“Update on Immunotherapies (CARs and BiTEs) for Solid Tumors” (Saul Priceman, PhD) [#117]

Brad Power and Kayla Yup
October 23, 2024

“Every institution under the sun, but certainly in the United States, should be doing cellular immunotherapy, whether it's CAR-T cell therapy or other immunotherapy approaches, because I do believe that rewiring the immune system probably has a hand in every single human disease, and certainly in cancer. If we can redirect the immune system to identify that cancer, that is the most likely to provide durable therapeutic responses, as opposed to what we're all used to, which is types of chemotherapies or other druggable entities that you have to take over and over again.” – Saul Priceman, PhD

Meeting Summary

Advanced cancer patients see immunotherapy (a treatment leveraging the immune system) as offering one of the best paths to a durable response. Cellular immunotherapies have demonstrated success in achieving durable remissions for advanced cancer patients in blood cancers; however, they have had limited success in solid tumors, such as prostate, pancreatic, or breast cancer. There is one cancer vaccine approved, and it is in prostate cancer (Provenge). Supplementing a patient’s immune response by engineering their killer white blood cells to recognize, bind to, and eliminate the tumor is a new and transformational area of cancer immunotherapy. Several cellular immunotherapies are being heavily tested clinically for the treatment of prostate cancers and other solid tumors that have the potential to provide durable and even curative responses:

- **T cell bispecifics**: antibodies (proteins that help the body's immune system identify and destroy harmful substances like bacteria and viruses) that physically link T cells (white blood cells in the immune system which kill foreign cells) with cancer cells
- **TILs (tumor-infiltrating lymphocytes)**: white blood cells that are extracted from a patient's tumor and used to treat cancer
- **TCR (T-cell receptors) T cells**: protein complexes on the surface of T cells that recognize antigens and trigger immune responses
- **CAR (chimeric antigen receptor) T cells**: T cells (white blood cells) that have been genetically modified to express a synthetic receptor that enables them to better identify and kill tumor cells

Saul Priceman, PhD, is the Founding Director of KSOM/NCCC Center for Cancer Cellular Immunotherapy Research at the University of Southern California. He is uniquely qualified to describe the landscape of new immunotherapy treatment options available to cancer patients with solid tumors. He is a scientist with a strong understanding of cancer biology and tumor immunology for the preclinical/clinical development of novel cancer immunotherapies, with over 15 years of in-depth knowledge of molecular and cellular biology related to cancer and inflammation/autoimmune research, with a strong focus on metastatic disease in prostate, breast, and ovarian cancer. His current laboratory research focuses on clinically relevant metastatic cancer models to develop combination therapy strategies to improve the durability and potency of CAR-T cells, and ultimately the overall immunotherapy response in solid tumors. He received a B.S. in microbiology from UCSB and a PhD in Molecular and Medical Pharmacology from UCLA.

How does your immune system fight cancer?

The immune system has evolved to protect us from pathogens such as bacteria, viruses, and fungus. When an infection arises, the immune response is triggered, all of the infection is eliminated, and then the immune response goes back down. But a memory of the infection persists, and you get a healthy memory cell, so that if you see that pathogen again, it can react quickly.

What are the challenges in leveraging the immune system to fight solid tumors?

- **Immune system exhaustion**: The immune system can get tired of fighting cancer if it sees the tumor too much. If the tumor doesn't completely go away early in the process, the immune cells become exhausted, and are just not as functional. They may need to be reactivated.
- **Tumor heterogeneity and evolution**: We go after a target which is uniquely on the cancer cell (e.g., PSMA or PSCA in prostate cancer), but the target has to be expressed on 100% of the cancer cells to get a complete response, but they aren’t. There's heterogeneity, or a mosaic of cell types that make up the cancer cells. So we get less than a 100% response. Some of the cancer cells without the target survive.
- **Hiding**: The immune system never saw the tumor in the first place, because tumors can be clever, able to block recognition by the immune system.

How do immunotherapies work to treat cancer?

Immunotherapies (a treatment leveraging your immune system) offer one of the best paths to a durable response -- they are fighting a biological system (your cancer) with another system (your immune system), rather than the hit-and-miss, less durable approach of targeting a biomarker with a single drug or poisoning your cancer with chemotherapy. The idea is to try to find what's different about the tumor that is allowing it to avoid the immune system. Sometimes the tumor turns things back on that are generally turned off in people, sometimes it turns up the volume on things that are generally turned down. So if you can find these reactivated genes, you can perhaps get the immune system to recognize them and attack them. But the immune system doesn't usually recognize them without a vaccine because a successful tumor shields itself from the immune system by being a terrible antigen-presenting cell. Immunotherapies offer a treatment option to nearly every cancer patient because they are neither targeted to a specific “tissue of origin”, like lung cancer or colon cancer, nor are they targeted to a biomarker, a protein that your cancer cells overexpress, like BRCA or EGFR.

What is happening at the cutting edge of immunotherapy approaches in solid tumors?

“Bispecific T cell engagers” and “CAR-T cells” are two types of immunotherapies currently being tested against solid tumors.

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- **Bispecific T cell engagers (BiTEs)**: antibodies (proteins that help the body's immune system identify and destroy harmful substances like bacteria and viruses) that physically link T cells (white blood cells in the immune system which kill foreign cells) with cancer cells. The idea is that this linkage will trigger the activation of T cells and induce targeted killing of the tumor cells. There are currently over three BiTEs being pursued for treatment of prostate cancer. For example, AMG 160, a BiTE that targets Prostate-Specific Membrane Antigen (PSMA, a receptor that is uniquely on prostate cancer cells), was found to elicit a robust response rate with limitations related to toxicities and anti-drug antibodies in a Phase I clinical trial. AMG 509, a BiTE targeting STEAP1 (six-transmembrane epithelial antigen of prostate 1, is a protein that is overexpressed in many types of cancer, such as prostate cancer, and is a promising target for cancer therapy because it is specific to cancer cells and on the membrane), showed better efficacy and less toxicity in phase 1 (safety) studies, and will likely proceed to phase 3 (efficacy studies). Next generation PSMA bispecifics are also being tested.
- **CAR-T cells**: T cells (white blood cells) that have been genetically modified to express a synthetic receptor that enables them to better identify and kill tumor cells. There are various CAR T cell therapies being developed to target PSMA and PSCA (Prostate Stem Cell Antigen, another receptor uniquely on the surface of cancer cells) in prostate cancer. Dr. Priceman published a list of some clinical trials currently testing these therapies. His lab at City of Hope is working on CAR T cell therapies for four cancers in particular: prostate, breast-to-brain metastasis (which is breast cancer that has spread to the brain), ovarian cancer, and pancreatic cancer.

What can you access today?

- Sipuleucel-T (also known as Provenge) is FDA approved for prostate cancer.
- Bispecific T cell engagers for prostate cancer, which are in clinical trials. (For example, AMG509: targets STEAP1 in a clinical trial.) About 30% of patients had their PSA (a blood measure of prostate cancer strength) drop 90% or more. Most patients had a PSA reduction of 50%, which is striking. In coming years, the toxicities will be better managed, and this trial indicates that “cold” solid tumors (those that usually don’t respond to immunotherapy) can respond.
- CAR-T cell therapies for prostate cancer, which are being tested in clinical trials. (Note: some trials on Dr. Priceman’s list may no longer be actively recruiting or may have been terminated, need to check https://clinicaltrials.gov for the latest.)
- Combinations of immune checkpoint blocking antibodies (in clinical trials). (See for example the slide titled: Select ongoing checkpoint inhibitor trials in mCRPC.)

What will be available soon?

- Other BiTEs
- A faster CAR-T manufacturing process: “vein-to-vein” (blood extraction through engineering and reinfusion) will go from about six weeks to a week or two.

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- “Allogeneic” vs. “autologous” CAR-T: make CAR-T cells from a healthy person and treat dozens of people (vein-to-vein time of zero) vs. using the patient’s T cells

What is being researched for the future?

- Distinguishing characteristics between cancers that are immunologically “hot” (will respond to immunotherapy) and those that are “cold” (manage to hide from the immune system)
- Combining therapies to turn “cold” cancers “hot” in solid tumors (will respond to immunotherapy), such as pancreatic cancer
- Tests to predict whether a patient will respond to an immunotherapy

How can I learn more about immunotherapies for solid tumors?

- See our discussion with Dr. Sumit Subudhi on “Update on Immunotherapies for Metastatic Castrate Resistant Prostate Cancer” [#66]
- Lisa Butterfield on cancer vaccines here
- Willy Hoos on personalized neoantigen vaccines here
- Gary Onik on personalized in vivo immunotherapy for “cold” cancers here
- BostonGene on predicting immunotherapy response with a diagnostic test here
- Matthew Dons on growing your white blood cells here
- Contact Dr. Priceman to further explore the use of AI and machine learning in predicting patient response to CAR-T-cell therapy and on making "cold" tumors more responsive to immunotherapies at priceman@usc.edu

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Meeting Notes

KEYWORDS

CAR-T cells, cancer immunotherapy, solid tumors, prostate cancer, cellular immunotherapy, USC, City of Hope, immune checkpoint blocking, bi-specific T cell engagers, PSMA, PSCA, clinical trials, AI in cancer, patient response prediction, adoptive cell therapy

SPEAKERS

Saul Priceman (76%), Brian McCloskey (13%), Robb Owen (7%), Rick Davis (2%), Roger Royse (2%)

CHAT CONTRIBUTORS

Rick Davis, Robb Owen, Alane Watkins, David Plunkett, Alexander Lalov, Steven Merlin, Chris Apfel, Roger Royse, Brian McCloskey

SUMMARY

Brian McCloskey introduced Dr. Saul Priceman, highlighting his expertise in CAR-T cell therapy. Dr. Priceman detailed the evolution of CAR-T cells, their effectiveness in hematologic malignancies, and challenges in solid tumors. He discussed the importance of identifying immunologically cold tumors and the potential of bi-specific T cell engagers. Dr. Priceman shared success stories, including a glioblastoma patient with dramatic responses and a prostate cancer patient with significant PSA reductions. He emphasized the need for better predictive models to identify responding patients and the potential of AI in enhancing immunotherapy efficacy. The session concluded with a Q&A addressing various aspects of CAR-T cell therapy and its applications.

OUTLINE

Introductions

- Dr. Saul Priceman has expertise in CAR-T.
- He has recently moved to USC.
- He worked previously at City of Hope.
- He has a vision for expanding cellular immunotherapy at USC.

