Expert Interview with Alan Venook, MD, on colorectal cancer and the promise of immunotherapy for prevention and treatment

Dr. Alan Venook is a nationally renowned expert in gastrointestinal cancers such as colorectal cancer (CRC) and liver cancer. He is based at University of California, San Francisco (UCSF) and holds the Madden Family Distinguished Professorship in Medical Oncology and Translational Research. He is also the Shorenstein Associate Director for Program Development at UCSF's Helen Diller Family Comprehensive Cancer Center. Dr. Venook has a deep interest in clinical trial designs for the treatment of gastrointestinal malignancies and served as the Chair of the Gastrointestinal Committee of the Alliance for Clinical Trials in Oncology.

Dr. Venook earned his bachelor's degree from Rutgers University, and his medical degree from UCSF. He completed his residency in internal medicine at UC Davis. He joined the faculty of UCSF in 1988.

In this interview, Dr. Venook shares his thoughts on

- His motivation to focus on gastrointestinal (GI) cancers
- A recent study that shows the promise of first-line immunotherapy for rectal cancer (Cercek et al., 2022. New England Journal of Medicine - *NEJM*) and its implications for future treatments and Lynch syndrome patients
- The relevance of the gut microbiome to CRC and cancer treatments
- The shifting demographic in colorectal cancer (CRC)
- Changes in screening recommendations
- How to be an informed patient
- His observations regarding the difference between right- and left-sided colon cancer

Dr. Venook, you specialize in gastrointestinal (GI) cancers and have been in the field for many years. What spurred your interest GI cancers and especially colorectal cancers (CRCs)?
I wanted to work in an area that was really underserved and underexplored, and GI cancer seemed like a good area. Frankly, it was a practical issue of where the opportunities were; finding an area that was open and had opportunities for me. Obviously, I find it very interesting. CRC, particularly, is unique in that it's one of the very few cancers that can be cured even after it's metastasized. We didn't know that when I started and ours was one of the first groups to demonstrate it. We've learned a lot about the disease since I started. We have a lot of treatments for CRC now, but it's a complex disease and we are still playing catch-up. It has been challenging especially with the limits of efficacy of immunotherapies.

On the topic of immunotherapy, what do you think about the recent study (Cercek et al., 2022, see summary below) that treated rectal cancer patients with neoadjuvent immunotherapy and saw complete remission in all patients?

This is the first study I have seen that shows complete remission in every single patient. Nothing's ever hundred percent, so they must not have treated enough patients to see non-

responders. Nonetheless, it's remarkable that every single patient treated went into remission. It is also remarkable that there was no toxicity. I believe that this may be the only journal paper I've ever seen on a clinical trial that had no toxicity. Again, they probably didn't treat enough patients.

Memorial Sloan Kettering (MSKCC) has sort of led the field in what's called “total neoadjuvant therapy” (TNT) for rectal cancer. In TNT, chemotherapy and radiation is done up front before surgery. Memorial had looked at TNT in dMMR/MSI-high patients and found that a surprising number of patients didn't get the full benefit of neoadjuvant chemotherapy, about one out of three did not (Cercek et al., 2020). Based on those results, it seemed logical to flip the paradigm and go with the immune checkpoint inhibitors (ICIs) upfront.

A previous study from the Netherlands (NICHE study) (Chalabi et al., 2020) had looked at immunotherapy in patients with primary colon, not rectal, cancers in a neoadjuvant setting – ICIs given as primary treatment. They took the patients to surgery six weeks in, so, they really didn't get a definitive glance, but they still saw really marked responses.

How long do you think it takes for different ways of treating patients to be adapted into to mainstream care? With the low toxicity seen in this study by Cercek and others, there doesn’t seem to be a lot of harm in trying neoadjuvant ICI.

The short answer is that it depends. If it's a subtle or nuanced difference, it can take a very long time. There’s harm if you're not vigilant and miss opportunities. We have to follow the data, and when the data tells us to make changes, we should go ahead and make changes. But most oncologists don't live and breathe one disease. Therefore they may go with what they're used to, but it’s our job to be ready to turn on a dime.

A lot of cancer care is dictated by the National Comprehensive Cancer Network (NCCN) guidelines, rightly or wrongly. And I happen to be the vice chair of the NCCN panel for guidelines to colorectal cancer and this neoadjuvant immunotherapy will be in discussion. Do we change the guidelines? It's all consensus. It's unusual that a 12-15 patient study could change the standards of care, but I think this is one of the times where, in my opinion, it might. If you change the guidelines, you need to include the proper caveats about exactly what you have to do, the right follow up and surveillance, etc. You can't be nonchalant about it.

