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Released: 12/30/2024
Valid until: 12/30/2025
Time needed to complete: 1h 14m

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Novel Neoadjuvant and Adjuvant Immunotherapy Strategies for GI Malignancies: The Evidence

**Announcer:**
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**Dr. Venook:**
This is CME on ReachMD. I'm Dr. Alan Venook. In this brief lecture, I'll review some of the novel neoadjuvant and adjuvant immunotherapy approaches that are used in gastrointestinal malignancy patients. I'll talk a bit about gastric, hepatocellular, and colorectal cancer.

A good example of studies that have been done into great detail so far is in gastric cancer. We're in a classic study. The KEYNOTE-585 looked at the role of neoadjuvant treatment with pembrolizumab and chemotherapy in locally advanced patients with both gastric or GE junction cancer. In a study by Shitara published just recently in *Lancet*, they demonstrated that if you combine chemotherapy, whether FOLFOX or FLOT, with pembrolizumab or, on the other side, patients getting a placebo, the likelihood of a complete pathologic response was dramatically improved when pembrolizumab was added to the chemotherapy, whether FLOT or FOLFOX, to the point of a P value of less than 0.00001, pretty remarkable result.

However, and one of the sobering things about immunotherapy that we need to know more about, is in that study, even though there was a dramatic difference in pathological complete response, there was no overall survival then. That was demonstrated by Shitara recently, and very, very discomforting, because we expect progression-free survival or responses to translate into long-term benefit.

So is it possible that the immune therapies give us something in the beginning and then we lose it at the end as the disease progresses? Not clear. But a sobering finding, obviously something that we need to think about as I'm talking about other uses of the immunotherapies, which are more and more being looked at in the neoadjuvant setting.

A similar example is in the MATTERHORN study. This is by Yelena Janjigian, which is also looking, in this case, at durvalumab in these same population of patients. Again, the role of neoadjuvant or adjuvant, and remains to be seen in this study, but we await results to see how that will impact outcome.

Then finally, in another study, very similar to these, looking at the use of tremelimumab and durvalumab in MSI-high gastric cancers. And these are patients you might expect to respond to the checkpoint inhibitor with durvalumab. This study has looked at pilot data so far, at least, in a complex study, which so far suggests that patients, again, are likelier to have a pathCR with the lower stage they are, but many patients will go to pathologic CR in this setting, again, with MSI-high disease. And remains to be seen, though, to be tested definitively in a randomized trial to see if patients do better.

So the message in gastric cancer, at least, is the treatment seems to improve the initial result or the initial decrement in cancer tumor. It's not clear, though, that it improves outcome down in the long term. That may have to do with the biology of gastric cancer as a

dominant issue in terms of finding the maximum impact of this therapy.

Now, hepatocellular carcinoma is also being studied in the same setting, and that is the so-called EMERALD-2 trial. We're also awaiting results. In this case, this is as adjuvant therapy following resection of hepatocellular carcinoma.

What I think of the most exciting, most interesting result, and that is of the NICHE trials, NICHE-1 and 2. This was work done by Chalabi in Italy, and published first is so-called NICHE-1, which these are patients who got one dose of a checkpoint inhibitor and an anti-CTLA4 treatment. And just after one dose of each and 6 weeks later going to surgery, the majority of patients had major pathologic responses. And then NICHE-2 included a cohort of patients from NICHE-1 and found that, again, in the MSI-high population, almost every single patient had a complete remission, a complete pathologic response in the primary tumor. So MSI-high patients appear to get dramatic benefit from neoadjuvant checkpoint inhibitor, and that certainly could lead to a change in standard of care.

Now, the most fascinating finding, I think, in the NICHE trial, though, is a small cohort of patients who had MSS cancer, that is microsatellite stable cancer, typically not responsive to checkpoint inhibitors. About 1/4 of patients had major pathologic response from the primary. It tells us, of course, that primaries and metastases have different biology, and we may be up against a very different outcome. We're facing very different outcome if we can deal with the primary separate from the metastasis. That's a research question, but again, I think a fascinating observation and one that gives us hope that perhaps we'll find, at some point, the ability to interfere or to use the checkpoint inhibitors in patients who have MSS, microsatellite stable, colon cancer.

And then finally, there's the NEOPRISM-CRC study, which looks at neoadjuvant therapy in colon cancer patients. And that, again, we await the final result for that study.

But in general, I think the important message is that these immunotherapies may play a greater role, or a very important role, in the neoadjuvant setting, although it remains to be seen how it will impact patient long-term outcome.

Thank you for your attention.

**Announcer:**
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