Overview of Cancer and Immune System

- The immune system can be rewired to treat various diseases, especially cancer.
- Cancer is complex. It is a mosaic of different cell types.
- Cytotoxic T cells have a role in identifying and killing cancer cells.
- Tumors can be immunologically cold or warm, e.g., in prostate cancer and melanoma.

CAR-T Cells and Bi-Specific T Cell Engagers

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- Current immunotherapies, such as CAR-T cells and bi-specific T cell engagers, have limitations and big potential.
- CAR-T cells have a role in targeting cancer markers.
- The clinical data and FDA approvals for CAR-T cells in hematologic malignancies show the potential.
- CAR-T cells, bi-specific T cell engagers, and antibody-drug conjugates are different in terms of efficacy and durability.

Challenges and Future Directions

- There have been challenges and successes in applying CAR-T cells to solid tumors, with glioblastoma and gastric cancer as examples.
- The challenges of applying CAR-T cells to solid tumors include the tumor microenvironment and antigen heterogeneity.
- Dr. Priceman’s lab works on PSCA-directed CAR-T cells for prostate cancer, including animal studies and clinical trials.
- Multi-targeted approaches have big potential.
- There are ongoing trials and collaborations at USC and other institutions to advance cellular immunotherapy.

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TRANSCRIPT

Brian McCloskey 0:00
I'm a co-founder of the Cancer Patient Lab.

We're very honored today to have Saul Priceman join us.

Before I get into an introduction to him, I wanted to remind folks of a few things regarding this session. First off, this is not medical advice, so please make sure to consult your physician before you take any action on any information that you would learn today. We are a nonprofit, and so all of our expenses are paid for through the great support of our community. If you'd like to join or if you'd like to donate, please go to our website and hit the donate button and you can make a donation there.

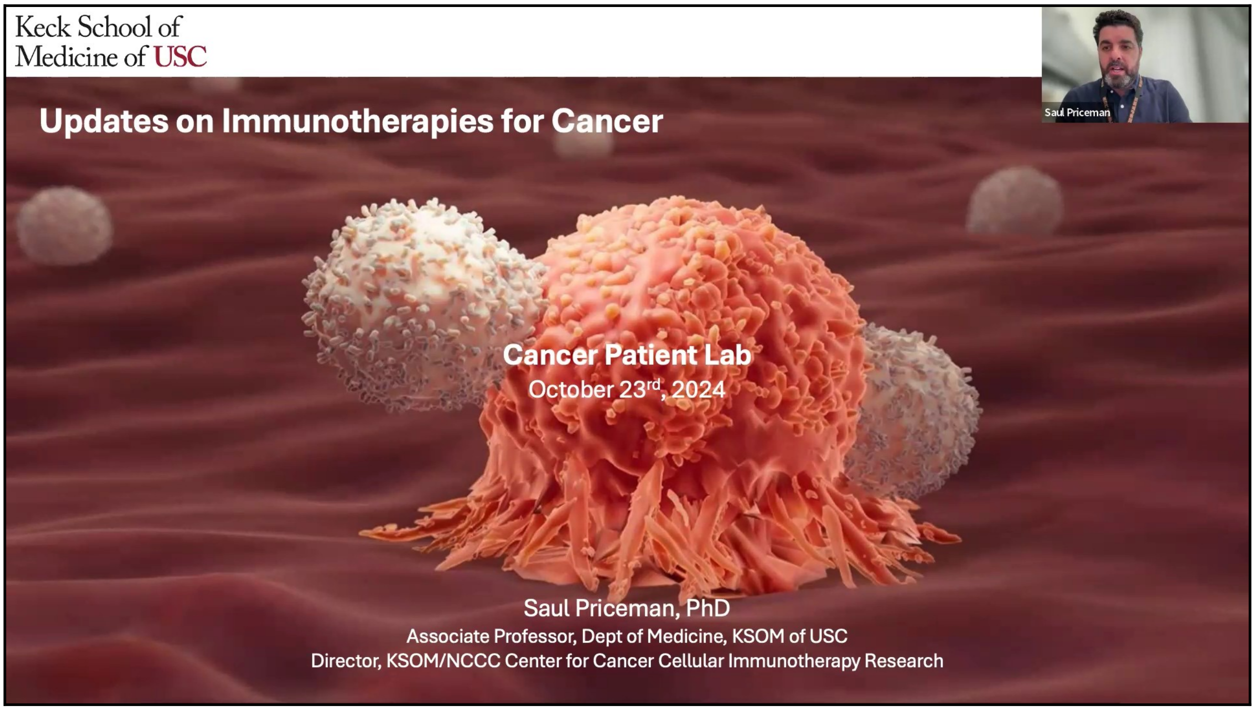
I am super excited to have Dr. Saul Priceman join us today. I've known Saul now for probably four years or so when we met in DC at a convention, and Saul has been very helpful in my journey as a prostate cancer patient. I'm happy that he's here. For many years, he was driving the CAR-T development at the City of Hope, and just in September, Saul became the founding director of the Keck School of Medicine and Norris Cancer Center, cancer cellular immunotherapy research at USC. He is an expert in CAR-T and has driven many, many programs.

Today he's going to talk about what CAR-T is, particularly as it relates to solid tumors, which is going to be most appropriate for our community, and what the latest and greatest is with CAR-T. I'm excited to have him join us, and looking forward to an interactive conversation.

Saul Priceman 3:09
A little background to me. I'm 45 years old, and I've lived in Los Angeles for 42 of those years. I went to UC Santa Barbara for undergrad. I worked at a company called Amgen, which you may have heard of in Thousand Oaks for a couple of years, and decided to go get my PhD at UCLA. After that, I went straight to City of Hope, and have spent the last 14 years there as a postdoctoral fellow and moving all the way through junior faculty to an Associate Professor position, and then, as Brian said, in September, I moved to USC to lead their cancer cell therapy center. It's a great opportunity, because, you know, City of Hope has been well established in this area, with 40 plus years of bone marrow transplants, which is the most—someone's going to get mad at me—but the archaic version of cellular immunotherapy, and over the last 20 or so years, have been doing what we now term as synthetic engineering and adoptive cellular therapy, and I'll describe that. My move to USC is really to build that out here.

The idea is that every institution under the sun, but certainly in the United States, should be doing cellular immunotherapy, whether it's CAR-T cell therapy or other immunotherapy approaches, because I do believe that rewiring the immune system probably has a hand in every single human disease, and certainly in cancer. If we can redirect the immune system to identify that cancer, that is the most likely to provide durable therapeutic responses, as opposed to what we're all used to, which is types of chemotherapies or other druggable entities that you have to take over and over again. And there's no evolution of that therapy—once you have resistance to that therapy you're in need of something else, rather than what the immune system could provide, which is something that evolves with the cancer and could be there for much longer or indefinitely.

We could go into an immunology 101, and we could describe how you know when you're vaccinated at a very young age or infected with something at a very young age, your immune system recognizes it, and *can* recognize it for the rest of your life. If we can do that with cancer, that would be the best approach.



Brian McCloskey 6:23
We've got a pretty scientific crowd even with our patients, so don't hold back.

Saul Priceman 6:31
I love that. I have 30-odd slides, so I'm going to run through some of them, and I may skip some of them, but they'll be there. And I can send the slide deck over to the Cancer Patient Lab, and you can all read through it, and I'm obviously always around if there are questions. We can provide my email address.

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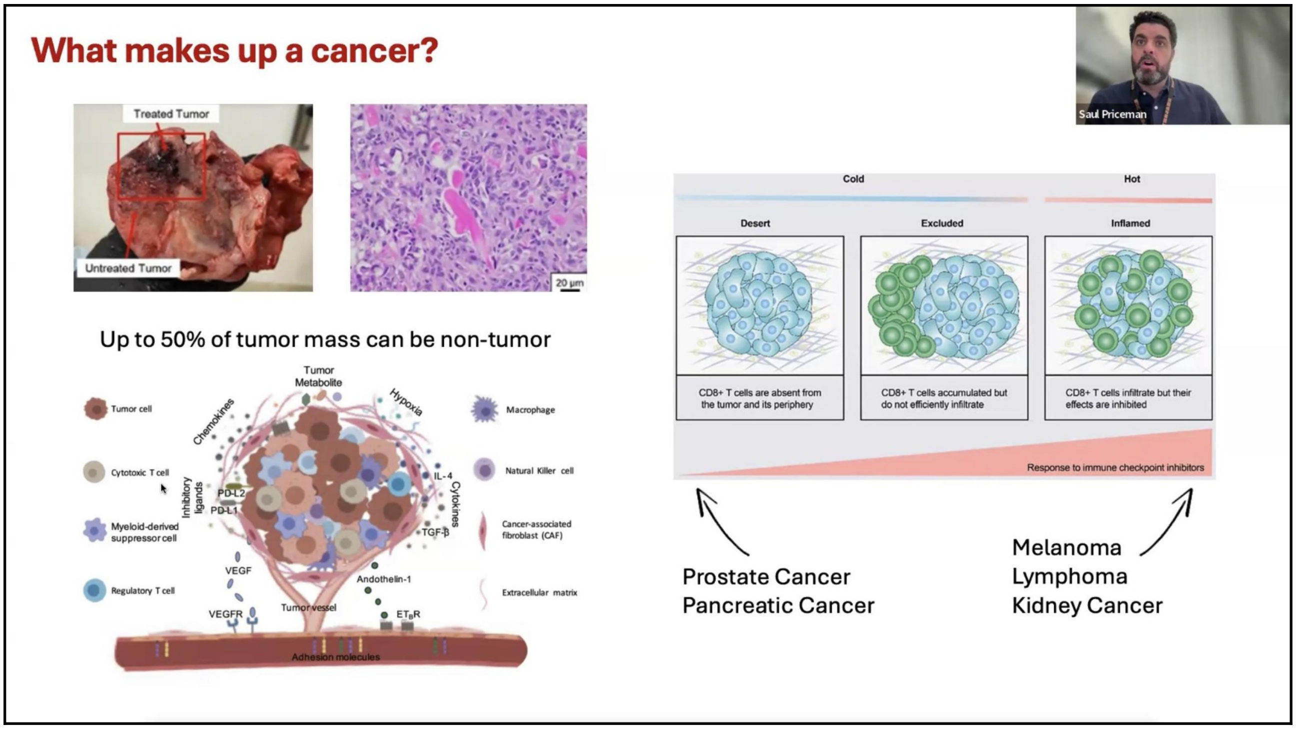
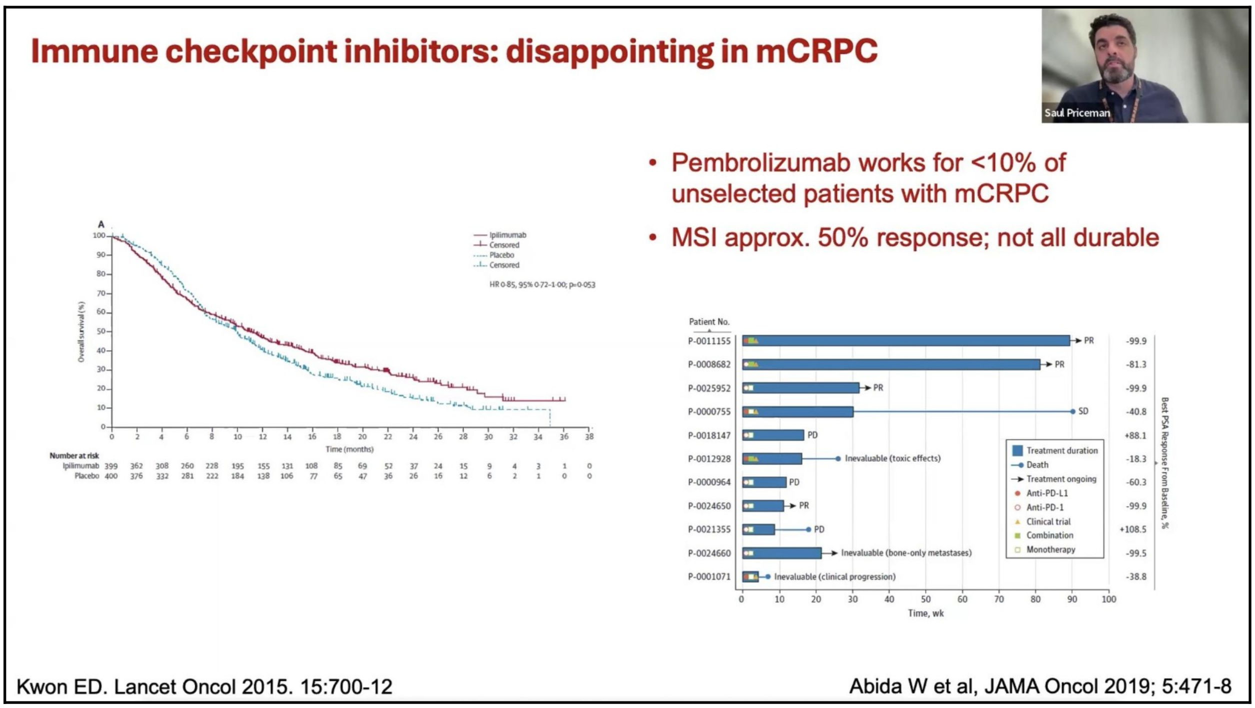