A concern in moving ICI up front is that you may miss the opportunity with patients who don't benefit from the ICI but may get substantial benefit from chemotherapy. I think that one of the problems with immunotherapy is that there is truly so much upside to immunotherapy that physicians don’t want to abandon it once they start it. Because they assume it's going to work. They may start with a single agent and if it doesn't work add in another. Then they may see so-called “Pseudoprogression.” I think there are more papers written about pseudoprogression than patients who've actually had pseudoprogression. It's talked about a lot. The danger is that these patients may never get chemotherapy due to physician and patient bias, and that may disadvantage some patients who might benefit from chemotherapy.

Given the low toxicity, how feasible is it to use ICIs in primary prevention for high-risk individuals, such as Lynch syndrome patients who are at a high risk for developing CRC and other cancers?
It is an interesting question. The problem with the ICIs is that they could have major downsides. I have a patient who is a perfect candidate for everything else, got a single dose of the PD-1 blocker Pembrolizumab, an ICI, just one dose, and has essentially myasthenia gravis. The patient had to be intubated and has been in our rehab for four months. Myasthenia gravis is an autoimmune neurologic disease, which is admittedly very unusual, but it happens. Probably one in 25 patients on ICIs have a major consequence, therefore, going into healthy beings with that kind of risk is not tenable.

How good an indicator is the MMR/MSI status in predicting response to ICIs?
As seen in Keynote 177 (Andre et al., 2020; Diaz et al., 2022) and other studies, even dMMR/MSI-high colon cancer is not uniformly responsive to ICIs. However, in the recent Cercek et al., 2022 study, all dMMR/MSI-high rectal cancers responded. Why is that? There are many differences between the colon and the rectum. Memorial Sloan Kettering has collected a lot of biospecimens, so they'll have a ton of molecular data and a real opportunity to figure out the differences.

Can you discuss the relevance of the gut microbiome to cancer therapy? What is your opinion on using the microbiome to predict treatment responses and direct treatments?
We've known that the gut microbiome influences treatment responses for a long time. One of the observations is with the conventional chemotherapy drug, Capecitabine, an oral chemotherapy drug that's used frequently in patients with colon cancer. It was observed that patients in the US tolerate a much lower dose than patients in Europe. Now, we've got quite good evidence that that's almost directly related to the microbiome. Capecitabine is a prodrug that has to be activated in a couple of steps by several enzymes in order to be effective. People can have biota with activating and/or inactivating enzymes. These enzymes can change how the drug is processed and can play havoc with the dosing and predictability of the drug.

The microbiome has a huge impact on the whole immune system. I think that's why the immune therapies may not work well in colon cancer. It's also probably why patients with liver metastases with MSI-high tumors are less likely to get benefits from ICI than those with other sites of metastasis. Because the liver is sort of an immune island.

The problem with the microbiome is that it is very complex. Until the last decade we didn't have the computational power to even sort through it. It is said that there are more microbiota in the microbiome than there are cells in the human body. I don't know who counted them, but that alludes to the complexity of the microbiome.

In the future, I expect the gut microbiome to be incorporated into detection and treatment of cancer. I won't be in the field by then. Jim Allison won the Nobel Prize for ICIs that he'd been fiddling with for 10 or 15 years before he really put two and two together. Hopefully, we will

figure out the microbiome and how it influences the immune system and immunotherapies without taking so long.

What other immunotherapy approaches apart from ICIs do you see as promising? Where does adoptive T cell therapy stand for CRC?
Ideally, you would want to generate a unique CAR-T (chimeric antigen receptor T-cell) for each patient. One challenge is that it takes several months to prepare the T-cells. And you need patients who are Olympic athletes, patients to be in very good condition. These patients will already be having standard therapies, and you hope that they don't deteriorate while the T-cells are been prepared. There is also the issue of efficacy with this therapy. Another problem, with any therapy actually, is that the nature of the disease changes from the time you put a patient on the study to the time you actually get to treat them. This could be a very daunting experience. However, we do have a program at UCSF and we've got some patients who've made it through.

What are the major challenges in CRC space right now?
The biggest issue right now is the preponderance of young people with CRC. For the last decade or so, we've been seeing an influx of young people with CRC. The incidence of CRC in people over the age 60 has gone down dramatically because of screening, but I would say that it's made-up for by the increase in younger people. So, the net incidence is about the same.
A vast majority of cases are at advanced stages like stage 4, because colon cancer symptoms take a while to develop. We probably have two dozen patients in our care at UCSF who are under the age of 40 with advanced CRC. If someone happens to have a cancer that bleeds that is good luck because that could lead to early detection. Otherwise, the cancer can be there for years before its detected. Then, there are times when there are symptoms, but it doesn't occur to the patient or the doctors that it could be CRC.

