“Update on Immunotherapies for Metastatic Castrate Resistant Prostate Cancer” (Sumit Subudhi) [#66]

Brad Power
August 3, 2023

“When we give immunotherapies, our goal is to shift the immune tumor microenvironment in a patient's cancer, so that we're getting less of the bad ones, and more of the good ones.” – Sumit Subudhi

“The backbone of immunotherapy treatments in prostate cancer is likely going to require T-cell bispecifics.” – Sumit Subudhi

“One of the major issues in prostate cancer that we haven't overcome yet, and why immunotherapies have largely failed, is because we treat it as a ‘one size fits all’.” – Sumit Subudhi

Meeting Summary

Patients with advanced prostate cancer and their caregivers face a daunting challenge. Though early stage or localized prostate cancer is highly treatable, the 5-year survival rate for metastatic prostate cancer is less than 30%. While there are many systemic treatment options (hormonal therapy, chemotherapy, vaccine, and radioligand therapy), for these patients, each treatment eventually fails. Advanced cancer patients see immunotherapy (a treatment leveraging the immune system) as offering one of the best paths to a durable response.

Immunotherapies have demonstrated success in achieving durable remissions for advanced cancer patients; however, they have had limited success in solid tumors, such as prostate cancer. There is one cancer treatment vaccine (sipuleucel-T or Provenge) approved, and it is in prostate cancer. Although it does not provide durable responses, it improves a survival benefit without much toxicity. Immune checkpoint therapies, T-cell bispecifics, and CAR T-cells are immunotherapy strategies that have the potential of providing durable and even curative responses in patients with metastatic prostate cancer.

Dr. Sumit Subudhi is uniquely qualified to describe the landscape of new treatment options available to advanced prostate cancer patients, especially immunotherapies. He is an associate professor in the Department of Genitourinary Medical Oncology at the University of Texas MD Anderson Cancer Center. His research focuses on investigating the immunological mechanisms responsible for tumor rejection and clinical benefit. He is the principal investigator of multiple immunotherapy clinical trials for patients with prostate cancer, and he conducts translational laboratory studies related to those trials. His research enables the development of novel immunotherapy strategies for the treatment of advanced prostate cancer. He received the Prostate Cancer Foundation’s Young Investigator Award in 2014 and the V Foundation–Lloyd Family Clinical Oncology Scholar Award in 2017. Dr. Subudhi holds a BA in biology from The University of Pennsylvania and an MD and PhD from The University of Chicago.

Why immunotherapy?

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We all know that the immune system can be used to fight infections, whether viral or bacterial, or even for example COVID, where many of us have been vaccinated to help fight it. With immunotherapy we're trying to manipulate the immune system to kill cancer cells.

The immune system is different from other treatment options, such as a therapy targeted at a genomic mutation, because it is a biological system that is fighting the cancer, which can lead to more durable responses, and even cures.

The immune system …

- **Is adaptable**: as the cancer transforms, a good immune system will recognize that transformation and still recognize that cancer and be able to kill it.
- **Has specificity**: it recognizes foreign and self.
- **Has memory**: you should be able to get a memory response that's durable, if not curative. That's unique relative to the other drugs for prostate cancer, where you get on average about six months to a year.

How do immunotherapies fight cancer?

The immune system is made of a number of kinds of cells in the tumor microenvironment. Not all of the cells in the immune system are good, i.e., kill the tumor cells. When you get immunotherapy, your goal is to shift your immune tumor microenvironment so that you’re getting more of the good immune cells, and less of the bad immune cells.

Do immunotherapies work equally well for all types of cancer?

CAR T cells have been more effective in blood cancers, like lymphoma, and less effective in solid tumor cancers, like prostate cancer. Some cancers, such as melanoma or lung cancer, respond better to immunotherapies (e.g., immune checkpoint therapies), while others, like prostate cancer don’t. For some cancers there are more good immune cells present (e.g., cytotoxic T-cells) or more bad immune cells present (e.g., immunosuppressive myeloid cells).

If you have metastatic castration-resistant prostate cancer, your chance of having bone metastases are somewhere between 70% to 80%. Immunotherapies have struggled to work on bone metastases.

What are the current approaches to increase T-cells in the tumor microenvironment?

- Vaccines, e.g., Sipuleucel-T (Provenge)
- Immune checkpoint inhibitors, e.g., anti-CTLA-4 (Ipilimumab)
- CAR (chimeric antigen receptor) T-cells, e.g., targeted at PSMA (prostate-specific membrane antigen)
- T-cell bispecifics, e.g., PSMAxCD3

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These therapies should be considered in combinations with other therapies.

What are the promising future approaches to immunotherapies?

- **T-cell bispecifics**: The backbone of immunotherapy treatments in prostate cancer will likely be T-cell bispecifics. One arm recognizes the T-cell, and the other arm recognizes the cancer. It can bring the T-cell directly into the cancer. In addition to PSMA (prostate-specific membrane antigen), other targets to latch onto which are being looked at in prostate cancer and have gotten the most attention are STEAP (six-transmembrane epithelial antigen of the prostate, a prostate-specific cell-surface antigen highly expressed in prostate tumors), TROP2 (Trophoblast cell-surface antigen 2, correlated with poor clinical outcomes and highly expressed in metastatic, treatment-resistant prostate cancer), and B7-H3 (also known as CD276, a member of the B7 family of immune checkpoint proteins, a cell surface immunomodulatory glycoprotein overexpressed in prostate cancers).
- **Myeloid cells**: There is research into drugs that can transform bad immunosuppressive (myeloid) cells into good ones, and manipulate the ratio, so you have more good than bad.
- **Biomarkers predictive of responses:** We need to do a better job of identifying the subsets of patients who will likely respond to treatments. There is too much “one size fits all” today. Fortunately there are emerging tests (e.g., from BostonGene) utilizing whole exome sequencing (WES) and bulk RNA-sequencing (RNA-seq), which show your tumor mutational burden, “microsatellite instability”, and mutational and immune landscapes. You can be immune-rich non-fibrotic, immune-rich fibrotic, or have an immunological desert. The efficacy of immunotherapy may be limited if you have highly fibrotic cancer, and if you have immune-rich, non-fibrotic cancer, you are more likely to respond (across all tumor types). Microsatellite instability also provides guidance. If you are “MSI high”, microsatellite instability high, that means that there are regions of your repeated DNA that have changed in length – show instability – and your mismatch repair is not working properly. If your test shows you are immune-rich fibrotic, you are not likely to respond to anti-PD-1 (e.g., pembrolizumab [Keytruda]), and you should consider a combination trial. Taking Keytruda alone, if it fails, may eliminate you from other trials, because a lot of these trials for novel immunotherapies exclude you if you have had prior immunotherapies, with the exception of Provenge. Furthermore, BostonGene have analyses looking deeper than “bulk RNA-seq” to “single-cell RNA-seq”. Understanding the spatial relationships of where the various immune cells are within the tumor microenvironment is important. What if the T-cells are in the margin of the tumor and not in the center of the tumor? Testing companies which have the infrastructure and money are decreasing the bioinformatics analysis time from six months to four weeks, and the costs are going down.
- **Immunotherapy combinations**: For prostate cancer, the backbone most likely will be a T-cell bispecific. Then, depending on what the resistance mechanism is, you probably have to add an immune checkpoint therapy. In addition, because prostate cancer has a

lot of myeloid cells in it, you probably also need a drug targeting immunosuppressive myeloid cells (e.g., agents targeting the adenosine pathway).

- **Adaptive design trials for immunotherapy combinations**: Adaptive design trials allow modifications to a trial after its initiation, without undermining its validity and integrity, to make it more flexible, efficient, and fast. For example, an adaptive design trial for immunotherapy combinations could start off with everyone getting PD-1. The responders would keep on PD-1, and the non-responders would start adding things, e.g., a vaccine. Then you could start identifying who actually needs more therapies in combination and who doesn't.
- **Combining radiation therapies with immunotherapies**: There is research into figuring out the ideal radiation dose, and which of the radiation therapies (proton, SBRT, or EBRT) are ideal for promoting the immune system. For example, some researchers believe that a lower dose of radiation will leave behind some of the cancer cells but also some of the good immune cells, which can then be combined with immunotherapies to get a better response.
- **CTLA-4 inhibitors**: Most immune checkpoint inhibitor attention goes to PD-1/PD-L1 inhibitors, like pembrolizumab (Keytruda). Using a similar mechanism, ipilimumab (Yervoy) binds to another protein expressed on T-cells, CTLA-4, blocking its inhibitory signal on T-cells, which allows the T-cells to destroy the cancer cells. In 2014, a study indicated that the antibody works by allowing the patients' T-cells to target a greater variety of tumor antigens, rather than by increasing the number T-cells attacking a single antigen. Now that ipilimumab and tremelimumab are off patent, a new generation of CTLA-4 inhibitors are being developed, because CTLA-4 inhibitors have the ability to drive T-cells into a cold tumor and also cause antigen spread. In addition, some of the patients who have responded to PD-1 have responded because of previous failures from anti-CTLA-4. There are indications that anti-CTLA-4 drugs modulate the tumor microenvironment so that in the future anti-PD-1 can be effective.