I thought I'd start here: What makes up cancer? When I was growing up and learned about cancer, I thought it was all cancer cells sitting in a mass, but the reality is, it's a mosaic of all different types of cells. So if you just looked at a gross tumor (where gross can refer to the palpable or visible extent of the tumor, and a gross description may include the size, appearance, and weight of the tissue without using a microscope), which is gross by definition, but also gross by histology, you can see that there's a lot going on there. And if you just take that little bit and you look at it at a high magnification, at the different cells, you can appreciate that there are tons of different types of cells there.

I'm going to show an animation that shows you what cells there could be. Here shown in dark brown is a tumor cell, but you also have immune cells, mostly fibroblasts (connective tissue cells that synthesize the extracellular matrix and collagen), which make up the tissue integrity, and you have vasculature and other cell types. I'll go into a bit more detail about the immune system, but not too much. I mean, we could spend hours on this.

There are cytotoxic T cells, which we really focus on, which are your killer cells. They actually identify virally infected cells or cancer cells, and literally touch them, poke holes in them, disrupt their cellular integrity, so that they [the cancer cells] ultimately die. Those [cytotoxic T cells] are the things that fight off infections.

We term cancers on a spectrum, with the two ends of the spectrum being immunologically cold and immunologically warm. Some tumors have an immune response [in the case of immunologically warm tumors]. Their makeup of the tumor could be such that up to 50% of the mass is infiltrated by immune cells. What are they [the immune cells] doing there? They're actually seeing the cancer, and they want to fight the cancer, but they're being overcome by some mechanism. This contrasts with immunologically cold tumors, where there's literally nothing happening: the immune system has not recognized it [the tumor], or did and has given up, or the tumor evaded that recognition, and those immune cells have left the country. They're not seeing anything. The most common examples of that, unfortunately, are prostate cancer and pancreatic cancer. There are a number of those cancers that are deemed immunologically cold, and there are some cancers that are immunologically warm, meaning they have an immune response happening that has to be unleashed in some way. For melanoma, lymphoma, kidney cancer, and a number of others, if you put an immune checkpoint blocking antibody (for context, [immune checkpoint proteins](#) regulate the immune system by turning it off. Normally this is needed to prevent an immune response from becoming too strong and damaging. However, in the context of cancer, you would want your T cells, cells of the immune system, to be active and able to kill tumor cells. The goal of immunotherapy drugs called immune checkpoint inhibitors, which work by blocking checkpoint proteins from binding their partner proteins, is to prevent T cells from being turned off)—that's the classical immunotherapy—you can release a brake that's being put on the immune system and the immune system can now recognize the cancer.



The term mCRPC here refers to metastatic castrate-resistant prostate cancer (prostate cancer that no longer responds to hormone therapy that lowers testosterone). The response rate to the immune checkpoint blocking antibodies compared to the control in metastatic castrate-resistant prostate cancer is relatively underwhelming. There's little response. There have been responses demonstrated in some patients who have what's called microsatellite instability which creates more DNA mutations in the cancer cell (a microsatellite is a short segment of DNA that repeats. Microsatellite instability occurs when there’s a defect in DNA mismatch repair, leading to replication errors and an accumulation of mutations within microsatellite repeat sequences).

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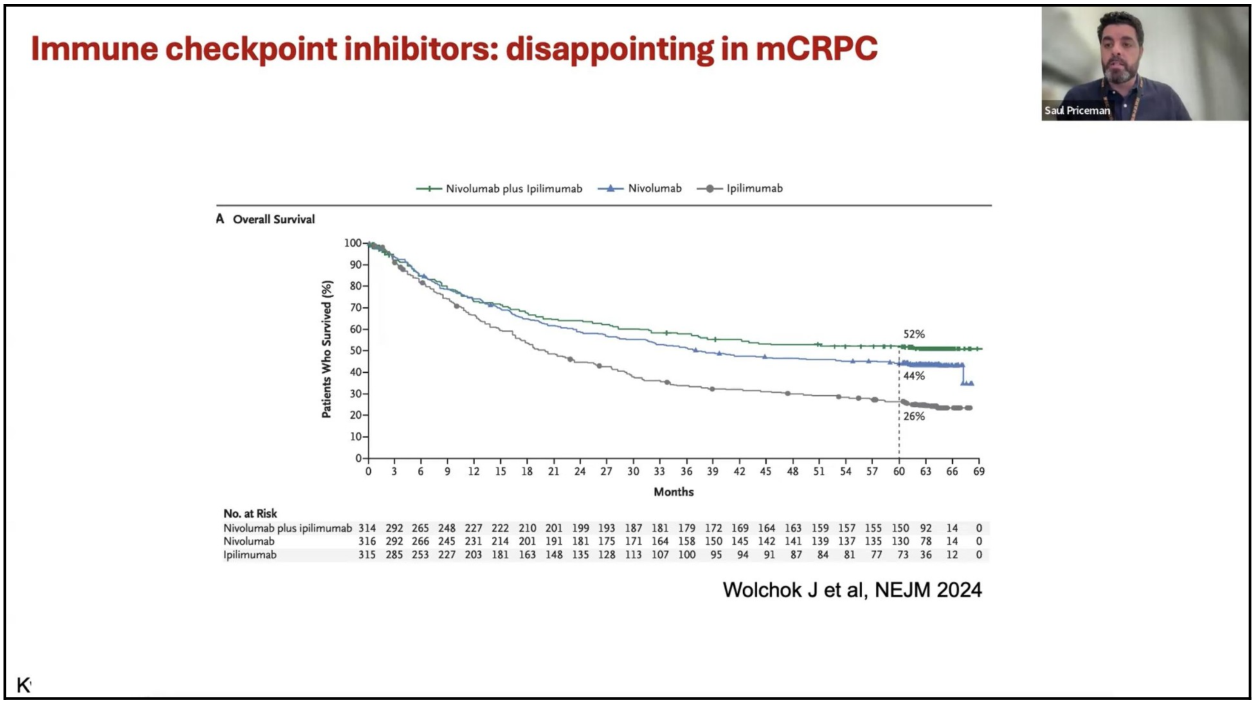
They're more likely to present antigens to the immune system. They're more likely to respond to an immune checkpoint blocking antibody.



That's in contrast to melanoma, which I mentioned before. Unfortunately, this survival curve doesn't show what used to happen; the survival curve used to drop off completely before, let's say, 24 months. Now, you're getting a durable curative response in about 25% of patients. If you combine some immune checkpoint blocking antibodies, you can provide curative responses to about 50% of patients with advanced melanoma, which is striking and suggests that in immunologically warm tumors, you *can* redirect the immune system to recognize and fight off the cancer in a durable way.

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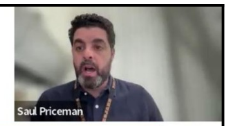
Select ongoing checkpoint inhibitor trials in mCRPC



Name/NCT	Agent(s)	Design	Population
NCT04946370	Pembrolizumab and ARPi +/- 225Ac-J591 for mCRPC	Phase I/II	mCRPC post ARPi (no prior chemo)
NCT04090528	pTVG-AR DNA Vaccine and Pembrolizumab	Phase II	mCRPC (prior ARPi OK)
NCT05445609	Vidutolimod + Pembrolizumab	Phase II	mCRPC post ARPi and chemotherapy
NCT05733351	Vudalimab (Xmab20717)	Phase 1 Multiple cohorts	mCRPC with Olaparib, post Olaparib, with chemo
NCT04471974	ZEN-3604, Enzalutamide and Pembrolizumab for mCRPC	Phase II	mCRPC
NCT04848337	PLANE-PC: Lenvatinib + pembrolizumab in NEPC	Phase II	NEPC defined by low PSA with liver mets as well as histology or serum ChrA

Going back to prostate cancer, there are a number of trials where they're combining immune checkpoint blocking antibodies with other therapies. And I won't go through the list [of clinical trials], but I will send this to you. These are the NCT numbers (National Clinical Trial (NCT) number is an identification number assigned to a clinical trial by ClinicalTrials.gov when it is registered). You can find them [the clinical trial numbers] depending on where you live and what you're eligible for. I'm a scientist, so I won't go through the inclusion/exclusion criterias for these trials, but you should look at them. They are combinatorial therapies based on mechanistic hypotheses that suggest that these combinations with checkpoints will improve the responses in otherwise immunologically cold tumors like prostate cancer.

