samples from the same patients, tested again with comprehensive genomic sequencing.

Concordance Between ctDNA and Tumor Profiling

Concordance between circulating tumor DNA and tumor profiling in CRC patients used Foundation-ACT (F-ACT, which is the liquid) and FoundationOne (F1), which is the tumor sample per alteration for insertions/deletions and substitutions, looking specifically at the NCCN-mandated alterations for CRC, with less than 60 days between F1 and F-ACT. There was a 92% concordance. The patient numbers are pretty small—15 patients, depending on the level you are looking at, from zero to 0.5%

Author Conclusions

The authors concluded there was a concordance between tissue and blood genomic profiles that was pretty high—more than 90% in NCCN-recommended genes *NRAS*, *KRAS*, and *BRAF*, and that certainly is very interesting. It is not 100%, but close enough.

Not surprisingly, it was noted that those patients with Stage IV cancer, whom you would expect would have a larger tumor burden, had more circulating tumor DNA than earlier stage patients.

Some patients who may be eligible for clinical trials require the availability of *NRAS*, *KRAS*, and *BRAF*. We didn't have the tissue because the patient came from a different institution. Time is often of the essence, and we have actually ordered a circulating tumor DNA test, one of the commercially available ones, which allows us essentially to get these alterations, find them, and move the patient to a clinical trial. There are very few instances in CRC where you won't have tissue, and so the applicability of this, at least as a pretreatment diagnostic test, is probably less in this particular cancer. Its utility may be to follow-up on the alleles, the clones, etc., but at this point of time, this study is very encouraging in terms of letting us know that we could safely order this test and have a good level of interpretation that is likely to match what is going on in the tissue sample.

John Marshall: Thanks so much for that, Dr Saab.

Discussion: Clinical Practice Implications

Dr Bendell, are you using circulating tests at all, ctDNA, kind of tests, in your practice, whether it is for inclusion on a clinical trial, or monitoring, as Dr Saab suggests?

Johanna Bendell: I haven't been as much into the uptake of blood-based tumor testing outside of a clinical trial. I think we are not at the place where lung cancer is yet, where you can really have good reliability in knowing that your blood-based assay is going to give you what a tumor-based assay will give you in terms of answers, so I have not been using as much blood-based testing. I think our hope is that we will eventually be able to use circulating tumor DNA-type testing.

Discussion: ctDNA Profiling

John Marshall: I have to say, I am worried about a 90% concordance rate, as you referred to it. Particularly with EGFR-targeted therapy, where we have some evidence that if you are wrong it might grow the tumor faster. We know about tumor heterogeneity, so we all want this kind of circulating test, but I think we may all agree that tissue-based testing is still the gold standard while we are watching for these blood-based tests to evolve. Dr Saab, what do you think?

Tanios Bekaii-Saab: I think tissue-based testing remains queen or king. This remains our gold standard. It is important to get tissue that is within a year from the institution of treatment, at least prior to initiating any chemotherapy, because some profiles change, although we can argue *KRAS*, *NRAS*, and *BRAF* are really pretty stable across tissue, and tissue-based testing remains the gold standard until we get concordance with blood-based testing closer to 100%.

Tumor Characteristics

Johanna Bendell: The concept of tumor sidedness has really become an issue now for patients with CRC. We have always known from multiple randomized studies that patients with right-sided CRC tend to have a poorer prognosis than patients with left-sided CRC, and now we even think that we may be able to differentiate treatment regimens based on the sidedness of the cancer. It probably has something to do with molecular biology, but there may be other factors in play.

Abstract 558: SCOT: tumor sidedness and the influence of chemotherapy duration on DFS

We saw at ASCO-GI 2018 three abstracts that looked at tumor sidedness. The first one was from the SCOT study; this was part of the overall IDEA study, which was the worldwide study that looked at 3 versus 6 months of adjuvant chemotherapy.

In the Scottish, or the SCOT study, they looked at both the Stage III patients as well as the high-risk Stage II patients, and what they looked at in the data that they presented at ASCO-GI this year was sidedness in terms of 3 versus 6 months of treatment.