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Meeting Notes

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Discussion Outline

1. Introduction to Dr. Subudhi. (0:02)
2. Not all immune cells are good for prostate cancer. (6:13)
3. Biospecifics and how they work. (12:33)
4. Oncogene-driven transformation. (19:51)
5. What’s the next effective therapy for patients who are not responding? (24:35)
6. Hormonal ablation vs. High androgen therapy. (28:13)
7. Where do you find the most effective use of provenge? (35:04)
8. Optimal time to pursue BiTEs (Bispecific T-Cell Engagers). (40:01)
9. Prostate cancer and immunotherapy. (46:42)
10. Tumor microenvironment and immunotherapy. (53:07)
11. Is anti-CTLA-4 making a comeback? (59:00)
12. TLR agonists to boost immune response in prostate cancer. (1:06:44)

SUMMARY KEYWORDS

prostate cancer, patients, cancer, immunotherapies, T-cells, question, tumor, talking, vaccine, therapy, showed, respond, immune system, data, psm, specific, trial, ablation, targets, lung cancer

SPEAKERS

Sumit Subudhi (73%), Ricardo Salgado (5%), Rick Stanton (5%), Jonathan Starr (4%), Gitte Pedersen (3%), Brad Power (3%), Brian McCloskey (3%), Rick Davis (1%), Robert Gurmankin (1%), Russ Hollyer (1%)

Meeting Transcript

Brad Power
We're very honored to have Dr. Sumit Subudhi with us today to talk about the cutting edge of immunotherapies in prostate cancer and other topics from his research.

We all know about the unfortunate passing of our good friend Bryce Olson, who was an inspiration for all of us. The first time I met Dr. Subudhi was when Bryce originally put out a cry for help. He had run out of pathways to drug, and he said, “I've hit a wall. I don't know what to do.” We reached out to Dr. Subudhi, and he called Bryce on a Sunday evening. He immediately said, “Tell me more about your case; I'm there for you.” He was very supportive. He was

amazing. He's been that kind of person who's just there when there's a cry for help. He comes back, and he helps the people with their decisions.

We are very appreciative of Dr. Subudhi for making himself available, knowing that he's a very busy and accomplished clinician.

Sumit Subudhi 2:18
Thank you, Brad, for your very kind introduction.

I actually didn't know that Bryce had passed away, but sorry to hear that. He was definitely a fighter.

Prostate cancer is personal to me. My father has prostate cancer. And he's battling that. He's being treated at Memorial Sloan Kettering Cancer Center. I told him what I tell my patients, which is, “I want you to live as long as possible with the best quality of life and in the process let us try to find your cure.” I strongly believe that immunotherapy is going to be the cure.

Just a little bit of my background. I got a PhD in immunology at the University of Chicago, and then I did my training at Memorial Sloan Kettering, where I met Jim Allison, who won a Nobel Prize in immunology, and I was in his lab while also getting clinical training with Howard Scher at Memorial Sloan Kettering. When Jim got recruited to MD Anderson, he asked me to help develop immunotherapies in prostate cancer. And that's what I have done at MD Anderson for almost a decade now, because of that, and I'm going to share with you where I think the direction the field is going. And by the way, Dr. "Subudhi” is the name that I use when I'm wearing a white coat in the clinic, but just refer to me as “Sumit”. The way you say it is similar to a girl's name, “Sue”, and “mitt” as in a baseball mitt, and so “Sumit”.

Sumit Subudhi 4:12
I should point out that in the last decade, all I see in clinic are prostate cancer patients and nothing else and my focus is on immunotherapies and prostate cancer.

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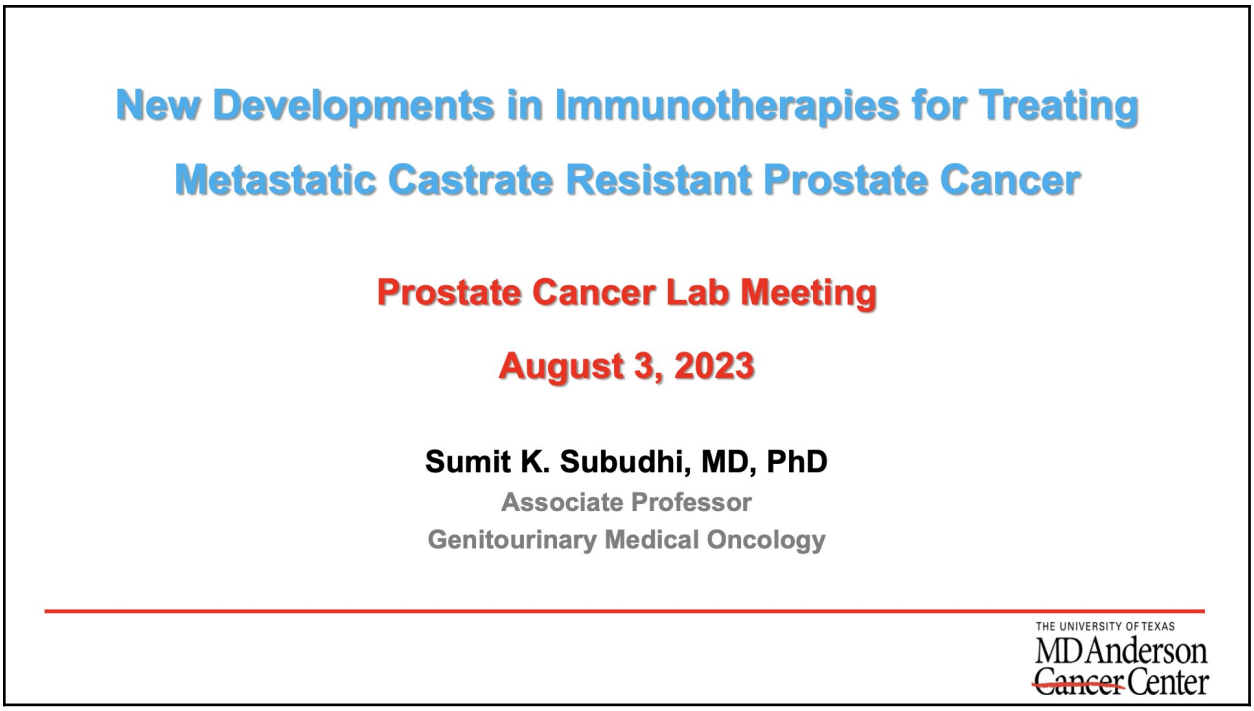
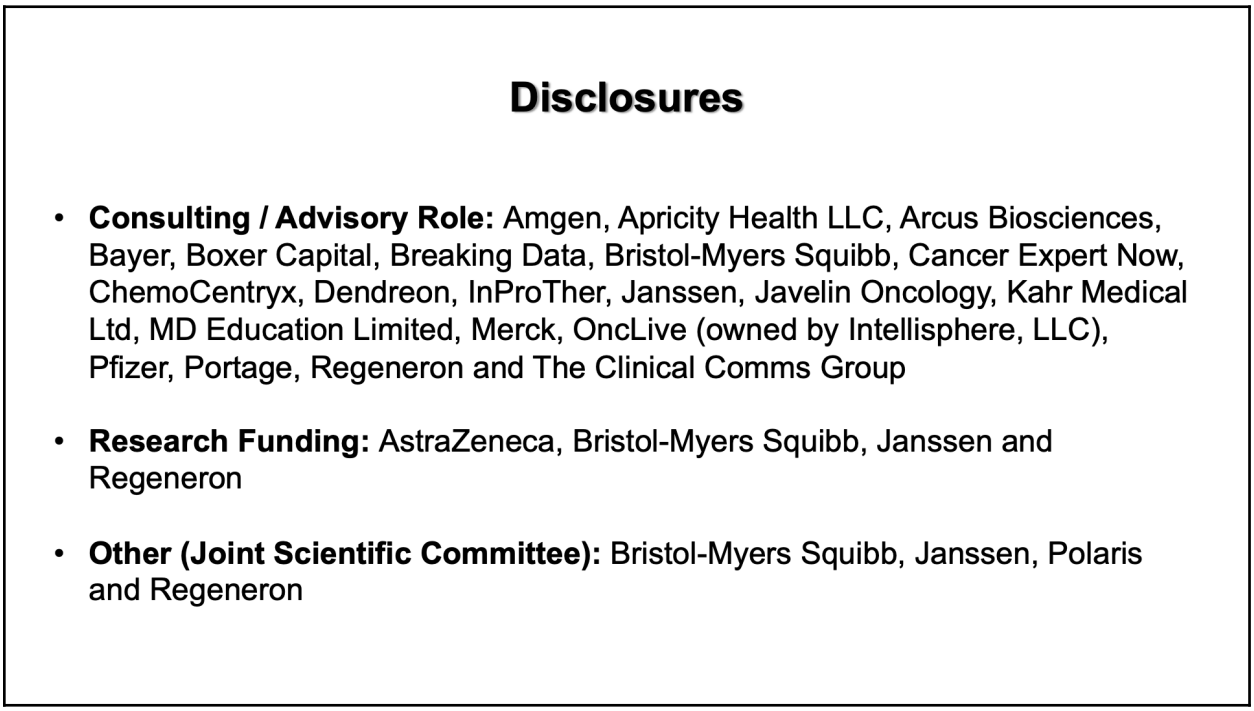