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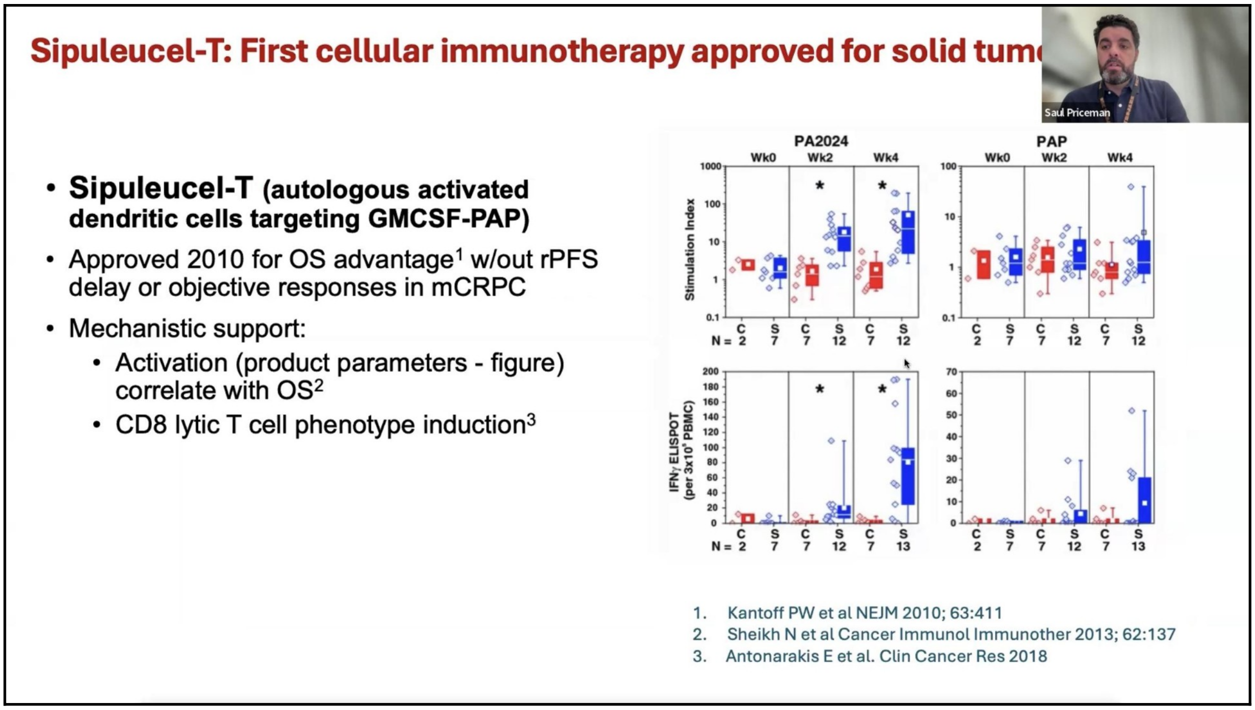

Many, many years ago, the first FDA-approved cellular immunotherapy [made from a patient’s own immune cells] was actually for prostate cancer. It was called Sipuleucel-T. Many of you may know this, and I won't go through the details of this either, but it's basically one of the immune cells called a dendritic cell, which is the guy that goes to a tissue, finds some bad stuff, gobbles it up, and presents that to the T cell. The T cell then recognizes exactly what that gobbled up stuff is, and then goes out and finds those things and kills them. (In other words, a dendritic cell is a specialized immune cell that plays a key role in activating the immune response against a detected threat). Pretty smart scientists decided we're going to take those dendritic cells out. We're going to give them what they need to present to the T cell, and we'll infuse them back into patients. The responses have been okay. They're not really great, but what they did suggest was that even in immunologically cold tumors, you could maybe develop a cellular immunotherapy that changes the landscape of treatment for patients.

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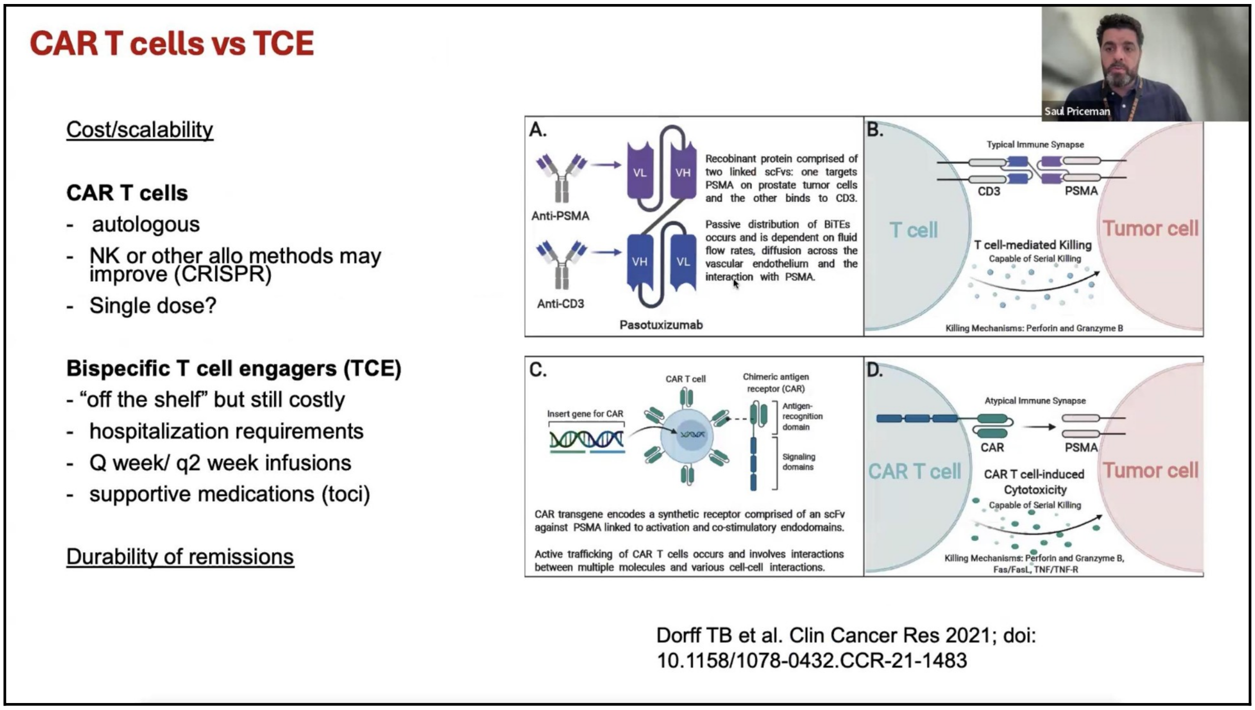

Then we get to the more active and more specific types of immunotherapy. So I'll cover those today.

These include:

- CAR-T cells, which stands for chimeric antigen receptor T cell
  - An illustration of a CAR-T cell is shown on the bottom right
  - We take T cells out of the body of Patient A. We engineer those T cells with a CAR, which is a synthetic receptor that's displayed on the surface of that cell. That then allows redirection of that T cell to identify a cancer marker. Then we put them back into the body, and they go seek out that cancer marker. When they identify that cancer marker on the surface of the tumor cell, they engage and kill that tumor cell.
  - I'll show you some clinical data and some FDA approvals that have already happened with CAR-T cells.
- Bispecific T cell engagers
  - Bispecific T cell engagers are a little more of a druggable version of that. It's not cellular therapy where you infuse a cell, rather you're infusing a drug. That drug physically links the T cell with the tumor cell using similar mechanisms. But it's an antibody with two specificities: it touches the T cell, it touches the tumor cell, and puts them in close proximity. The T cell gets excited and kills that cell.

These immunotherapies are being actively worked on in prostate cancer.

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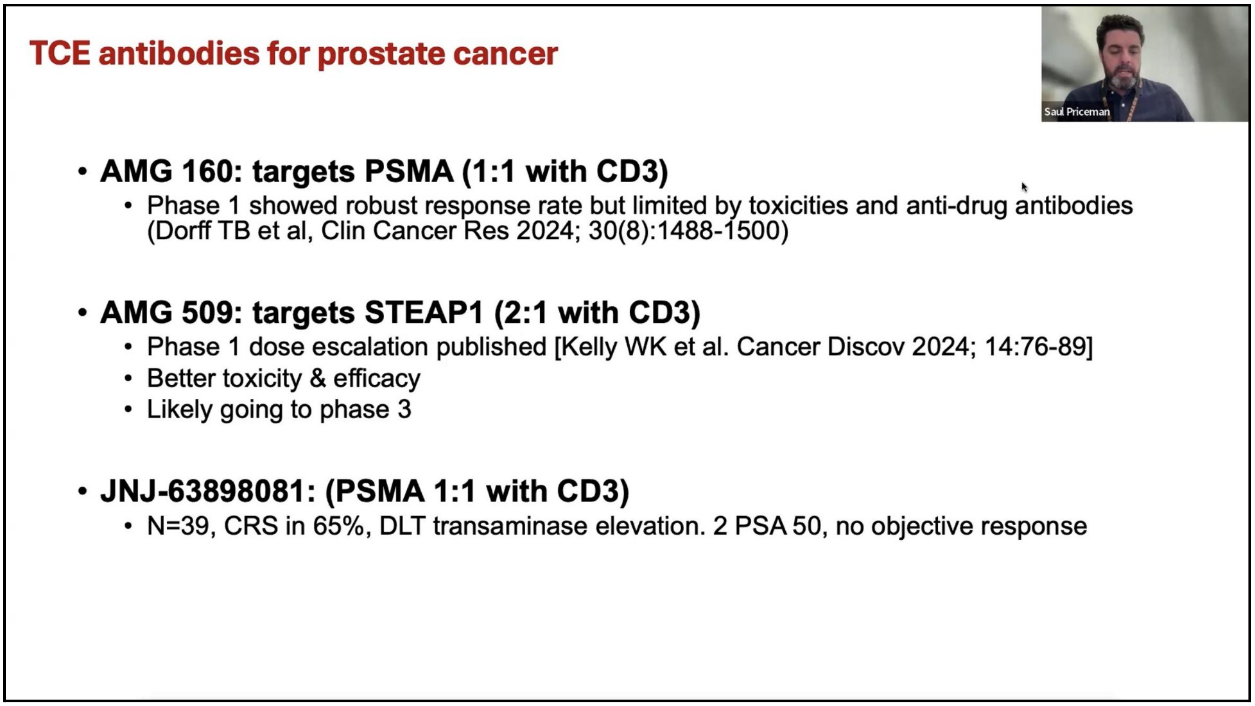

Backing up a little bit, I work on prostate cancer, but it's not my sole focus. Most immunotherapy people don't work on one cancer because they think that this type of immunotherapy can work for multiple cancers. I'm highlighting prostate cancer because it’s where we started.