Is this why some recent recommendations for CRC screening have been lowered from age 50 to 45? Do you think we should make the age even younger?
Screening people starting at 45 is not going to improve early detection. I guess it's better than starting at 50. But it's not going to make a big impact because although there are some cases between the age of 45 and 50, for the most part, the real increase is in 30-to-35-year-olds. The problem with increased screening is that there aren't enough gastroenterologists to do that. Also, when you do many colonoscopies, you're going to increase the chance of complications.

We need to figure out a simple test that can be used to screen for CRC less invasively. For example, a test that would detect protein biomarkers in stool. Or oncRNAs (orphan noncoding RNAs) that are excreted by cancer cells. At a recent conference, I saw phenomenal data from assays that are so sensitive, they can find oncRNAs in the stool. They could be predictive of cancer and therefore can be used for screening and identifying those who then need to get a colonoscopy. But, if it's too sensitive you're going to be putting people through too many colonoscopies.

Factors that increase the risk in the general population have a worse impact on high-risk individuals, such as lynch patients with inherited risk. What are some of the reasons for increasing CRC among young adults that they should know about?
This increase of CRC in young individuals is really mind boggling. It doesn't appear to have anything to do with heritable factors. Interestingly, it also does not appear to be due to the obesity epidemic. It's not only people with bad diets or with fatty livers or metabolic syndromes; we also see otherwise healthy people. We even see patients who are marathoners or triathletes.
The other thing that's even more distressing is the disproportionate impact it's having on people of color. Recently, a famous African American actor died of colon cancer at age 43 - this is not an isolated incident.

Aside from screening to detect cancer early, what are (early) interventions or preventative measures that are available for high-risk individuals?
There is no preventive therapy so far. For people truly at high risk, like with familial polyposis, the only choice is to remove the colon. The problem is the rest of the bowels are at risk for polyps as well. These people will not infrequently succumb to small bowel or other problems.

You've run many clinical trials, what are some of the challenges in planning and running clinical trials?
One challenge is that large clinical trials can take a long time to complete. The CALGB/SWOG 80405 study was launched in 2004 and I presented the results at the American Association for Clinical Oncology (ASCO) meeting in 2014. It was an almost 20-year process with 2300 patients. So, you need to have patients and patience.
It is getting harder to recruit patients for large, randomized trials which is how you would like to ask a good scientific question and be vigorous. But patients will come already decided on what they want based on a relatives' recommendation or an anecdote they've seen on social media. It is harder do a large trial with a control or placebo arm.

How can one be an informed patient?
You want informed patients, but you don't want them to be poorly informed or misinformed. There's so much misinformation on the internet and we are constantly battling with it. It's a real challenge. To me, it's interesting that people may know about pharmacogenetics, how an individual patient's genes effect the way drugs are metabolized. A common chemotherapy for multiple types of cancer is Fluorouracil (5FU). There's an enzyme responsible for metabolizing it called DPYD. Certain rare variants of this enzyme can put some people, maybe 2% or 3% of the population, at greater risk for complications. There's an advocacy group of family members of people who had complications of 5FU who are pushing for everybody to be screened for variants in DPYD. If we test everyone, we will find high-risk variants, but we will mostly find variants that we have no idea what to do with. For patients with these variants, it will be unclear what to do. Do we reduce the dose and run the risk of having a reduced impact on the patient's outcome?

Being informed also means understanding that there are a lot of unknowns. Doctors should be ready to explain to patients why they wouldn't do a test, as opposed to more and more patients demanding tests and getting them done. You should only do a test if you're prepared to do something with the results or know what to do with the results. I wrote an editorial a few months ago about a circulating tumor DNA (ctDNA) test (Venook et al., 2022). It was a blood test to find evidence that cancer was present in the body, but it couldn't tell you where it was located, what you could do about it, etc. So, you are giving people a death notice with nothing to do about it.

You've demonstrated the difference in outcome between colon cancers developing in the right vs. left side of the large intestine. Can you explain the process of figuring this out?
We carried out the biggest colon cancer study in the US, the CALGB/SWOG 80405 study (Venook et al., 2017). Some aspects of our results were different from a study that was done contemporaneously in Europe. I was trying to figure out the biological reasons to how this difference could be explained, and we put right vs left location of tumor as something to think about. However, to simplify the data sheets, we had not included the location of the primary tumor. So, we had to look through 2400 charts to collect this information, which took a while.