The title that Brad helped me with is “new developments in immunotherapies for treating metastatic castration-resistant prostate cancer”. The truth is, we're going to apply the same concepts in all prostate cancer settings: localized disease, as well as biochemical recurrence and hormone-sensitive prostate cancer.



Here are my disclosures, none of which are relevant for what I'm going to talk about today.

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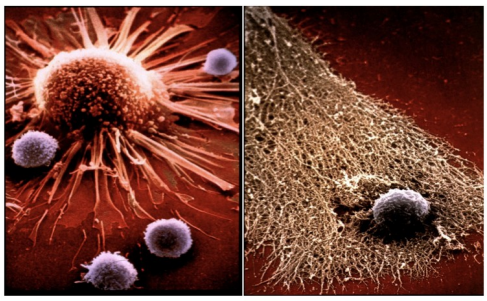
Why Immunotherapy?

- **Immune system can eradicate tumor cells.**
  - **Adaptability**
  - **Specificity**
  - **Memory**



Why immunotherapy? It's because the immune system can eradicate tumor cells. We've all known that the immune system can be used to fight infections, whether viral or bacterial, or even for example COVID, where many of us have been vaccinated to help fight it. We're trying to manipulate the immune system to also kill cancer cells. Why? Because the immune system is adaptable. Meaning that as the cancer transforms, a good immune system will recognize that transformation and still recognize that cancer and be able to kill it. It has specificity. And, more importantly, it has memory, meaning that you should be able to with a good immunotherapy strategy, get a memory response that's durable, if not curative. And that's unique from many of the other drugs that we have in prostate cancer, where usually, on average, we get about six months to a year out of many of our drugs.

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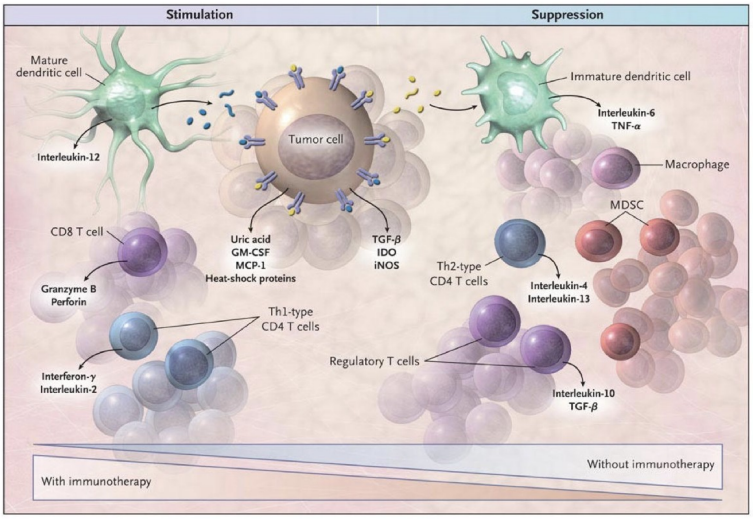

Finn ON et al, *New Engl J Med* 2008

This is a complicated slide, but there are one or two main points I want to get out of it. It's an old slide from 2008, but it really gets the message out.

In the middle here you have the tumor cell, and surrounding it is a bunch of immune cells. I want to point out that not all immune cells are good. All the ones on the right hand side of this tumor are examples of immune cells that help the cancer grow. All the ones on the left hand side here are the ones that help kill the cancer. So when you hear that, “Oh, this cancer has a lot of immune cells.” The next question to ask is, “Are they the good ones or the bad ones?”

Regulatory T-cells are an example of a T-cell that is bad for the patient, but good for the cancer, meaning regulatory T-cells help the tumor grow. Whereas CD8 T-cells are cytotoxic, and have the ability to kill the cancer. These are bad for cancer and good for us. So that's got to be a driver. The first point is that not all immune cells are good.

The second point is that when we give immunotherapies our goal is to shift the immune tumor microenvironment in a patient's cancer, so we're getting less of the bad ones, and more of the good ones. Okay, that's the goal of immunotherapies. Then we hope that will then lead to durable or curative responses.

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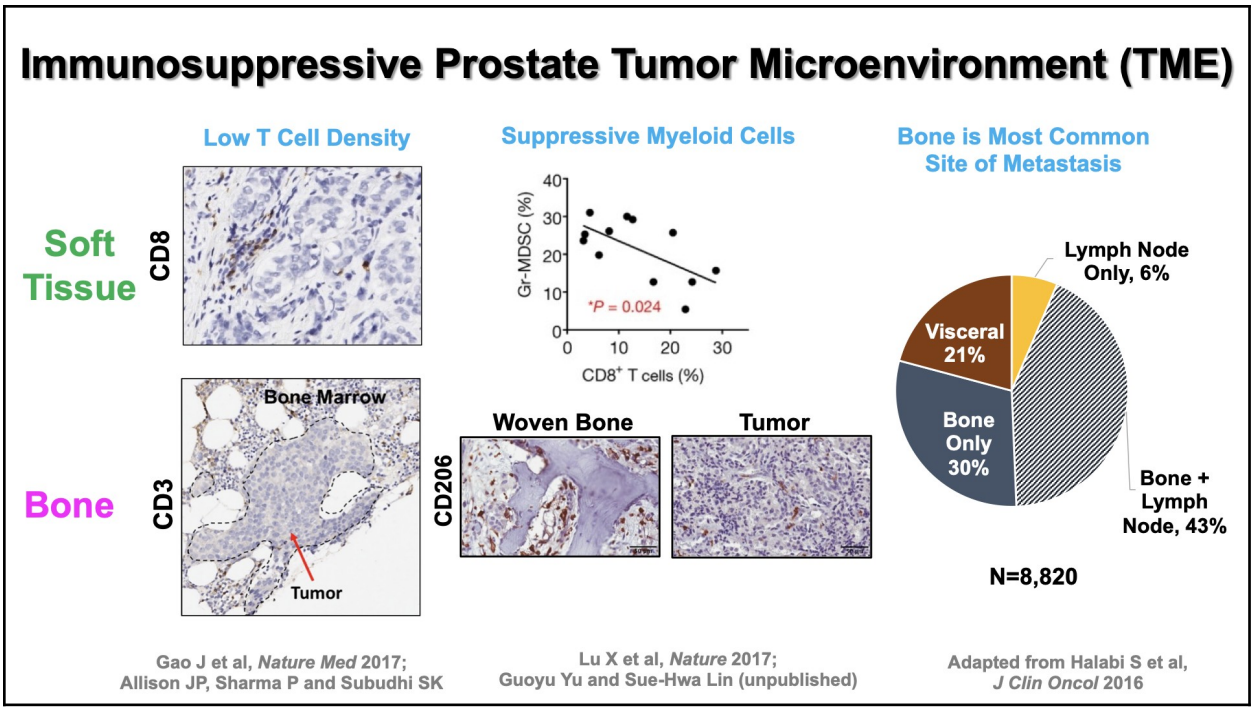

What's with prostate cancer? Why is it different? Why has it been a harder type of cancer to treat? This is the segue with immunotherapies. In contrast to what we see in lung cancer, that Ricardo [Salgado] can attest to, as well as melanoma – these are examples of what we call immuno-responsive cancers. One of the problems with prostate cancer is that there are very few T-cells present.