There are now actively more than three bispecific T cell engager therapies that are being pursued in prostate cancer:

1. One targets our favorite, PSMA, which is Prostate-Specific Membrane Antigen (an antigen that is generally highly expressed in prostate cancer cells). PSMA has been all the rage in prostate cancer [research/treatment] recently because of its diagnostic utility, as well as its use in therapies like radioligand therapy, which is systemic radiation that's been approved for PSMA-positive prostate cancers (radioligand therapy involves use of molecules labeled with radioactive isotopes that specifically target cancer cells and deliver radiation directly to the tumor).
2. STEAP1, is a new kid on the block. It’s very exciting. I'll show some PSA responses with STEAP1 bispecifics.
3. Next generation PSMA bispecifics are also being tested.

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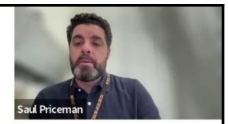
AMG160: adverse events



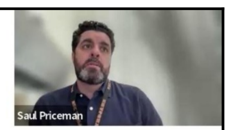
TEAE	Dose expansion (N = 56)	
	Any grade n (%)	Grade ≥ 3 n (%)
Cytokine release syndrome	55 (98.2)	9 (16.1)*
Anemia	20 (35.7)	11 (19.6)
Hypophosphatemia	20 (35.7)	9 (16.1)
Alanine aminotransferase increased	12 (21.4)	3 (5.4)
Aspartate aminotransferase increased	11 (19.6)	3 (5.4)
Platelet count decreased	8 (14.3)	3 (5.4)*
Hypertension	4 (7.1)	3 (5.4)
Neutropenia	4 (7.1)	4 (7.1)*

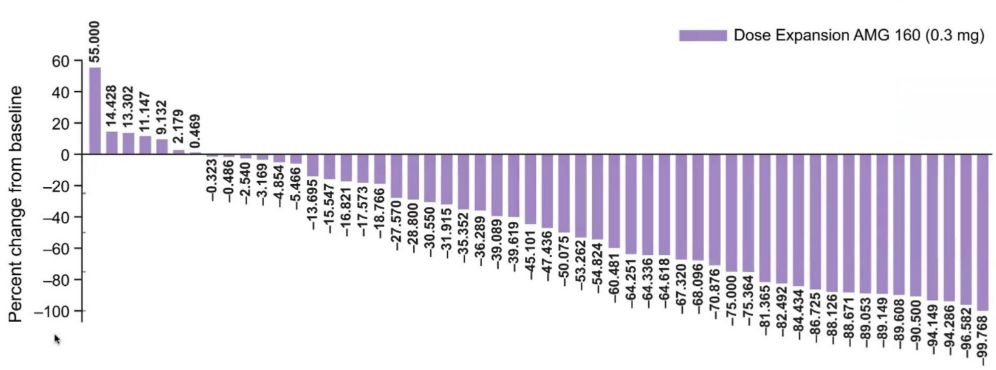
*Includes one patient who experienced a grade 4 event
Abbreviation: TEAE: treatment-emergent adverse event

Dorff TB et al, Clin Cancer Res 2024

I'm not going to go through adverse effects very much, but none of these immunotherapies are without immunological responses and some adverse toxicities. You can see here that the most common adverse effect is cytokine release syndrome, which is a response to inducing an immune response in a patient where they have more cytokines being produced. Cytokines are mediators of the immune response. The syndrome can be somewhat dramatic—it’s typically resolved—but in more severe cases, that can actually cause mortality.

PSA responses with AMG160 (PSMA TCE) at full dose





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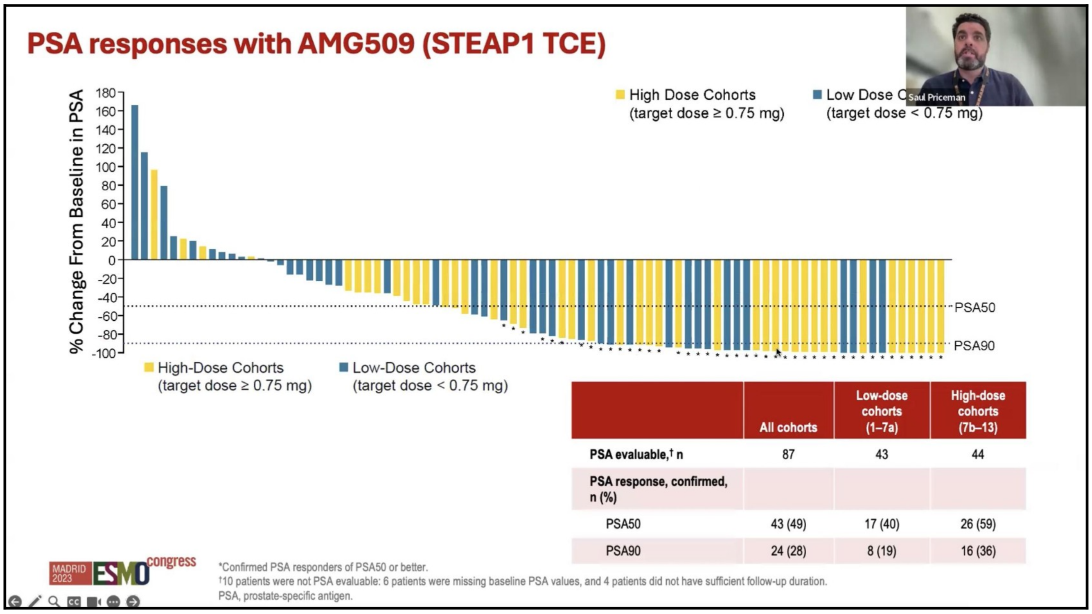
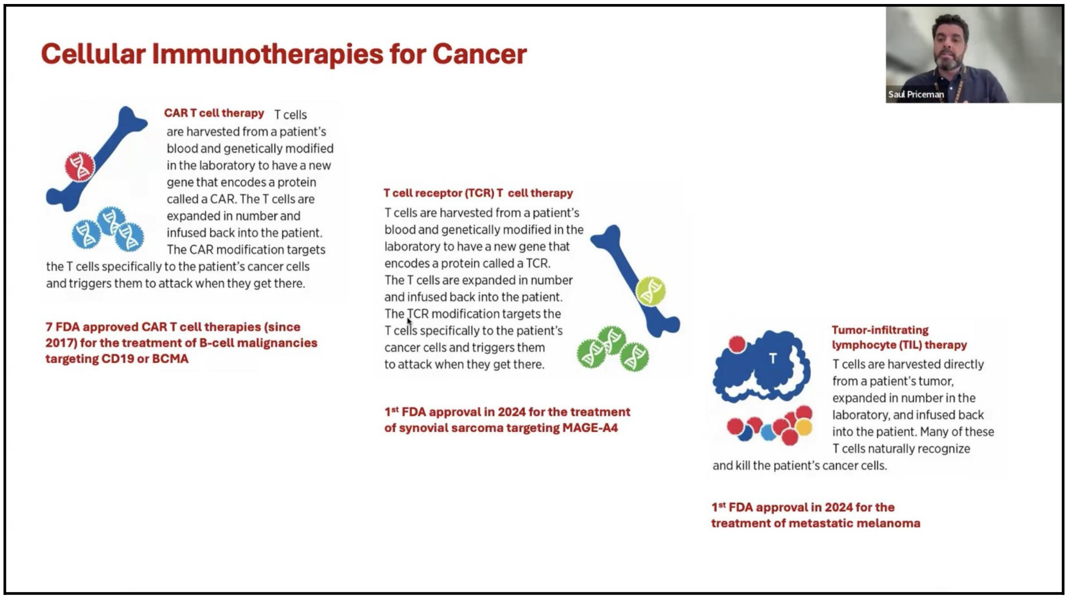
The PSA responses are a measure of prostate serum antigen, which is a biomarker of prostate cancer progression. You can see that anything below the zero line and closer to the -100 means a dramatic response, almost a complete response, and higher means that patients progressed. Most patients, two thirds of them, had a response. Some of them had a pretty dramatic response with PSMA. Whether the responses are durable or not, we're still understanding that.



If you look at that and compare that to STEAP1 bispecific T cell engagers, look at how many patients got close to 100% reduction in PSA, which means they had a pretty dramatic response. Overall, about 30% of patients had a PSA 90, which means it dropped 90% or more. Most patients had a PSA 50, which is pretty striking. That means that if done right, and maybe in years to come, we will absolutely do it right. We can get rid of the toxicities that are associated with these therapies, and we can have dramatic therapeutic responses, even in prostate cancer, which is immunologically cold.

“Update on Immunotherapies (CARs and BiTEs) for Solid Tumors” (Saul Priceman, PhD) [#117]



I'm just going to go through the three general buckets for cellular immunotherapies.