SCOT Design

One thing that we have known, and this proves it to us again also in the earlier stage setting, that patients with right-sided tumors do have a worse disease-free survival at 3 years, 80% for the left sided and 73% for the right sided.

Kaplan-Meier plot of DFS by sidedness

Even if they adjusted for tumor and end stage, because thinking that the right-sided tumors might be caught later because the stool is still liquid on the right side of the colon, so are they caught in a more advanced stage and therefore have a poor prognosis? When they adjusted for those, it improved the outcomes for the right-sided patients, but it did not completely account for that difference in three-year disease-free survival. Something to really remember is that there may be something intrinsic to the right-sided colon cancers that portends a poor prognosis.

Author Conclusions

They also looked at 3 versus 6 months of treatment, and really you don't need to take the tumor sidedness into consideration when deciding on 3 versus 6 months, because it didn't really impact or make any difference between using the shorter versus longer in terms of sidedness.

Abstract 742: Sidedness, mutations, and survival in Stage IV colon cancer: a U.S. population-based study

A US-based trial looked at patterns of care using data from the Surveillance, Epidemiology, and End Results (SEER) data registry, and they looked at sidedness, microsatellite instability (MSI) status, and *BRAF* mutational status.

HRs for Stage IV colon cancer patients who were tested for *KRAS* and received any chemotherapy by sidedness (n = 587)

What the investigators observed is that patients with right-sided tumors were generally older, female, more likely to be African American, more likely to have poorly or undifferentiated tumors, and had higher microsatellite instability, or MSI high, about 14% versus 7% for left-sided tumors.

Author Conclusions

Looking at the very large dataset from SEER data registry, investigators saw that right-sided tumors were more likely to be *RAS* or *KRAS* mutated and *BRAF* mutated, a lot of poorer prognosis factors being associated with right-sided tumors.

They also observed what we have seen in randomized clinical trials, that treatment with EGFR inhibitors is associated with better survival or less chance of death from disease in the left-sided tumors than in right-sided tumors.

Abstract 830: Predictive value of primary tumor location (TL) in patients (pts) with *PAN-RAS* wild-type (WT) metastatic colorectal cancer (mCRC) receiving chemotherapy (CTX) with or without cetuximab or panitumumab (C/P): an updated meta-analysis

Abstract 830 reported on predictive value of primary tumor mutation for people receiving chemotherapy with or without cetuximab or panitumumab.

Study Design

This meta-analysis reviewed the literature on randomized controlled trials of cetuximab or panitumumab and chemotherapy plus or minus cetuximab or panitumumab that looked at outcomes in left- or right-sided CRC. The review included three first-line randomized controlled trials and one second-line randomized controlled trial.

Author Conclusions

What they saw here was very consistent with other data that we have seen, and that we have just discussed, from the SEER data registry, which is that when you give an EGFR inhibitor with chemotherapy both first line and second line, there was a significant OS benefit for patients with left-sided tumors, with a hazard ratio of 0.76, as opposed to no significant benefit for patients with right-sided tumors.

Discussion: Tumor Sidedness

John Marshall: That was a terrific review of those abstracts, Dr Bendell. Dr Saab, how is all this right-sidedness, left-sidedness shaking out for us today as we the cross it with molecular testing?

Tanios Bekaii-Saab: I think these studies just continue to confirm pretty much our clinical practice and continue to confirm that EGFR inhibitors have a prime role on left-side tumors. Interestingly, when we think about the earlier stages, the presence of left versus right sidedness, it seems to also predict for prognosis, which is something we knew all along for 20 to 30 years. This just shows it in a prospective way that patients with left-sided tumors do better than patients with right-sided tumors, and the patients with right-sided tumors are more likely to progress and to progress earlier.

On the other hand, what the cumulative knowledge from these studies suggests is exactly what we do in the clinic; we can still get some benefit from EGFR inhibitors on the right-sided CRC, except for OS. It seems that you may see some additional response on PFS, but not necessarily a survival benefit. This goes back to the question on the right-sided CRC, can we still use EGFR inhibitors? The answer is yes. The next question is when do you use them? My bias on this is I would wait for at least to give them regorafenib, perhaps even test one or two, before going on an EGFR inhibitor on the right-sided, wild-type tumors.