This is a protein staining of a patient's prostate cancer, and the brown staining is the T-cells, and there are just very few there. If this was melanoma or lung cancer, most of this would be covered in brown staining. What I'm showing here on the right, is that there are also bad immune cells known as suppressive myeloid cells. There's a graph that shows an inverse relationship: the more of these bad cells you have, the less of the good T-cells you have. This graph shows that there's an inverse relationship within the patient's prostate tumor, and each symbol here represents an individual tumor, so different prostate tumors. What I showed at the top was soft tissue, but in patients with bone metastases, the same thing holds true. The dotted line on the bone slide is the patient’s bone metastasis. Surrounding the bone metastasis is normal bone marrow, which is chock full of T-cells. But inside the cancer itself there are very few T-cells. And again, when we look at the suppressive myeloid cells, looking at a marker for them (CD206), you can see inside the tumor itself, there are very few T-cells, but a lot of these suppressive myeloid cells.

Why does it matter? Because bone metastases represent somewhere between 70 to 80% of patients with metastatic castration resistant prostate cancer. So it's something that we see in the clinic quite a bit. And if we're going to try to cure a majority of patients with prostate cancer, we do have to think about the bone microenvironment.

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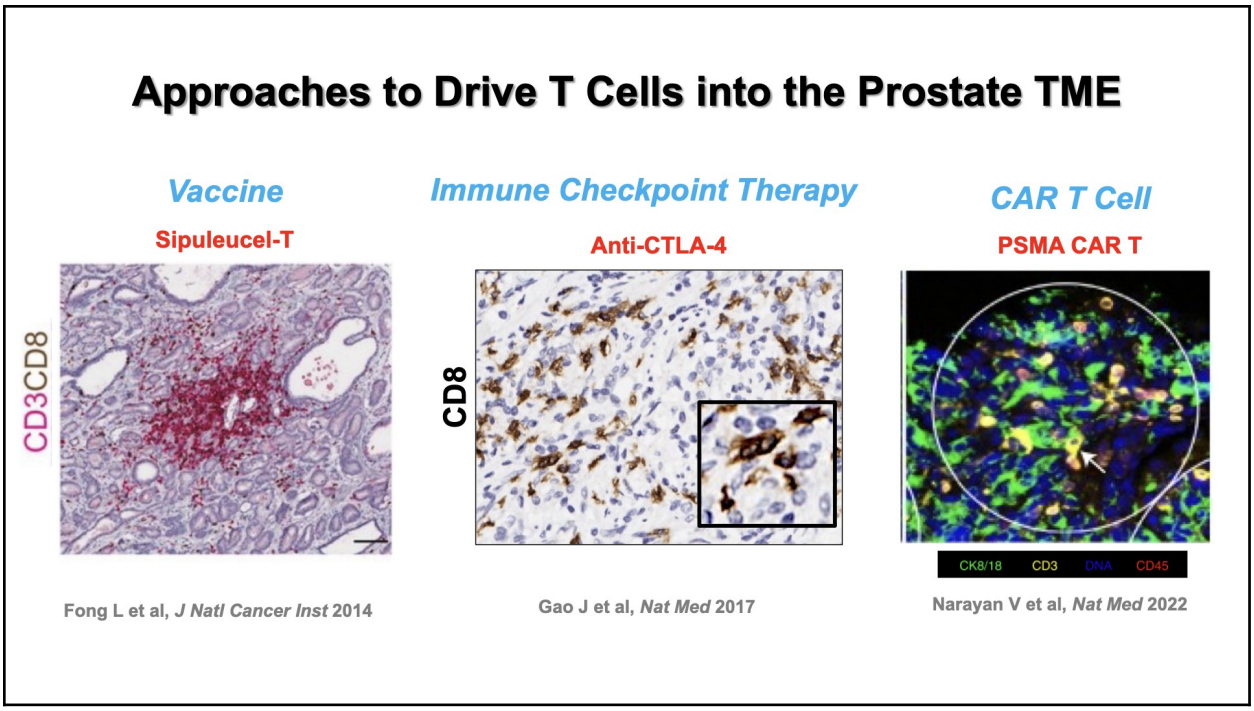

What are the approaches to drive T-cells into the prostate tumor microenvironment?

There are vaccines. One is already FDA-approved since 2010, known as sipuleucel-T, or Provenge. Larry Fong’s group at UCSF has shown that you can drive T-cells into the tumor site. This is a soft tissue tumor site.

Our group has shown that you can use immune checkpoint therapies or immune checkpoint blockade with anti-CTLA-4, in particular ipilimumab, to drive T-cells in. And what this high magnification is showing is that the T-cells are right next to the tumor cells. So you're really getting them right in there.

And then more recently, the group at Penn led by Carl June has shown that PSMA CAR T-cells can also drive T-cells in. Using a yellow staining here to show the T-cells getting into the tumor, which is in green.

There are many different strategies that have been used. But the truth is, most of the strategies have failed to work in the bone. It's really hard to get it to work in the bone. So what other strategies are there?

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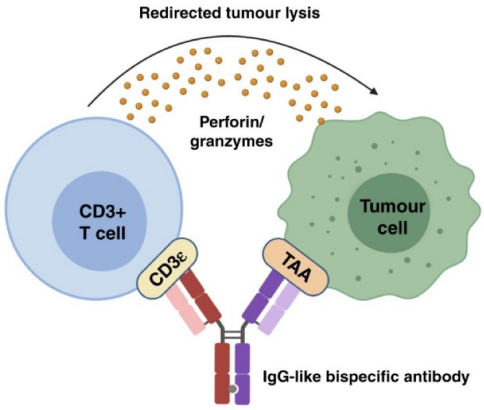
T Cell Bispecifics: Mechanisms of Action

- **Recruit / activate immune cells**



CD3 bispecific T-cell redirection mechanism of action in cancer immunotherapy

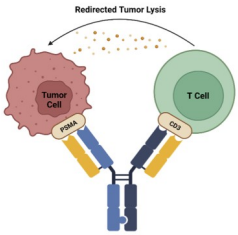
Singh A et al, *Br J Cancer* 2021

Recently T-cell bispecifics have been FDA approved in melanoma as well as in multiple myeloma and liquid cancers and are starting to make their way in prostate cancer.

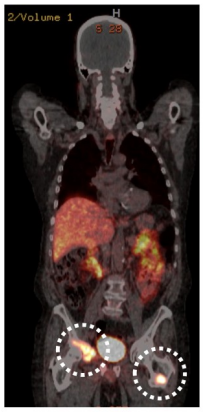
How do these T-cell bispecifics work? I think about them like a heat-seeking missile. The missile has two arms. One arm recognizes the T-cell, and the other arm recognizes the cancer. Basically, it can bring the T-cell directly into the cancer.

Does Driving T Cells into the Bone TME with PSMA Bispecfic Overcome Resistance to Improve Efficacy?

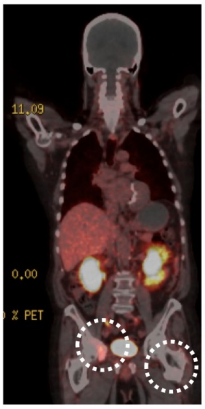
Bispecific



Pre-Treatment



On-Treatment



Pre-Treatment		On-Treatment	
SUVMax	SUVMax	SUVMax	SUVMax
27.6	38.1	6.7	1.8

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Here's an example of a PSMA T-cell bispecific combined with immune checkpoint therapy, anti-PD-1, which is FDA-approved in melanoma and lung cancer among many other types of cancers.

What we're seeing is a patient before treatment, before you receive the T-cell bispecific plus anti-PD-1. I've highlighted the orange lesions which represent lesions in the bone. I told you how hot these lesions are, by this metric called SUVMax, which is from PSMA PET/CT scans. I bet you Oliver Sartor probably showed you some of this when he was talking about PSMA radioligand therapy, called lutetium or Pluvicto. After treatment, you can see that one of these lesions is almost disappearing. And this is only after a couple of treatments. And so you can see the numbers going significantly down. So we've now shown with biopsies that we're actually driving T-cells in here. I believe that the backbone of immunotherapy treatments in prostate cancer is going to require T-cell bispecifics.