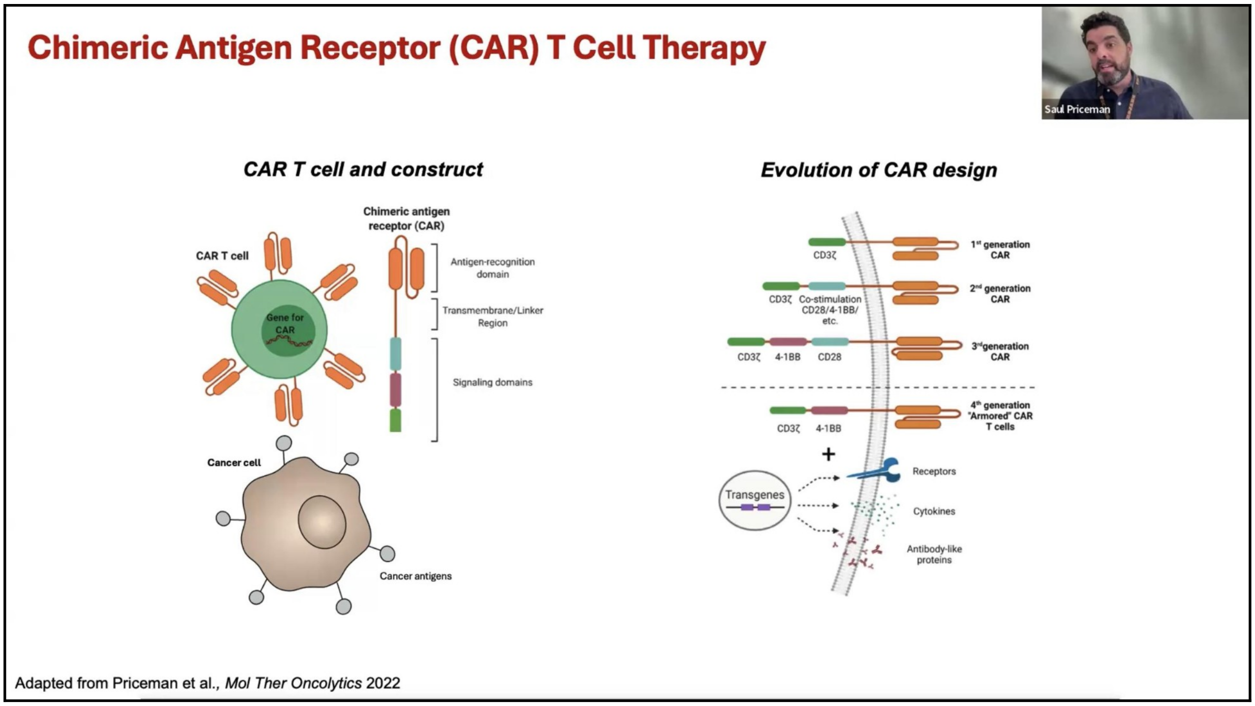
One is CAR-T cells, and I'll go through much of that in a minute.

Another one is an engineering approach as well, but we're not putting a CAR on it, we're actually putting a receptor called a TCR, that is the native receptor that the T cell uses to recognize a virally infected cell or a cancer cell. There are reasons why people are doing this, as opposed to CAR-T cells, and I won't go through that in detail.

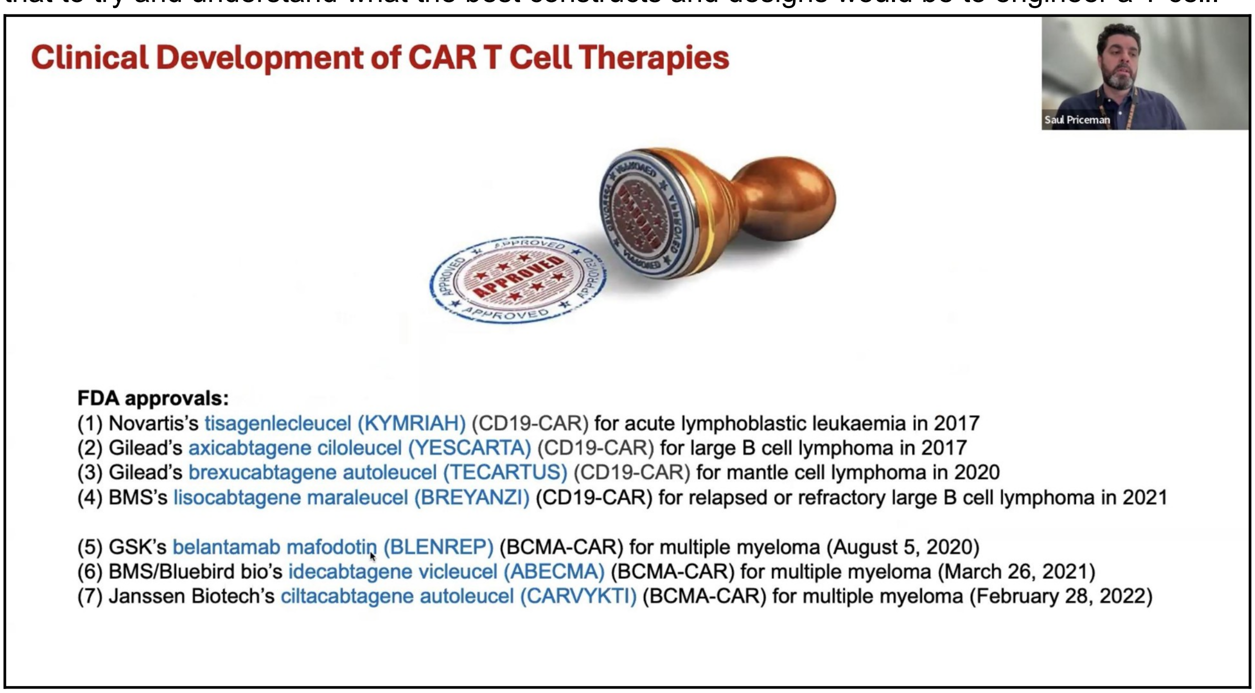
Then there's a more crude method that in many ways has been really effective, which is just taking a tumor out of a patient, resecting it out of the patient, cutting it up, getting the T cells out of that tumor, and growing those in a dish and then infusing those back in. As opposed to synthetically engineering those cells, you're just taking the guys that are already in the tumor and growing them up to billions and putting them back into the same patient. And as you can imagine, unfortunately, just from a technical standpoint, this works for tumors that are immunologically warm because you need those T cells to already be sitting in the tumor.

Saul Priceman 19:06
I think this is a very complicated field, and I wanted to make sure you left with more insight, maybe than than previously, and will allow you to look at papers and read them more constructively and talk to your clinical teams about these types of therapies.

“Update on Immunotherapies (CARs and BiTEs) for Solid Tumors” (Saul Priceman, PhD) [#117]

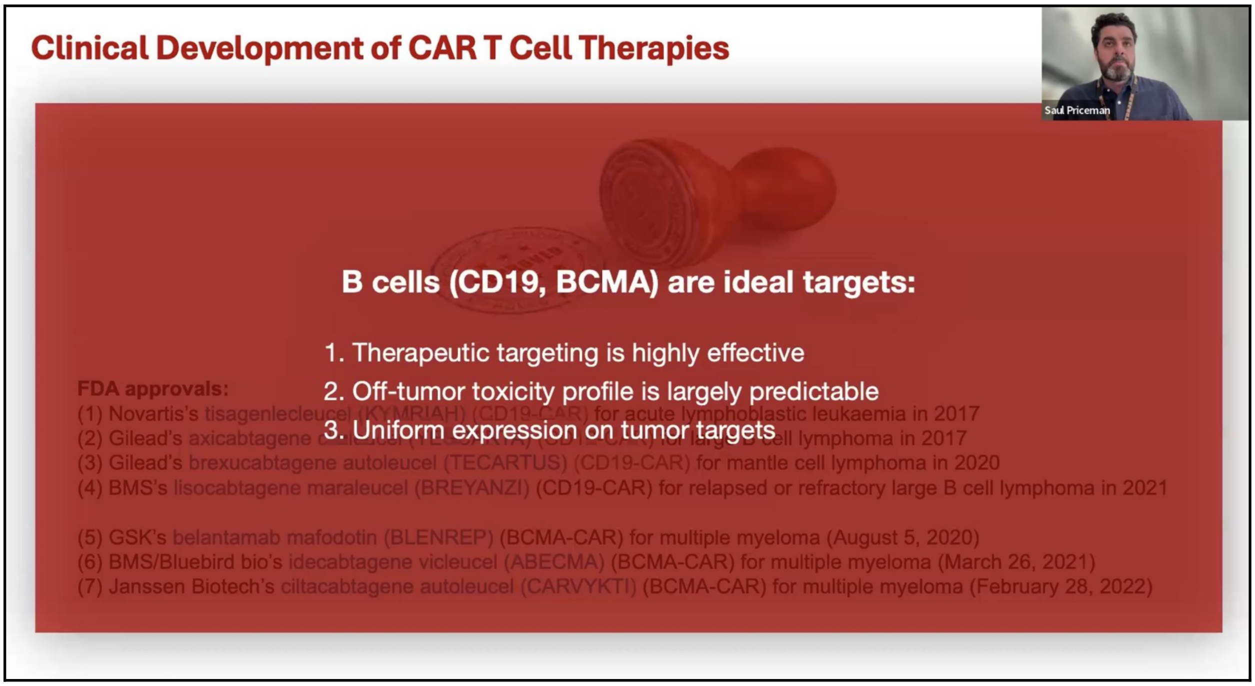


CAR-T cells are pretty cool. Again, we take T cells out of the body, from the blood, and we engineer them using viruses that don't give you a viral infection, but do what viruses do best, which is insert genes into the genome of that cell. In this case, we're inserting a chimeric antigen receptor (CAR) that gets made into a protein. The protein shuttles to the surface, and you have a CAR sitting on the surface of the T cell that recognizes a cancer. This has gone through multiple evolutions, because it is synthetic design. You can actually make any DNA gene sequence that you want in a lab and put it into a T cell. So we've been going to town with that to try and understand what the best constructs and designs would be to engineer a T cell.