John Marshall: I really like that adjuvant analysis, because we have had this tendency that when there is a patient with a bad prognosis, and now we are adding right sidedness to that list, that we should give them more chemotherapy, that we should treat them more intensively. What is really nice about that is it says "Yes, you have a bad prognosis" or a worse prognosis, and more chemotherapy is not going to change that. That is a really important message from me.

Discussion: Toxicity

What I am really struggling with, and I would love to hear your take on this, is that whether it is FOLFIRINOX/bev (leucovorin, fluorouracil, irinotecan, and oxaliplatin plus bevacizumab) or left-sided *RAS* wild-type, *BRAF* wild-type EGFR therapy, we have had this bias—maybe different from our European colleagues—that yes, we know there is a survival benefit, or a response rate benefit, but we don't like the toxicity, so we are willing to forego randomized proven survival response rate benefit because of toxicity. I wonder if there are other disease areas where we pass by a more effective regimen because we are worried about toxicity? Are you struggling with the same issue, Dr Saab?

Tanios Bekaii-Saab: Yes, it is a tough one. I think about it every time I see a first-line metastatic CRC patient, with left-sided, *RAS* wild-type cancer, and for the past 10+ years that is how we have been thinking. Our European colleagues have essentially been a little bit more flexible in testing the waters, so I still see that reluctance and frankly, even with the discussion with the patients, I think we overemphasize the toxicities because that is our own bias into it, and that is how we lead them on.

Slowly but surely, we are trying to shift this a little bit, especially in the better-performing patients, to consider an EGFR inhibitor earlier on, in first line, in those patients where we think there may be a much bigger benefit, but I do struggle with this.

John Marshall: Dr Bendell, what do you think? It seems to me that we should either be giving FOLFIRINOX/bev or some sort of EGFR-targeted therapy in first-line treatment, because those are our two best regimens; what is your reflection on that?

Johanna Bendell: In terms of EGFR inhibitors with chemotherapy, I think there are very good data there. I think when you look at the numbers and the curves from the different studies you see that a lot of it is being driven by a small population at the tail end of the curve, and I think that we are really obligate to try to figure out who those patients are, not just *RAS* wild-type, because there are probably other factors in consideration.

I think FOLFIRNOX/bev is a great regimen. We have seen even hints toward maybe some suggestion that the survival data may be better using FOLFIRNOX/bev versus a doublet chemotherapy with bev in the first line, but knowing the toxicities that are associated with this regimen, you want to also keep it for a hardier patient. We go back and forth about the marathon of treating metastatic CRC. Certainly we want to maximize overall survival, but we also want to maximize quality of life, so we have to take those into consideration when thinking about what regimen to choose.

Although I think FOLFIRNOX/bev is a great regimen, and again, in the TRIBE study, after about 6 months of treatment, they went onto maintenance therapy, thus the duration of the intense chemotherapy is shorter with the use of maintenance, I still think you have to think about reserving that for your hardier patient. We spoke about with the EGFR-associated rash: is that something patients want to have for approximately a year of their life when they are first diagnosed with CRC? All of these are discussions and things to consider when you are talking with your patient.

Final Discussion: Key Insights in mCRC

John Marshall: Dr Bendell, we think of you as one of the great leaders in new drug development. Results from your study, cobimetinib versus atezolizumab, were negative; we are sorry. We wanted that study to be positive. How are we moving forward in the world of metastatic CRC today? What are some of your key insights there?

Johanna Bendell: A lot is going on in terms of CRC. We are doing a lot more research. You alluded to the cobimetinib plus atezolizumab study, which has now been disclosed to be a negative trial, but I think I want to come back to the original data that were presented, suggesting that maybe there is a population of microsatellite stable patients that we could potentially convert to responders to immunotherapy if we give them the right combination. Maybe that wasn't cobimetinib plus atezolizumab, but maybe there are other immunotherapy combinations which are currently in phase 1 treatment and are being developed that might be able to impact survival for these patients. Certainly, we have new molecules that have also shown interesting preliminary data, including the bispecific antibodies, like CEA-TCB, where you take one part of the antibody binds to a T-cell receptor

and the other part of the antibody binds to the tumor, trying to bring the tumor and T cells together.