Robert Gurmankin 14:46
I recently started on Keytruda because I have all the biomarkers.

I have two questions. One is with the ICI (immune checkpoint inhibitor): what, if anything can be done to enhance the tumor microenvironment for infiltration? Because I know, like you said, it's pretty cold.

And then my second question is: even if you don't get good T-cell infiltration, has anyone looked at whether, if you will activate T-cells, will it work on circulating tumor cells and help prevent seeding?

Sumit Subudhi 15:35
Great questions. Keytruda is the anti-PD-1 therapy. And it is FDA-approved for patients who have a high TMB, or tumor mutational burden, or patients with mismatch repair defects. And this is in the context of prostate cancer. So I imagine you have one or both of those features. And that's why you're getting it.

Robert Gurmankin 16:12
Actually, I have all three: I am MSI (microsatellite instability) high as well.

Sumit Subudhi 16:18
The theory behind MSI high is related to the mismatch repair defect. The data came out of Wassim Abida’s paper at Memorial Sloan Kettering. We actually trained together when we were there. He showed that there was a 50% response rate with Keytruda, or anti-PD-1 therapies alone with patients like Bob, but the durable response rate is actually 25%. So which of these patients is going to have lasting responses? It's only 25%. So with my patients that have what Bob has, I offer them anti-PD-1 therapy, like Keytruda. But I really try to hold them for when we have combinations, like what I just showed you on the slide, like a T-cell bispecific plus anti-PD-1, to try to enhance that durable response rate from 25%, to light the fire.

So then Bob was asking, “What are choices that he could combine with it?” Well, if you're getting standard of care, one of the things I would consider is some sort of radiation therapy. Sometimes that can boost the immune system to make the Keytruda more effective. Again, this is more experimental; I don't have a lot of strong data to support it. But I do have the phase 3 trial with ipilimumab plus radiation, which almost became FDA-approved but just barely failed to meet its endpoint of overall survival in patients with metastatic prostate cancer. When they didn't combine it with radiation, the trial was a complete failure. So there's support for irradiating some of the bone sites and making the immunotherapy more effective. But again, for most of my patients, I may try it, but I tell them that if it was up to me, or if it was my own father, I would wait until we have a good combination.

We strongly believe that mismatch repair defects are very different in prostate cancer, compared to colorectal cancer. You might have heard last year of a Sloan Kettering group where 18 out of 18 patients with colorectal cancer and MSI high all had responses to anti-PD-1 therapy. This is never going to happen in prostate cancer. The reason why is that prostate cancer is much more immunosuppressive. So even with the MSI profile, you are only going to get approximately a 25% durable response rate. So I hope that answers your first question.

Your second question is whether or not you're hitting the circulating cells? I would say the answer is we definitely are because the 25% wouldn't have durable responses if we weren't. But do we have biological proof of it? No, we just have clinical proof. The fact that you're getting these durable responses.

Ricardo Salgado 19:51
Like Brad said, I'm a little bit different because I'm on the lung side. It's different from the prostate side. Not only on the lung, but also oncogene driven because it was ALK positive. There was a transformation from ALK non-small cell to a small cell, of which there are only eight reported cases in the world. That makes it an outlier, for all but a few things. Usually we don't do immunotherapy because usually it's relatively cold. However, because all of a sudden, my TMB (tumor mutational burden) went high, from like 0.8 to 7.7. We combined nivo (nivolumab, or Opdivo, an anti-PD-1 checkpoint inhibitor) and ipi (ipilimumab, or Yervoy, a monoclonal antibody medication that works to activate the immune system by targeting CTLA-4, a protein receptor that downregulates the immune system), and that actually cleared my brain mets (metastases), and got me to a complete response. So knock on wood, that had a phenomenal response. When the other stuff wasn't working, to be honest, like the chemo kind of working in the progression site, but not in the brain, you didn't pierce the CNS (central nervous system). And then once we scanned the second time, it happened. Just to give you that context.

But more importantly, you were talking about immunosuppressive cells, like myeloid cells. I've read that you can deplete them with capecitabine (a chemotherapy), or are there some other complementary things that you can do?

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My second question is: you were just talking about radiation, which is something that I'm considering right now. The standard, under a limited stage of small cell lung cancer, is concurrent chemoradiation. But in my case, it was extensive. And again, very rare. I spent some time with some of your colleagues (at MD Anderson) like Jim Welsh, understanding, “Hey, will the radiation actually kill some of your soldiers? Or could it enhance it?” Any thoughts on that would be appreciated.

Sumit Subudhi 21:43
Great questions. I was going to say, I hope you met Jim.

In regards to myeloid cells, it goes back to one of my first slides where I was talking about the immune tumor microenvironment. Not all myeloid cells are bad, some are actually good. And you want them, and some of them are bad, and you want to get rid of them. And that's the trick. That's where we're struggling in the field. Because right now, we have ways of depleting many of them, but then we're depleting some of the good ones as well. What we're trying to work on are drugs that can actually transform the bad ones into good ones, and manipulate the ratio, so you have more good than bad. And that's an active field of investigation, and not just in prostate across all cancers, because we believe that's actually contributing to a lot of the resistance to immune immunotherapies across all cancers.

Jim Welsh is one of the leaders in the field of combining radiation therapy with immunotherapies. I've seen his data, and we're collaborating with him on the prostate cancer side. I believe he's correct, that normally, when we give radiation for cancer, we're trying to kill everything that we focus that radiation beam on. Some of you may have gotten, or may have had localized prostate cancer, and you might have received radiation for the localized prostate cancer. What the radiation doctors are trying to do is kill the entire cancer microenvironment. So that's also going to kill some of those good immune cells. What Jim is thinking about is maybe not giving such a high dose of radiation, but giving a lower dose, where you may not effectively kill all the cancer cells, where you're going to boost the immune system so that it can work more effectively with the immunotherapy similar to what we're talking about with Bob Gurmankin. Someone put in a chat that Dr. Eleni Efstathiou, who used to be here at MD Anderson and now is at Methodist, sometimes combines radiation therapy with immunotherapy. Now the problem is, it all depends who you talk to with radiation therapy, because if you talk to people like Jim, he's going to say, “Don't give high doses." Traditional radiation oncologists will give high doses. So you have to be careful, and we're still trying to figure out what's the ideal dose, and whether you do proton or SBRT or EBRT. There are many forms of radiation therapy, and we still don't know what's ideal for promoting the immune system.

Ricardo Salgado 24:35
If you're already on let's say, PD-L1 and CTLA-4, all the trials always say that including vaccines, ETCs (endogenous T-cell therapies), or bispecifics help your immune system. By adding one of these, a year on from here, if it is still working, would it be an effective shift to add a bispecific, versus if I started PD-1 or the CTLA-4 right next to the bispecific?

Sumit Subudhi 25:16
What you're asking about is: if you're a responder, and all of a sudden, your body stops responding, or the cancer comes back, what's the next effective therapy? Can you go back to the CTLA-4?

Ricardo Salgado 25:32
No. I'm asking, for example, let's say you're responding, and it's still working. And if you had to compare (1) you add the CTLA-4, the PD-L1, and the vaccine at the same time together. Or (2) something that you want, the ETC, isn't available right now, so you have to go on the PD-L1 or CTLA-4, and then all of a sudden, whatever, the bispecific or the CAR-T shows up in a year from now, is that going to be less effective because you already started the PD-L1 and CTLA-4 a year before versus in an ideal trial, it's 40 days before you start these things.

Sumit Subudhi 26:19
In anyone that's responding, I wouldn't add anything else to it. But I think what you're trying to say is, even with someone responding, would you add these more novel treatments like CAR T-cells?

I wouldn't add it because we have no evidence that in someone that's responding, that adding more is going to actually help. Like, for example, if you add a vaccine to it, you may distract the immune system from actually doing what it's doing. Because it's going to focus on what the vaccine is asking. I would just be careful. If you're responding I would just let it be.

Ricardo Salgado 27:14
That’s interesting, because I thought that when you have MRD (minimum residual disease), you're responding and the vaccine has very limited toxicity, you unleash the vaccine right there and then because microscopically there could be some stuff that you just can't see.

Sumit Subudhi 27:32
There could be, but at the same time, the vaccine is only focused on a few cancer antigens or proteins that are expressed. And they may be ones different from what is actually progressing in your body. So it could distract the immune system.

