

Perspectives in the Treatment of Colon Cancer with Leonard Saltz, MD



LEONARD SALTZ, MD, is a medical oncologist at Memorial Sloan Kettering Cancer Center. Currently as the head of the gastrointestinal (GI) oncology service, Saltz has a career of over 28 years involved in developing new therapies for colorectal and other GI malignancies.

AJMC®: What defines targeted therapies in cancer treatment?

SALTZ: I can make a coherent argument in that there is no such thing. I mean let's look at what we use for metastatic colon cancer. There's 5-fluorouracil, a drug that is going to turn 60 years old in the next month. Most people would not call that a targeted therapy, which just shows you how meaningless that term is because we know the target—it targets thymidylate synthase. Because we know what it targets, it just represents chemotherapy, all chemotherapy has a target. Irinotecan, another cytotoxic, targets topoisomerase I but we don't think of that as targeted therapy. Oxaliplatin cross-links DNA also, so I don't think that's what anyone has in mind. Now let's get to the newer drugs. Cetuximab and panitumumab latch onto the EGFR [epidermal growth factor receptor] and the hypothesis had been that that's the target and people who had more of that target would be more vulnerable and people who didn't have that target wouldn't be vulnerable, and that has turned out not to be true. I don't think cetuximab or panitumumab are any more or less targeted than 5-fluorouracil. We just happen to know what they interact with on the cell. And, most people have turned the more modern term of targeted therapy as precision medicine or personalized medicine. Well, we can personalize it a bit in that we look for mutations in the *RAS* gene in the tumor and if we see them, we see that the EGFR targeting drugs won't work.

AJMC®: What is the current role of genetic testing in colorectal cancer and which tests are done clinically?

SALTZ: There are a few things that need to be considered standards in colorectal cancer. Probably the most important thing is testing the tumor for the presence of microsatellite instability, also referred to as mismatched repair deficiency. This is a critical factor now because although a very small percentage of metastatic colorectal patients will be mismatch repair deficient—it could be as low as 2%, for those people—the PD-1 [programmed death 1] inhibitors are extremely effective. We need to be sure we are not missing the opportunity to help those people. Patients with the far more common mismatched repair proficiency or microsatellite stable disease do not benefit from currently available standard immune checkpoint inhibitors. So, it's a very small subset, but we need to identify this subset. There is confusion because mismatched repair deficiency is present in about 15% of all diagnosed colorectal cancer, but most of those people have a good prognosis and never get to metastatic disease, so by the time you get to the treatment of metastatic disease, it's nowhere near 15% and it's somewhere between 2% and at best 4%. So, that's one molecular study. The other issues are basically exclusionary markers. We look at *KRAS* mutations, *NRAS* mutations »

and *BRAF* mutations, all of which are indicators that the EGFR inhibitors, cetuximab and panitumumab, are not going to be effective and be counterproductive. And so, when we see those markers, we take those drugs out of consideration for treatment. *BRAF* is potentially something that may be targeted in the future with combination of EGFR and *BRAF* inhibitors, but thus far, there has been modest activity in clinical trials and that combination is not either FDA approved or in the NCCN compendium so it can't be considered part of standard practice. Those are probably the ends of standard molecular markers at this point. There is interest in whether the very limited population that have expression in HER-2 might be treatable with HER-2 targeted

therapies but that too is something investigational and not standard practice, not something that one can prescribe as standard billable for routine practice. It is not FDA approved or recognized in any compendium recognized by Medicare. Other than that, there are questions about whether next-generation sequencing assays looking for actionable mutations is something that we should be doing for patients and I think the answer is that if you are in

a research setting and you have access to research trials with specific targeted inhibitors, that's something worth pursuing. But thus far, that is not something we consider part of standard practice because we don't have actionable mutations that we have standardly available drugs.

AJMC®: In terms of reimbursement for genetic testing in colorectal cancer, what is the current policy you have seen for broad panel testing, including next-generation sequencing testing versus genetic testing paired with treatments?

SALTZ: So, I'm not an expert in this topic but I'll give you some general comments. I think it's clear that people don't need to be constrained to the specific paired approved test

for the FDA. For example, any test for *KRAS*, *NRAS* and *BRAF* is acceptable. However, the question of whether a NGS [next-generation sequencing] assay is approvable or not is one that I don't think has been adequately answered and I think if one is assaying for the standard billable targets, *KRAS*, *NRAS*, and *BRAF*, and uses a NGS assay to do so, that's probably okay as long as one is billing for the identified standard targets. I don't think it's considered a billable standard practice to do broad NGS assay in cancer right now, and I don't think colorectal cancer is unique one way or the other.

AJMC®: What are some of the advantages of doing a broad assay if one is able to and how does that data potentially help inform future treatment?

SALTZ: A lot depends on what you know before you get your NGS assay. Our approach here is to use our NGS assay to get the standard information and we are also able to get the mismatched repair deficiency information or the microsatellite instability from the NGS assay. So, we can do one assay where we get microsatellite instability, we get *KRAS*, *NRAS*, and *BRAF*. That's what I can say is useful and that I can say is standard practice. To prescribe appropriate medicine and meet standard expectations, you need that information. The other information that we can use in the context of being a research center with a robust drug development program is to try to pair people with rare mutations to drugs we have in development to match them, but I can't say it's part of standard practice.

AJMC®: What standard setting organizations are most important in determining coverage of treatment?