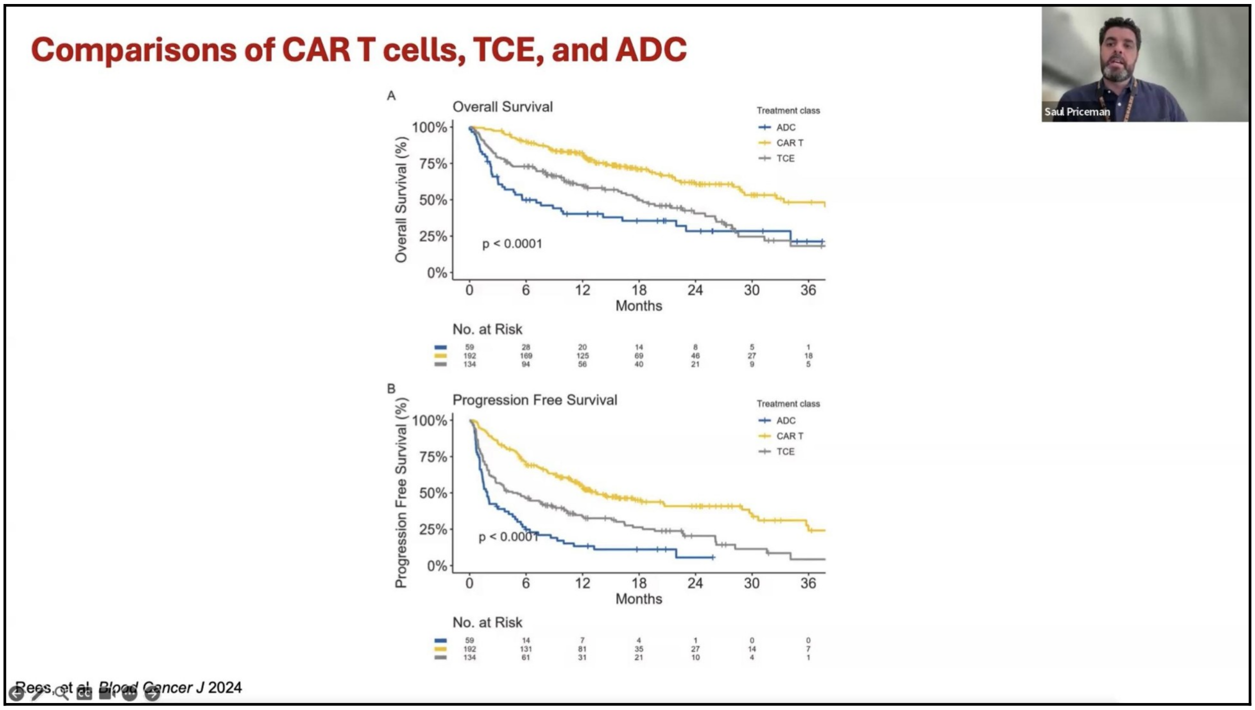
“Update on Immunotherapies (CARs and BiTEs) for Solid Tumors” (Saul Priceman, PhD) [#117]

Because of that, we've now seen seven FDA approvals, all in the context of hematologic (blood) malignancies like lymphoma, leukemia, and multiple myeloma. They work exceptionally well in certain diseases. As an example, in Acute Lymphocytic Leukemia (ALL), where patients are multiply refractory (not responsive) to other therapies, including bone marrow transplants, and have exhausted all other options, if you infuse patients with a CAR-T cell targeting CD 19, which is the molecule we go after in B cell malignancies like ALL, almost 90% of the time you go into complete remission within 28 days. About 40% of the time, you have a complete response that's durable for a long, long period of time. That is striking, because otherwise, these patients have no other therapeutic options. And with that, we're really trying to figure out how to do this for solid tumors. And I'll go through that.



What we've learned is that some antigens, some targets that we go after in cancer—specifically for lymphoma, leukemia—are really good. They are good for reasons we understand and for some reasons that we are still trying to appreciate.

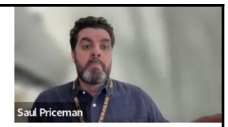
“Update on Immunotherapies (CARs and BiTEs) for Solid Tumors” (Saul Priceman, PhD) [#117]



Now you can do the following, which is compare what's better — a bispecific T cell engager (TCE), a CAR-T cell or ADC (antibody drug conjugate). ADC is an antibody, a targeting molecule, tethered to a chemotherapy that you infuse. That targeting molecule does what it does on CAR-T cells and bispecific T cell engagers—it sees the cancer cell and now that chemotherapy goes into the cancer cell. If you compare those three therapies in one disease—this is multiple myeloma—CAR-T cells were the most significant in terms of response and durability of response, compared to bispecific T cell engagers and antibody drug conjugates. This isn't to say that in prostate cancer, we'll see the same, but at least it tells us that we can benchmark CAR-T cells as a very viable approach for certain diseases.

“Update on Immunotherapies (CARs and BiTEs) for Solid Tumors” (Saul Priceman, PhD) [#117]

Where are we with CAR T cell therapy for solid tumors?



Antigen	Diagnosis	Signaling Domain	Vector	T Cell Product	IL-2 after T Cells	Comment	References
CD133	HCC, PCA, CRC	41BBζ	LV	ATCs	N	3/23 PR, 14/23 SD	24
CEACAM5	CRC, PDCA, stomach, esophagus	ζ	RV	ATCs	Y	7/14 SD; on target/off cancer toxicity—lung	25
EGFR	PCA	41BBζ	LV	ATCs	N	4/16 PR, 8/16 SD, 2/16 NE	86
EGFRvIII	HGG	CD28.41BBζ	RV	ATCs	Y	17/18 NR, 1/18 NE due to TRM[b]	16
GD2	NB	CD28.OX40ζ	RV[c]	ATCs	N	5/11 SD	87
GPC3	HCC	CD28ζ	LV	ATCs	N	2/13 PR, 1/13 SD, 4/13 NE	88
HER2	CRC	CD28.41BBζ	LV	ATCs	Y	1/1 TRM[b]; on target/off cancer toxicity—lung	18
HER2	sarcoma	CD28ζ	RV	ATCs	N	1/10 CR; 3/10 SD	89,90
Mesothelin	MPM, PCA, OVCA	41BBζ	LV	ATCs	N	11/15[d] SD	91
PSMA	prostate	ζ	RV	ATCs	Y	2/5 PR	71
ROR1	TNBC, NSCLC	41BBζ	LV	ATCs	N	4/6 mixed response; 1/6 SD; 1/6 not reported	72
VEGF-R2	metastatic CA	–	RV	ATCs	Y	1/23 PR	e
B7-H3	meningioma	41BBζ	LV	ATCs	N	1/1 evidence of ALV	73
IL-13Rα2	HGG	ζ	plasmid	T cell clone	N	1/3 tumor necrosis	74
IL-13Rα2	HGG	ζ	plasmid	T cell clone[a]	N	imaging study; outcome not reported	75
IL-13Rα2	HGG	41BBζ	LV	ATCs	N	1/1 CR	22
Mesothelin	MPM, lung CA, breast CA	CD28ζ	RV[c]	ATCs	N	2/21[g] CR, 5/21 PR, 4/21 SD	76
MUC1	SVA	41BBζ or CD28ζ	LV[h]	ATCs	N	1/1 tumor necrosis	92

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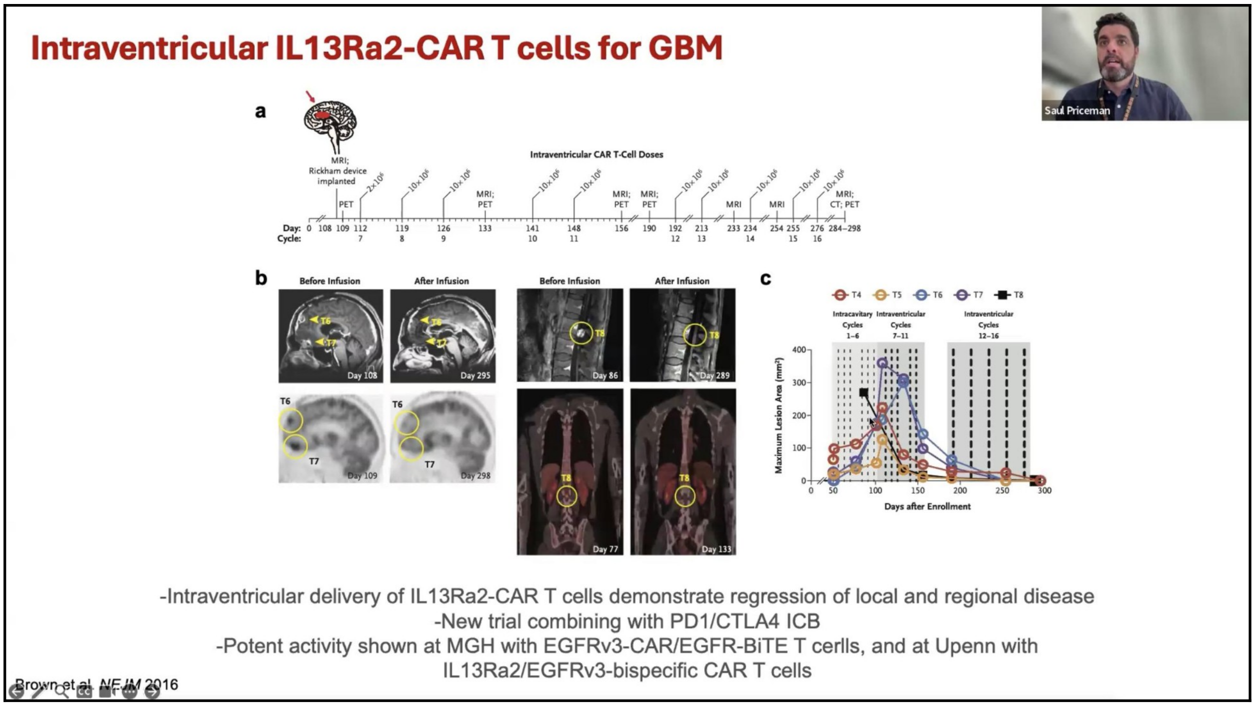
If you look at solid cancers, we've gone after a number of targets. I showed you PSMA and STEAP1 for prostate cancer, but look at all of these targets that we're going after. There are a ton of targets we've gone after and a ton of diseases—hepatocellular liver cancers, neuroblastoma, sarcomas, prostate triple negative breast cancer—tons of different types of cancers. If you compare the responses here, unfortunately, to hematologic (blood) malignancies like ALL and lymphoma, we have not appreciated the same level of response. There are a number of reasons for that which we're all evaluating.

“Update on Immunotherapies (CARs and BiTEs) for Solid Tumors” (Saul Priceman, PhD) [#117]



I just wanted to highlight a couple of responses. This was actually at City of Hope. This is how nimble cancer centers can be. We targeted glioblastoma, which is the most deadly form of brain tumor. If you infuse T cells that we engineer into the bloodstream, their chances of getting to the brain are very limited, compared to if we gave the T cells directly into the brain. So this trial actually gave the T cells directly into the brain, into the tumor. In some patients, the T cells were delivered into the tumor cavity that remained after they did a tumor surgery and removed the tumor.

In one patient, which we published many, many years ago now, they had their tumor removed, they infused the T cells, and those T cells never came back, but he had multifocal disease. He had more regions of the brain that had lesions, and he also had a spine metastasis. We had preclinical lab mouse data that suggested that we could give these T cells not directly into the tumor bed, but rather into the ventricle that houses the cerebrospinal fluid and bathes the central nervous system. Our hypothesis was that these T cells would then distribute all around the brain and the spine, and you could target multiple regions rather than just injecting them directly into one site and asking those immune cells to then migrate to another site. And that's exactly what happened: he had a dramatic response and regression of his multifocal brain and spinal metastases, and you can see that quantified here. They were all growing after we gave intratumoral administration, and then when we turned to intraventricular, he had regression. We had to get to the FDA within 30 days and beg them to do this. This was a ‘first-in-patient’ ever to receive intraventricular CAR-T cells, and we saw this dramatic response. Unfortunately, the trial has had its challenges. We do not see this response in every patient—that's with every immunotherapy for reasons we can appreciate and some we don't. We have responses in some but not all patients.