Russ Hollyer 28:13
Dr. Sartor and Dr. Denmeade think that supraphysiological androgens, for example from the high testosterone portion of bipolar androgen therapy, induce the prostate cancer tumor cells to release immunogenic factors. What do you think about this?

Sumit Subudhi 28:27
I think that it's controversial. So we don't know yet. And Sam (Denmeade) and I talk about this all the time. The reason why it's controversial is that right now, we know that hormonal therapies can boost the immune system transiently. But we also have a lot of data, both in patients and in preclinical models, that long term hormones can actually cause a more immunosuppressive microenvironment. Sam is doing clinical trials as well as doing experiments in mice to try to

confirm his findings. But I have a feeling that when it comes to increasing hormones or taking out the AR pathway the positive immunogenic changes are going to be transient.
A note: when we talk about hormone therapies, we're not thinking about what Sam's doing. We're talking about hormonal ablation.

Russ Hollyer 30:02
To follow up, you said hormonal ablation therapies boost the immune system short term but decrease it long term.

Sumit Subudhi 30:14
That's right.

Russ Hollyer 30:17
How about increasing androgens to supraphysiological levels?

Sumit Subudhi 30:23
Sam Denmeade at Johns Hopkins is the only one that's really actively looking at that right now. They haven't shown me enough data to convince me. I'm data driven. There's a lot of hand waving that this can happen. A lot of things can happen. I can spin around and clap my hands and make the immune system do stuff. But I want to see the data.

Russ Hollyer 30:53
Yeah, me too. Do you have any idea when he's going to produce the data for this in mice or humans clinical trials?

Sumit Subudhi 31:00
We spoke recently, and he's actively doing it. I hope in the next six months or a year, they'll present it.

Jonathan Starr 31:21
You're talking about the cutting edge, I want to talk about the rusty back edge for a second which is the Provenge or sipuleucel-T. Every doctor I talk to has a different opinion about that. I would like to hear more. Is this an effective treatment or not? And are there certain conditions under which it is effective? And are in others, not? Is there any information on whether there is a tail of survival? I did look at this PROCEED study, which seemed to show a lot of survival benefit at low baseline PSA. On the other hand, maybe it's just that because they were low PSA, they were earlier in the progression or something like that. But anyway, I'm really curious to get something substantive from you about Sipuleucel-T. Is it something, or is it not?

Sumit Subudhi 32:46
Jonathan, I gotta be honest, everyone saw my disclosures, but I am a paid consultant with Dendreon, which is the company that makes Provenge. But I'm going to tell you what I truly believe. I just have to share my disclosures so that it's clear. But my understanding is that, “Yes, it is effective in a subset.” I'm trying to get Dendreon to publish this because I know Oliver

Sartor, as well as many other people, have about 5% of patients that have long-term responses. When I say long term, they've gone two to five years without needing anything else, except for the Lupron injections or the ADT alone. It is effective in a subset.

Let me just take a step back so that I get everyone on the same page. Jonathan's calling it an old drug. As I mentioned in my slide, Provenge was FDA-approved in 2010, over a decade ago. It was the first vaccine treatment for patients with active cancers. There are a lot of vaccines out there for people if you have never had cancer, like for head and neck cancers and things like that, that are virally-driven. Those are preventative, like the Gardasil 9 vaccine that they're giving teenagers to prevent certain types of cancers. But this was the first vaccine that was FDA-approved for people with active cancer and metastatic cancer. I want to tell you, the FDA label on it is for patients that are asymptomatic or minimally symptomatic. So if you're on narcotics for cancer-related pain, then you won't be approved for it. It also excludes patients who have visceral metastases – these are metastases outside of the lymph node and bone, meaning to the lung or the liver, or adrenal glands. So those patients are also excluded. So it's a narrow patient profile, but a majority of patients fit that criteria.

Where do I find it most effective? I tend to give it as a first line treatment to castration-resistant prostate cancer. As soon as I find hormonal ablation – I'll be a little more specific, as I believe the point was made really well with the last set of questions – as soon as I see a rise in PSA, that's when I start talking to the patients about Provenge and trying to give it because the data shows that the lower your PSA, the more likely you will have a benefit from Provenge.

I want to clarify that the PROCEED, as well as the registration trial, all showed that with Provenge, you do not change PSA. You do not change scans. Meaning, if your PSA is going up, your PSA will continue to go up. If your scans are showing worsening cancer, after you finish post-Provenge, your scans will even show even worse cancer. So then people always ask me, “Well, then how can you get a survival benefit if your PSA is continuing to get worse, and if your scans are getting worse after you get Provenge?” And my answer is that, instead of the cancer going 100 miles per hour, after you get Provenge, it likely goes 60 miles per hour, so that it's slowing down. That's the only way you can get a survival benefit without these other metrics changing. But like I said, I have 5% of patients where the PSA goes down or just stabilizes, and I don't need to do anything, including a patient that I treated, I think at the age of 44. And he's now 51. And I haven't had to do anything since then.

Jonathan Starr 36:54
Are you seeing any good combinations with Provenge?

Sumit Subudhi 36:59
I have a meeting with Dendreon and another company that I can't name, for potentially combining bispecifics with a vaccine.

Jonathan Starr 37:20

“Update on Immunotherapies for Metastatic Castrate Resistant Prostate Cancer” (Sumit Subudhi) [#66]

About the CombAT trial: I'm going to throw something in, and let me say I have no connection with this company or any company. I've been following this VERU-111 (sabizabulin), and it is like an oral taxane. It acts a lot like a taxane. It's an anti-tubulin. But it's somewhat different from a taxane. It looked very promising to me. They were going to come out, and then the FDA said, “Oh no, you have got to start all over again.” It is not so immunosuppressive because its side effects are so minimal. Apparently, I thought man, this might be a great thing to combine with Sipuleucel-T (Provenge). I'm wondering if that thought has ever occurred to you or anyone else?

Sumit Subudhi 38:19
Great question. So, by the way, Brad, you're right. Your group is savvier than the average patients that we see. Like understanding the mechanisms of taxanes and things like that. Impressive questions.

In certain cancers, like breast and lung, combining chemotherapy with immunotherapies have been shown to be effective.

Now, to your question, Jonathan, whether or not having an oral taxane that doesn't cause the myelosuppression that we see, would that be beneficial? It may not be because the reason why the taxane may be working, or traditional chemotherapies may be working, is not just that it's killing the cancer and releasing cancer antigens. But it also may be taking away some of the bad myeloid cells. We have to do the experiment. We have to test it out to confirm whether that's the case.

Jonathan Starr 39:36
I hope that sabizabulin survives, first of all, as an option, and perhaps you'll think about using it that way. Seems like an interesting clinical trial to do.

Sumit Subudhi 39:49
It does. I agree.

Brian McCloskey 40:00
A two-part question, focusing on your last slide regarding BiTEs (bispecific T-cell engagers). The target was PSMA.

My first question is: are there other promising targets for BiTEs?

My second question, which is related is: is there an optimal time to pursue BiTEs?

Some data on that is, I know that my RNA expression for PSMA has declined relative to 1000 prostate cancer patients, using Tempus data, pretty dramatically. It's actually been cut in half since 2016. I have three data points. I was in the 98th percentile. Now I'm in the 38th percentile. My SUV values (standardized uptake value, a result of a PSMA PET scan) are low to moderate

as well. And so that doesn't really seem like a great target for me to go after. I'm just curious, if I were to pursue a BiTE, would there be other targets to go after? And what is the right timing?

Sumit Subudhi 41:23
Let me try to first answer your first question. Other targets besides PSMA, the ones that are being looked at in prostate cancer and have gotten the most attention are:

- STEAP (six-transmembrane epithelial antigen of the prostate, a prostate-specific cell-surface antigen highly expressed in prostate tumors),
- TROP2 (Trophoblast cell-surface antigen 2, correlated with poor clinical outcomes and highly expressed in metastatic, treatment-resistant prostate cancer),
- and B7-H3 (also known as CD276, a member of the B7 family of immune checkpoint proteins, a cell surface immunomodulatory glycoprotein overexpressed in prostate cancers).

There are definitely others. But those are the ones that are definitely getting the most attention.

We have to remember with these immunotherapies, you may not need to have high expression; you just may need a little bit of expression. This is different from the radioligand therapies where we know, and Oliver Sartor probably shared some data coming from an Australian group and others, that you do need a threshold of PSMA expression on those PET scans to more likely respond to the lutetium or radioligand therapies. I think it's going to be different for immunotherapies, but it's too early to say. We've had some patients with lower expression PSMA that I wouldn't have thought would have responded to the bispecifics, that are. I wouldn't say that you're less likely to respond, at this point.