SALTZ: FDA approval or NCCN compendium listing is where you have the option to proceed. Going beyond that, you would need a third-party payer to approve it. The reality is that, the newer drugs are extremely expensive. We can't ignore that reality. That is a factor that undoubtedly would be considered under the third party that would be considering paying for it, and

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it is highly prohibitive to any individuals choosing to pay out of pocket, because most people simply don't have that much money. If you take a look at the idea of treating a *BRAF* mutated colon cancer with a commercially available *BRAF* inhibitor plus *MEK* inhibitor plus *EGFR* inhibitor, realistically you will be in the drug cost range of \$35,000 to \$40,000 a month. I think that "wow" is the usual response to that fact that people choose not to look at, and it is naïve of us to pretend that numbers like that are not going to go into factor in terms of consideration. Another very important thing for people to understand is, if you are treating a Medicare patient and you send in a bill and Medicare pays it, that doesn't mean that Medicare approved it. The approval process and the paying process are siloed separately, so they can come back and audit that at any time and determine that that was inappropriate, and call back the payment to cause damages.

AJMC®: What are some key takeaways that managed care professionals need to take into consideration to help oncologists and patients?

SALTZ: We want to make sure that we use the drugs that we have responsibly and appropriately to optimize care for patients. We have to be aware that we don't have the option to simply pick any drug we want and use it because we think it makes sense if it's not an approved indication, unless someone is able to absorb the substantial financial consequences of that. So, when we talk about the use of NGS assays and targeted therapies, we need to realize that outside of an experimental trial, that kind of thing is not something we practically can do, nor do I think we necessarily should because we don't know if it's the right answer. When you look at the published reports of the identification of actionable mutations, many of them, which are being published often by the companies that are providing and marketing the assays, define *RAS* mutation as actionable. I think that's not an appropriate way to define them. They are a bad thing to find, and we don't have an effective treatment for patients with *RAS* mutated tumors. We can say that we thought that *MEK* inhibitors were going to help, but the data don't support that. So, if we look for other putative actionable mutations; let's say we found a mutation for a particular gene, and there's a drug out there, for instance, I found a *CDK* mutation, and I had a hypothesis that palbociclib would be a useful treatment. There are no data, so the assumption that just finding the target means that I can use a drug and that drug will be meaningfully beneficial to the patient is incorrect. This would only be appropriate in a clinical trial that would generate data. Ultimately, we have to have data to tell us where drugs with

significant toxicity and significant cost are appropriate to use in a patient and where they are not.

AJMC®: In terms of genetic testing, how important is it to get genetic testing early on in the disease?

SALTZ: We rarely have genetic testing back before we initiate first-line therapy because the turn-around time takes a several weeks. I don't think that matters because I don't believe the data supports the use of first-line *EGFR* inhibitor in *RAS* wild type patients. That's the only information that would guide a first line decision. I published a piece few years ago, in *JAMA Oncology* on this topic, where it pointed out that the largest clinical trial on the topic is the intergroup 80405 study, which directly looked at front-line chemotherapy with either cetuximab or bevacizumab in *RAS* wild type patients, and it did not show a meaningful difference in terms of outcome. But the toxicity of *EGFR* agents is very difficult for people to tolerate front line. At the doses that are routinely used are twice the cost, so I don't see a reason why I would want to use these upfront. I think that we need to be obtaining the molecular information on mismatch repair status, *KRAS*, *RAS*, and *BRAF* when we initiate the care for the patient with metastatic disease. I would emphasize that thus far, we don't have any role for looking at *KRAS*, *NRAS*, *BRAF*, or any other genetic mutations in stage I, II and III disease. So, I am often puzzled when somebody refers a patient to me and says they have stage III *KRAS* mutated colon cancer, I wonder, "Why do we know that?" To me that's not an appropriate test to have sent. It is only in the setting of metastatic disease that the *RAS* information becomes relevant.

AJMC®: What is the role of potential adverse events with various treatment options in selecting appropriate therapy for each individual patient?

SALTZ: We have to think carefully about that one. We have reasonable choices. For example, front-line therapy is often based on either irinotecan-containing or oxaliplatin-containing regimens. The toxicities are different, while the effectiveness is very similar. The neuropathy of oxaliplatin would be much more of a problem to some people and less to others. Irinotecan is much more likely to cause alopecia than oxaliplatin. That may be irrelevant to some and very important to others. So, talking with patients can allow us to individualize treatment. Bevacizumab, which we often incorporate into the first-line regimens, is a higher risk in people with significant cardiac disease, and don't want bevacizumab on board in patients who might need urgent surgery. Those are settings where knowing the side effect profile of the drug might cause me to be more or less likely »

to use it. Cetuximab and panitumumab are only going to be effective in patients who get substantial skin rash. The rash does not guarantee the activity, but the absence of rash virtually guarantee that there isn't activity. We

need to have the patient prepare for that and discuss in terms of that relative risk and benefits, and whether that is the right drug for that individual.

AJMC®: What are other areas that are important for managed care, and if you could send one message to the managed care, what would that be in terms of the treatment of colon cancer?

SALTZ: One has to be aware that we are long past the days where one size fits all. We need to individualize care based on the overall medical and psychological condition of the

patient, who they are, what their preferences are, what their medical comorbidities are, and to some degree, what the molecular characteristics of their tumor are in terms of mismatch repair status, *RAS* mutation status and *BRAF* mutation status.

AJMC®: What do you see is the future of treatment in colon cancer, and how do you see it changing over the next 5 to 10 years?

SALTZ: I hope that some of the newer immuno-therapeutic approaches will show some benefit. It is exciting that immuno-oncology has transformed certain previously resistant tumors, and I hope that we will be able to bring meaningful benefit with immuno-oncology to the majority of the patients with metastatic disease, specifically those with micro-satellite stable disease. It's important to realize that we are not there yet, so that's why I'm hoping the clinical trials will deliver to use over the next 5 years. ■

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