Coincidentally, I was invited to give a memorial lecture for a colleague who had passed away. Looking through his publications in preparation for the lecture, I came across a very old study that basically looked at a bunch of therapies that we've long since abandoned. But in that paper, there was just a line that commented that patients with right sided primary lived for ten months while patients with left sided primary lived for fifteen months. This was many years ago when we were not nearly as effective with the therapies for colon cancer. I thought "wow" that's a big difference. I've never heard that. I was stunned that nobody followed up on it. So, this motivated us to look into the sidedness of the tumors.

In our study, we saw a stunning 15 - 16-month difference in survival between left- and right-side patients. And genetically it makes sense because the right and left colon come from different embryonic structures - the right colon comes from the midgut and the left colon comes from the hind gut. We are trying to understand the molecular features that make the right vs left colon cancer different, but we don't have an answer yet.

I love to talk about this observation that the right and left side cancers are different, for which I am credited for figuring out. But it's embarrassing that I've been taking care of patients for all these years and hadn't figured it out before. It's very humbling.

Dr. Venook, it has been such a pleasure talking with you. Many thanks for sharing your insights.

Promise of immunotherapy for DNA repair deficient rectal cancer
Cercek et al. 2022 NEJM

Summary: This small but significant study establishes the efficacy of immunotherapy as first line/primary treatment for a type of DNA repair-deficient rectal cancer. The patients received a

type of immunotherapy known as immune checkpoint inhibitors (ICIs). ICIs act by releasing the molecular breaks put on by cancer cells on the immune cells to stop the immune system from identifying and destroying them. The ICI given in this study was dostarlimab. It was given to the patients every three weeks for six months. This was different from standard practice in that immunotherapy was given as the first line treatment i.e., in a neoadjuvant setting before the main treatment. Surgery was planned for after immunotherapy. At the end of the six month treatment cancer had disappeared in all 18 patients and they avoided the need for surgery.

All the cancers in this study were deficient for a type of DNA repair called mismatch repair (MMR). Inability to repair errors in DNA due to deficiency in MMR (dMMR) results in high microsatellite instability (MSI-H) and the expression of cancer-specific proteins that help immune system identify the cancer cells.
This study is of particular interest to Lynch syndrome patients because they carry inherited mutations in MMR genes that put them at a high risk for CRC among other cancers. It raises the possibility of immunotherapy as first line therapy for Lynch patients with rectal cancer.
This study was conducted by Memorial Sloan Kettering Cancer Center (MSKCC) in New York with Dr. Luis A. Diaz Jr. as lead investigator.

Glossary:

Adoptive T cell therapy: A type of immunotherapy in which T cells (a type of immune cell) are given to a patient to help the body fight diseases, such as cancer. CAR-T is a type of adoptive T cell therapy, where the T cells are modified to better target and kill cancer cells before giving to the patient.

Familial adenomatous polyposis (FAP): A type of hereditary colorectal cancer, caused by pathogenic mutations in the *APC* gene. Many polyps (abnormal growths) form in the colon and the rectum and these may develop into cancer.

Immunotherapy: A type of treatment that uses a patient's own immune system to fight cancer. Treatments may stimulate/activate the immune system to better identify and attack cancer. Includes checkpoint inhibitors, CART-cell therapy, cancer vaccines.

Immune Checkpoint inhibitor (ICI): A type of immunotherapy. Although the immune system can recognize many cancers and destroy them, the cancer cells develop ways to evade the immune system. They can produce "immune checkpoints" that can suppress the immune response, to put "breaks" on the immune response. Immune checkpoints are normally used to prevent autoimmune reactions against healthy cells of the body. ICI drugs like PD-1/PD-L1 and CTLA-4 inhibitors take these breaks off the immune system, to help it recognize and attack cancer cells.

Lynch syndrome: The most common inherited CRC syndrome caused by germline pathogenic variants in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) and *EPCAM*. Affected individuals have an elevated risk of developing CRC as well as certain other cancers.

Mismatch repair (MMR) and Microsatellite instability (MSI): Mismatch repair (MMR) is a type of DNA repair pathway that is present in the cell. MMR pathway components are encoded by genes such as (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). MMR-deficient (dMMR) tumors have mutations in MMR genes and are thus unable to correct certain errors, resulting in tumors with high microsatellite instability (MSI-high) and mutational burden.

Neoadjuvant therapy: Treatment given first before the main treatment such as surgery.

Pseudoprogression: A phenomenon in which an initial increase in tumor size is observed, followed by a decrease in tumor burden. This phenomenon can benefit patients receiving immunotherapy but often leads to premature discontinuation of treatment owing to the false judgment of progression.

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