Then in regards to the optimal timing, in general, the field believes that the earlier in your prostate cancer journey that you're in – and when I say “journey”, I mean journey from initiating hormone ablation. We believe that's probably the best time to give immunotherapies because then you have less of the bad immune cells, like the immunosuppressive myeloid cells, because we know long term hormonal ablation will bring those bad cells along. That's data coming from Johann de Bono's group from the UK, as well as Chuck Drake's group when he was at Columbia, and many others. We think that earlier is better.

But as many of you know, most of the clinical trials start at the metastatic castration resistant setting. There's some success, then you start bringing it earlier and earlier. I'm sure Oliver Sartor showed you that with the radioligand therapy and lutetium.

Brian McCloskey 43:57
Expression may not be the key factor that we're looking at here.

What about targeting B7-H3 and TROP2? Is that being looked at? Why go after one target? Couldn't you be that much more effective if you went after two, three, whatever?

Sumit Subudhi 44:18

I think that the answer is, “Yes.” But the problem with all these different targets is that they're not important for the cancer cell. The cancer cells will live just fine because they're not driver targets. Similar to what we talked about regarding Ricardo, who has an ALK mutation for his lung cancer, that's a driver mutation. You stop that, then the cancer stops until it transforms into something else. B7-H3, PSMA, STEEP – those are not driver mutations. That's why I have issues with CAR T-cells. Because if you look at the liquid data for CAR T-cells, where it's FDA-approved, the biggest resistance mechanism is that the cancer just stops expressing whatever the CAR is meant for. That's the same thing that holds true with radioligand therapy, when you see the patients that are not responding anymore. It’s the lesions that don't express PSMA. That's the problem. The same thing is going to be true with CD3 T-cell bispecifics.

But there's data to suggest that the CD28 bispecifics can cause “antigen spread”. What do I mean by “antigen spread"? If the bispecific is targeting, say B7-H3, and the cancer downregulates it, the CD28 biospecifics trigger a broader immune response that will target other antigens such as PAP, or prostatic acid phosphatase, which is what Provenge is targeting. They can potentially target STEEP and PSA and other things. So what we want in a good immunotherapy is called “antigen spread”. That's how you can get the memory.

Gitte Pedersen 46:42
I am not a prostate cancer patient, but I want to really express my appreciation for the clarity with which you expressed your designs here. I've spoken with some of these patients, and they're so well educated, but the way you also express it is super, super clear.

I want to dig into your statement that if the treatment is working, you don't want to add to it. I don't know if you have seen the combinatorial treatments of individualized mRNA vaccines with checkpoint inhibitors and the results from skin cancer and pancreatic cancer, but I believe BioNTech has a trial in prostate cancer.

In my view, if you take the brakes off of the immune system, but you don't tell it what to do, you can be in a situation where it causes havoc. Some of the side effects are autoimmune diseases. If you combine it, and you boost effectiveness and the responder rates, you could potentially also decrease the side effects. What are your thoughts on the vaccine using mRNA technology in prostate cancer?

Sumit Subudhi 48:37
Let me address a couple things.

I want to clarify about adding on to treatments. When someone's responding, if someone's PSA is continuing to go down, and the scans show that the cancer is shrinking, I'm not going to add something to that person. However, we have a patient that's on one of our bispecific trials, where the PSA is going up, the scans are showing stable disease. We just reached out to Jim Wells, a radiation oncologist, to see if we can actually boost his immune system. So the patient is responding in the sense that he has a stable disease. He's not outright progressing. To me,

this particular patient is having a suboptimal response. I'm open to adding things. So I just want to be clear about that.

Yes, I've talked to that company (BioNTech) as well. They're early in their prostate cancer journey. mRNA vaccines are exciting. They give you the ability to – it was brought up in the last question about having only one or two targets – have multiple targets, including potentially neoantigens. Because with the technology getting better, you can personalize the vaccine, meaning the patient can give you their tumor, and then you can see what specific antigens are highly expressed. Many of you guys are using Tempus and other sorts of technologies to get there. Our group is working with Boston Gene as another. The reason why we've chosen BostonGene is because we believe their immunoprofiling is one of the best ones compared to other companies. But I’m not trying to say one company is better. But that's just been our experience so far.

Now let’s go to combinations. One of the major issues in prostate cancer that we haven't overcome yet, and why immunotherapies have largely failed, is because we treat it as a “one size fits all”. So what do I mean by that? When most people are diagnosed, they get a Gleason score, or they say, “Oh, you have a high risk, or low risk.” Then if you have localized cancer, they'll tell you to either do active surveillance or surgery or radiation or both. But once you become metastatic, it becomes like, “Oh, have you ever seen hormone ablation? Have you not?” It becomes a “one size fits all”. “How many lines of hormonal ablation have you had? Are you pre-chemotherapy or post-chemotherapy?” If we thought about that, like it was lung cancer – and Ricardo can attest to this – ALK mutations I think only represent – and I haven't thought about lung cancer in about 15 years, but back when I was a fellow, if I remember correctly, it only represents probably 2% to 3% of all lung cancers. If crizotinib, which was the first ALK inhibitor drug, was tested in all lung cancer patients, it would have failed. But what the lung cancer group did was they recognized that there's a subset of patients that are vulnerable to this type of treatment. And Ricardo is one of those people that benefited. What prostate cancer hasn't done is – let's go back to lung cancer: they have histology. They take the cancer, they look under the microscope, and they're like, “Oh, this is not non-small cell lung cancer, this is small cell.” Then with non-small-cell, they break it down into adenocarcinoma and squamous cell. This is just looking under the microscope, not doing any fancy stainings. Then they – and Haymaker (Cara Haymaker, Ph.D., Director, ORION core, Assistant Professor, Department of Translational Molecular Pathology) at MD Anderson is one of the leaders in this – genomically characterize the different cancers and say, “Okay, you're more likely to respond to this type of therapy, and these clinical trials.” I guarantee you, if immunotherapies were tested in all lung cancer patients, and we know that's true, those trials would all be negative. But when you select out from the lung cancers, don't treat them as a “one size fits all”, then you start seeing the benefits.

Where am I going with this? That's where we have to go with prostate cancer. We need to do the same things and identify the subsets because there are some people that actually truly benefit from PD-1 monotherapy. There are some people that need a combination of ipilimumab

plus PD-1, and then there are people that need triple therapy with myeloids. The issue with adding on more is you're also adding on toxicities. So we always have to balance this.

For some reason – we're hypothesizing, we don't know for sure – but prostate cancer patients tend to have more toxicities from immunotherapies than any other therapy. So if you look at immune checkpoint therapies, if you look at CAR T-cell, when you test them in prostate cancer, and I'm talking about the same exact therapies. So if you take a CAR T-cell, and you put it in pancreatic cancer, like a PSCA CAR T-cell, because pancreatic cancer also expresses PSCA, and you put it in pancreatic cancer versus prostate, you'll see more toxicity in prostate cancer. We believe the hormone ablation therapy may be contributing to that. So that's why I'm not a big fan of just throwing the kitchen sink.

I also think we need to do adaptive design trials. What is adaptive design here? So we start off with everyone getting PD-1, the responders, we just keep them on PD-1, the non-responders let's start adding things. Let's start adding the anti-CTLA-4 or vaccine. Let's start adding and start doing it that way. Then you'll start identifying who actually needs more, and who doesn't.

Gitte Pedersen 54:51
My second question is about the tumor microenvironment. I think you alluded to it because it's something you could see in an RNA seq dataset because the immune cells have individual unique biomarkers. My question is: Are you using Boston Gene to analyze your own RNA seq data?

Sumit Subudhi 55:18
I'll give you an example about this. BostonGene has a cancer cell paper from, I believe, 2021, when they looked at mostly melanoma patients, but they looked across many other tumors, and they show the human immune landscape. They have immune-rich fibrotic, immune-rich non-fibrotic, immunological desert, and some others. (The efficacy of immunotherapy may be limited in highly fibrotic cancers. Fibrosis may be subverting tumor immunity. Understanding fibrocity also suggests a therapeutic opportunity to target fibrosis in these tumor types to reawaken anti-tumor immunity.) It turns out the immune-rich, non-fibrotic are the ones that are more likely to respond across all tumor types.