We also have researchers doing work on solid tumor CAR-T therapies. We have personalized cancer vaccines, so even though the atezo-cobi study was negative, there is still so much hope right now in terms of drug development for patients with CRC. I think we are going to see a renaissance happening soon, as we start to do more profiling of our patients, and also developing more therapies, or next generations of immunotherapies to come.

Final Discussion: Personalized Medicine

John Marshall: Dr Saab, we talked about molecular profiling, what is your thought about personalized medicine? I know you are running a big clinical trial around the country called COLOMATE. I want it to be GIMATE; can you talk a little bit about how we are taking precision medicine and applying it to CRC?

Tanios Bekaii-Saab: Dr Marshall is also a big part of that effort. This the COLOMATE effort, which we already are starting, and it continues to be adapted.

It is essentially geared to the molecular richness heterogeneity of CRC and breaking it down into multiple subsets, so we know that there are some subsets that are very relevant, beyond MSI high immunotherapy, beyond *RAS* and beyond *BRAF*, we have *HER2*, we have *FGFR*, and in 4% to 8% of patients, we have *MET*. Every patient who progresses on a couple of standard of care therapies and then moves on to COLOMATE gets screened either by liquid-based testing or by tissue-based testing, although we will collect both liquid and tissue. We want to confirm that we are seeing these two as they have clinical relevance. They get assigned to different therapeutic arms, and these arms are powered individually to give us information about response or PFS.

We also have arms that essentially measure the emergence of clones and alleles, EGFR related, and re-challenge them with EGFR inhibitors. We also have innovative immunotherapy arms, BRCA, VUS, so really trying to look at every piece of CRC, every little piece of colon cancer, and see if we can match it with a therapy. I think this is really where the field is moving. We have enough of just asking the same question, right versus left, EGFR versus VEGF-3 versus 2; we have been asking those questions for 20 years. At this point of time we need to be more and more granular and make, essentially, CRC a disease that is driven by personalized treatment approaches.

John Marshall: I am very excited personally about a new area of science that, frankly, none of us knows very much about, and that is the microbiome. The more we

are looking at the bacteria that are involved in our GI tracts, we are recognizing the role they play in immune therapies, we are recognizing the etiology of colon cancer in some ways depends on the microbiome, so I am excited as we look forward, of understanding a lot around precision medicine, around immunotherapy, that the microbiome will teach us new lessons.

ASCO-GI 2018 Key Messages

Thanks very much for joining us. Let me do a quick, high-level summary about the data we have just brought forward from ASCO-GI 2018.

First, in the right patient, those with *RAS* wild-type/*BRAF* wild-type CRC, panitumumab and cetuximab are very much the same. Panitumumab may have a subtle outcome advantage, but these studies were not huge, and we can't say that for sure. They certainly have slightly different toxicity profiles, but in all of our opinions, they are basically interchangeable. One of the most important pieces of new data that Tony brought out was all about dosing of regorafenib and sequencing, and I really think this shifts our thinking about how much and when to use regorafenib. Earlier lines of therapy seem appropriate, start-low-go-high on the dosing.

Then, of course, we all know the story about right versus left. We need to understand that this is playing in the adjuvant setting as well but does not mean one should give more intensive chemotherapy. We certainly know it is a factor in choosing biologics, both on the left-side, with the inclusion of EGFR therapy, on the right-side, excluding or at least delaying EGFR therapy to later lines of therapy.

One of the most exciting areas is trying to get better biomarkers and the review that circulating tumor DNA is useful, not perfect in a field that is evolving. I think for CRC, we tend to base initial diagnosis on the tissue, where the role for circulating DNA will come in the future and will ultimately be useful. We are going to be using this kind of analysis in the selection for upcoming clinical trials, so you should be aware of it.

Thank you, Tony and Johanna, for this amazing discussion. I love working with you guys day in and day out, and thank you to our supporters for putting together this CME program. We hope it has been useful for you, and we hope it affects your practice and makes you a better doctor in the future.

[*Ends*]