This is where we can start using the landscape to help guide us. So what did we do with one of our patients? One of our patients actually was “MSI high”. (Microsatellite instability high: Microsatellites are regions of repeated DNA that change in length – show instability – when mismatch repair is not working properly. MSI testing looks at the length of certain DNA microsatellites from the tumor sample to see if they have gotten longer or shorter as a measure of instability.) He had the mismatch repair defects, as one of the first people who asked me a question today who is getting Keytruda. This person's MSI showed immune-rich fibrotic. So we're like, “You know what, we're not going to give you Keytruda, because you're more likely not to respond. We're going to try to get you on a combination trial.”

“Update on Immunotherapies for Metastatic Castrate Resistant Prostate Cancer” (Sumit Subudhi) [#66]

We are using it to talk to our patients, which is to say, “Look, you're more likely to be either the responder that only has a short duration, or you may not respond at all. Giving you Keytruda may eliminate you from other trials, because a lot of these trials that are doing novel immunotherapies in prostate cancer exclude prior therapies, with the exception of Provenge, because that's an FDA-approved immunotherapy.

Rick Davis 57:57
It must have been ten years ago, I sat across from Jedd Wolchok, and asked him about anti-CTLA-4 for prostate cancer, and he wasn't he wasn't overly enthusiastic. Ten years later, we really haven't seen ipi (Ipilimumab, Yervoy, approved in 2011 for melanoma) do too much. We've seen a lot more from the anti-PD-1s, if the guys have the right markers like Dr. Bob (Gurmankin).

My question is: pick your top three combinations with either anti-CTLA-4 or anti PD-1/PD-L1 to make the prostate tumor hot. How do you think we're going to make that hot with either immunotherapy? What are the top three candidates?

Sumit Subudhi 58:55
I want to clarify because the field is starting to make a comeback with anti-CTLA-4 because there's a lot of talk in the community, as well as some patients, that believe that PD-1 has taken over, and it has for the hot tumors. But at the same time, if you think of bladder cancer, it only has a 15% response rate. The majority of bladder cancers don't respond to it. In melanoma, it's only 30%. That means a majority of people – 70% – don't respond to it. So I just want to be careful. Yes, PD-1 has more FDA approvals, but for most cold tumors or unresponsive tumors, you do need the anti-CTLA-4. Not all, but most of them. So I think it's going to be making a comeback.

Now that ipilimumab and tremelimumab are off patent, you’re going to see the next generation of anti-CTLA-4 being developed, because they have the ability to do a couple of things: drive T-cells into a cold tumor, and also cause antigen spread. Those are things they could do. So I just want to clarify those points.

Tony Ribas from UCLA, who is a melanoma doctor, has shown that some of the patients who have responded to PD-1 have responded because of previous failures from anti-CTLA-4. So that anti-CTLA-4, his data suggests, and this is from patients, that anti-CTLA-4 modulates the tumor microenvironment. So that in the future anti-PD-1 can be effective. So just want to put it out there, that anti-CTLA-4 is making a comeback.

So then, “What are my top three?” When it comes to prostate cancer, which is what I think about the most, I think that something that can get at the bone, and this is where I feel like the backbone most likely will be T-cell bispecific in nature, at least at this time. Things may change. And then, depending on what the resistance mechanism is, you probably have to add an immune checkpoint therapy. In addition, because prostate cancer has a lot of myeloid cells in it,

you probably also need a myeloid inhibitor. Right now we're looking at the adenosine pathway and targeting that as a way.

Rick Stanton 1:01:39
I was very excited about Akoya Biosciences' (spatial analysis) technology to query the tumor microenvironment. But it seems to have no clinical utility. Do you have an interest in that? Or is that moving forward?

Sumit Subudhi 1:02:04
I'm not familiar with their technology. Can you expand on that?

Rick Stanton 1:02:11
It's imaging. Antibody. It'd be like a standard IHC stain except that it's antibody-driven with multiple color fluors. It's a stain and wash technology. You can go up to like 50 or 60 deep. Inquiry into CD-8, CD-4.

Sumit Subudhi 1:02:38
When we were talking before about BostonGene, and someone else was talking about Tempus, we were talking about doing bulk RNA-seq. Then more recently, single-cell RNA-seq has gotten in vogue. We believe, and this is what Rick is alluding to, that understanding the spatial relationship of where the various immune cells are within the tumor microenvironment is important, because the bulk RNA-seq doesn't tell you where the T-cells are. What if the T-cells are in the margin of the tumor and not in the center of the tumor? You don't get that information from this (bulk) approach. But these new technologies, such as CODEX, the one that you are referring to, maybe these are new spatial technologies at the single-cell level that will tell you the spatial relationships.

They can do, right now, I'd say, up to 40 to 50; closer to 40 is accurate. They'll give you higher numbers, but in our hands, we can feel confident with 30; 40 is starting to push the edge. But the people who invented it, like Garry Nolan (at Stanford), will say he can do 50 to 60.

One of the issues with it, and we're finding, is that the bioinformatics takes about six months. Our bioinformatics team takes six months to do it. Whereas companies like BostonGene are starting to use it, and they can turn it around in about four weeks because they have the infrastructure and the money to do it. That's the direction. When bioinformatics catches up and the cost goes down, that's definitely where we need to go.

Rick Stanton 1:04:53
On the bispecifics: I understand the two antibody arms, but what is the driving force to make that connection? In other words, how is that bispecific going to get to the tumor? Why wouldn't it just float around in the body and go away? Is it just the affinity?

Sumit Subudhi 1:05:19

We don't know what that threshold is. One of the things that we're doing with the companies that we're working with on the PSMA bispecifics is we're looking at pretreatment scans, as well as the pretreatment tissue by immunohistochemistry, because we want to look at the protein level as well as the transcriptional level to see what that threshold is to get a response. I have a feeling that there is probably some threshold where it's just too low. We have to answer the question, because it's so much easier to do it at the RNA level, than at the protein level. But sometimes RNA does not equal protein, meaning you can have high transcriptional levels or RNA levels, but it'll give you low protein levels. And sometimes they're correlated. These are the questions we have to ask, and we are asking,

Rick Stanton 1:06:20
How do you feel about B7-H3?

Sumit Subudhi 1:06:25
We're working with MacroGenics to try to bring that into our clinic.

Rick Stanton 1:06:30
I'm probably going to go on that clinical trial out of UCLA very shortly.

Sumit Subudhi 1:06:34
I've had some patients respond to it. I'm not running the trial; our Phase I group is, and I've sent my patients there, and some are doing well.

Rick Stanton 1:06:44
I hope I'm one.

TLR agonists (toll-like receptor initiators, potent vaccine adjuvants that help induce an immune response, activating dendritic cells, augmenting T-cell responses, and downregulating the suppressive effects of regulatory T-cells) to boost immune response in the TME (tumor microenvironment) was something that I was excited about five years ago. Is anything happening there?

Sumit Subudhi 1:06:59
The problem with a lot of TLR agonists is you have to inject them. Prostate cancer is not an easy cancer to be injected into, unless we can figure out how to inject it into the bone. But even that's going to be not easy to do. It's not something that you can just do in a clinic readily. Melanoma is a much easier cancer to do that.

Rick Stanton 1:07:26
I worked at Amgen for 17 years. I live in the shadow of Amgen. My Amgen homies I see on the park, they say, “Hey, we got this new bispecific. You really need to check it out.” Are you excited about Amgen’s bispecific?

Sumit Subudhi 1:07:45

Yes. We're running trials with them. I can’t share more than that. Because they're so early, and anything I say can change stock markets.

Rick Stanton 1:07:56
I was pals with Arcus Biosciences folks. I used to report to them while I was at Amgen, and I went on their PD-L1 adenosine inhibitor. (Adenosine suppresses the activation of naïve CD8 T-cells by inhibiting T-cell receptor signaling events.) It didn't work. Could I have gained predictive insights from RNA seq or other assays that would say, “Yeah, you're probably not going to respond.”?

Sumit Subudhi 1:08:25
I'm the national leader on that trial. I had some patients that did respond really well, and continue to.

Rick Stanton 1:08:35
In my youth, I developed a cancer battle map which contained the cells that you showed earlier – the good cells, the bad cells – and decorated the expression from RNA seq onto the battle map. I left that behind because I ran out of juice. Do you see value in that? Would that have any clinical utility?

Sumit Subudhi 1:09:23
It's hard right now because you have to contextualize it. That's why even when I tried to create an algorithm and share it with other institutions and colleagues, it's difficult to do because you need more context.

I know there are more questions. Please forward them through Brad.