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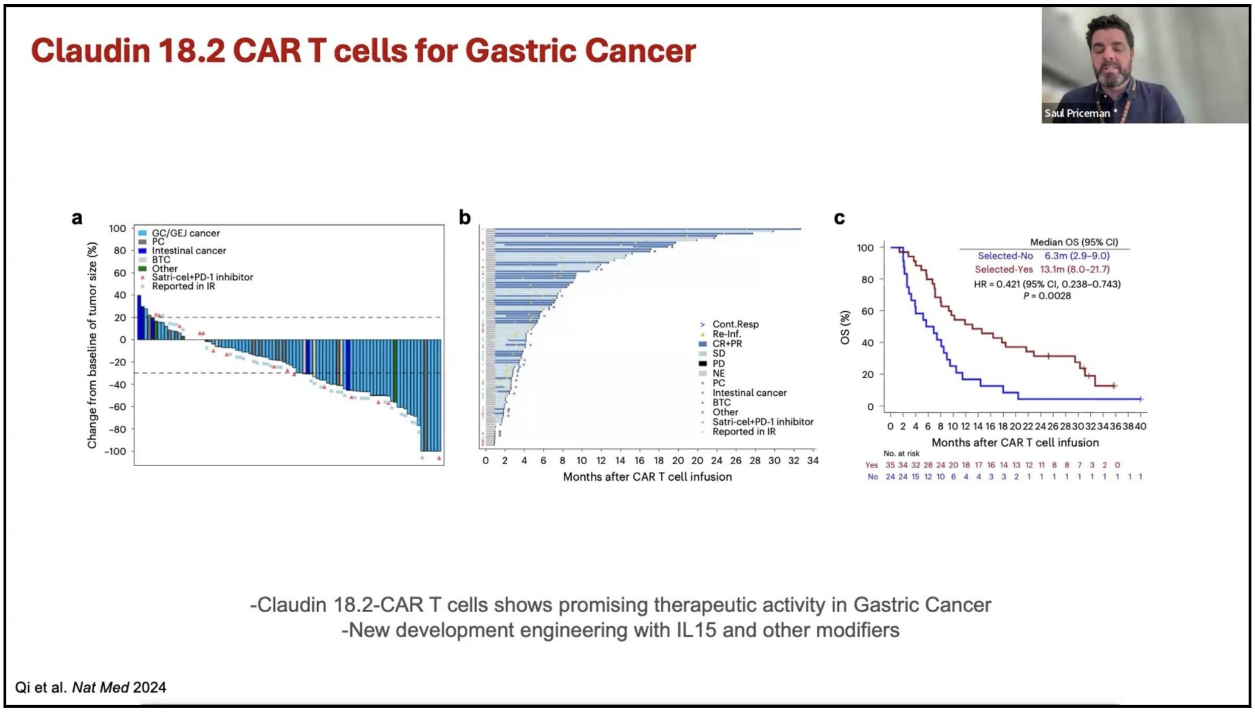
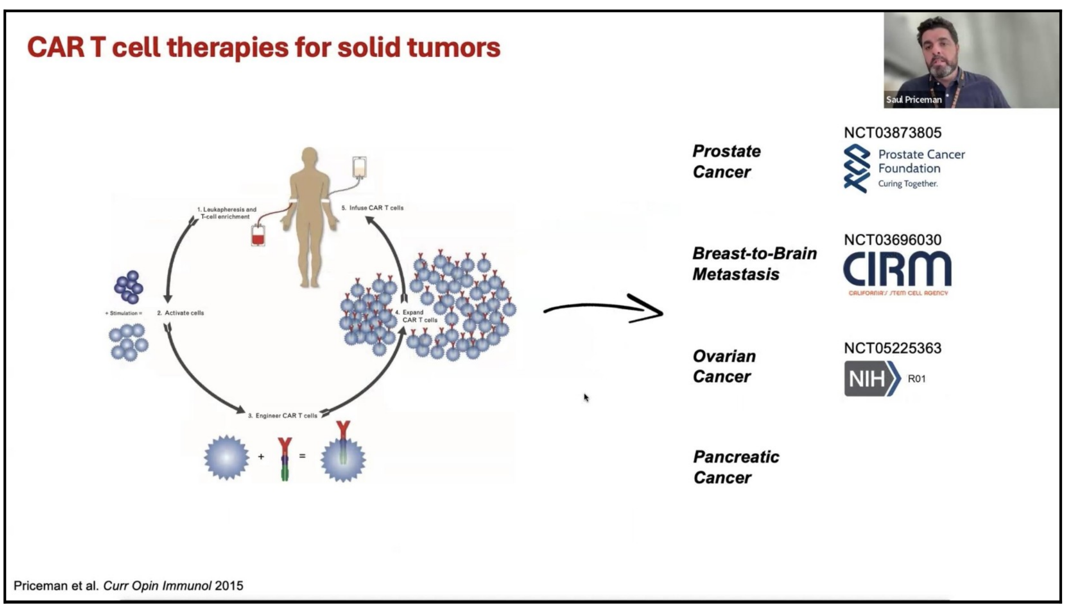


This is another trial for gastric cancer where you can see this is a measure of the reduction in tumor size. You can see some patients had an absolute eradication of disease, some patients had partial responses, and the survival looks better than historical and when comparing some selected patients who had higher expression of the target.



In my lab at City of Hope, we really focused on four diseases: prostate, breast-to-brain metastasis (which is breast cancer that has spread to the brain) and ovarian cancer, and now pancreatic cancer. We've worked with networks and collaborations—which is the beauty of this foundation, this series, as well as others that we all as scientists and clinicians partake in—and we're collaborating with a number of labs around prostate cancer.

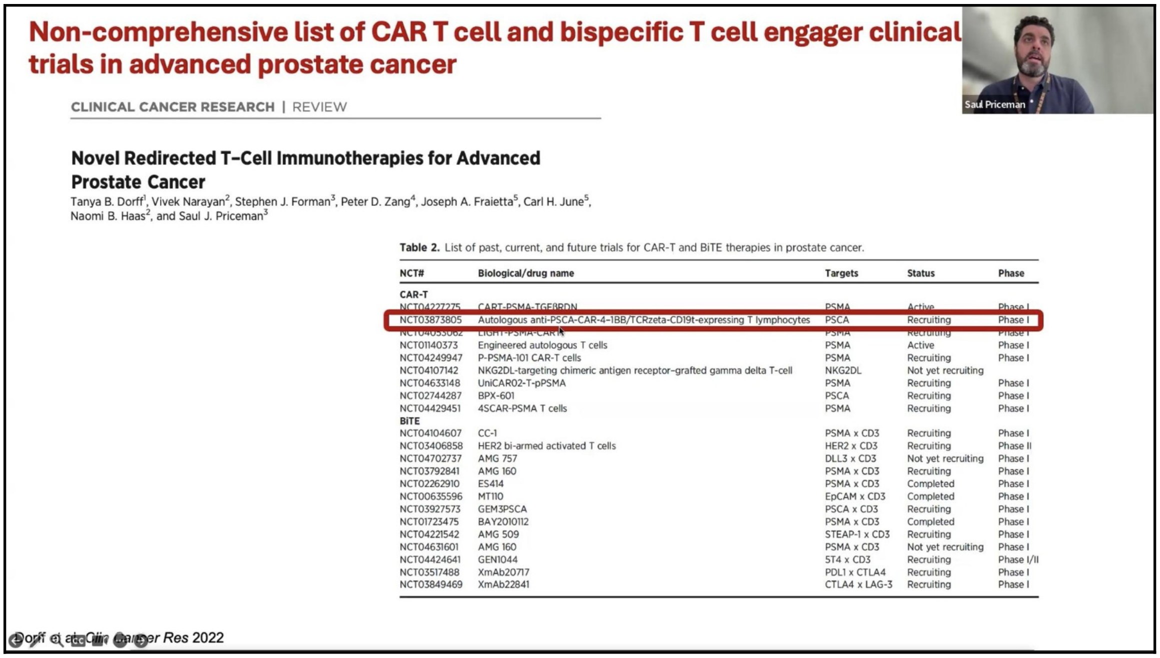
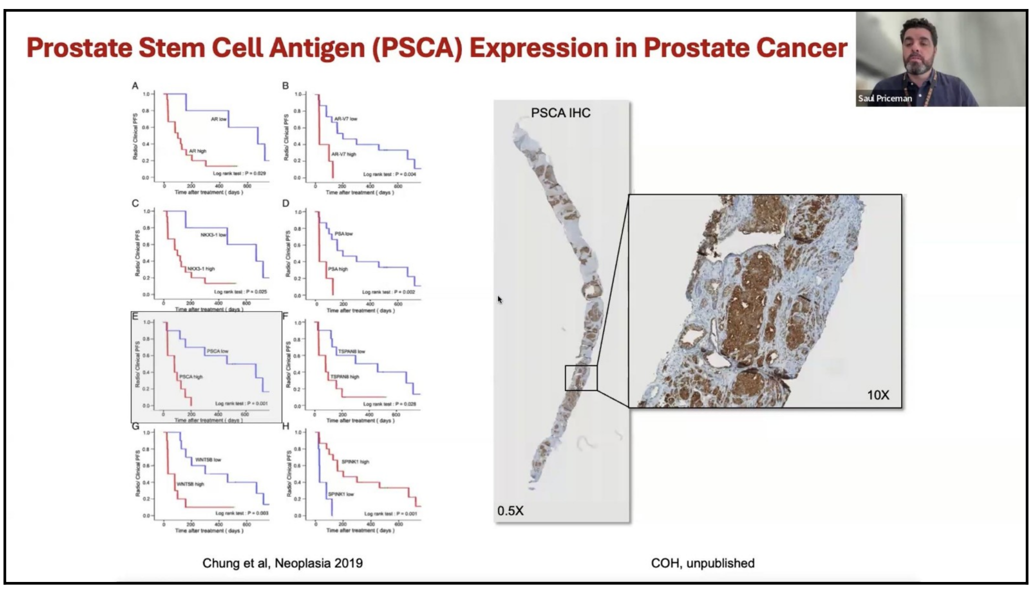


Table 2. List of past, current, and future trials for CAR-T and BiTE therapies in prostate cancer.

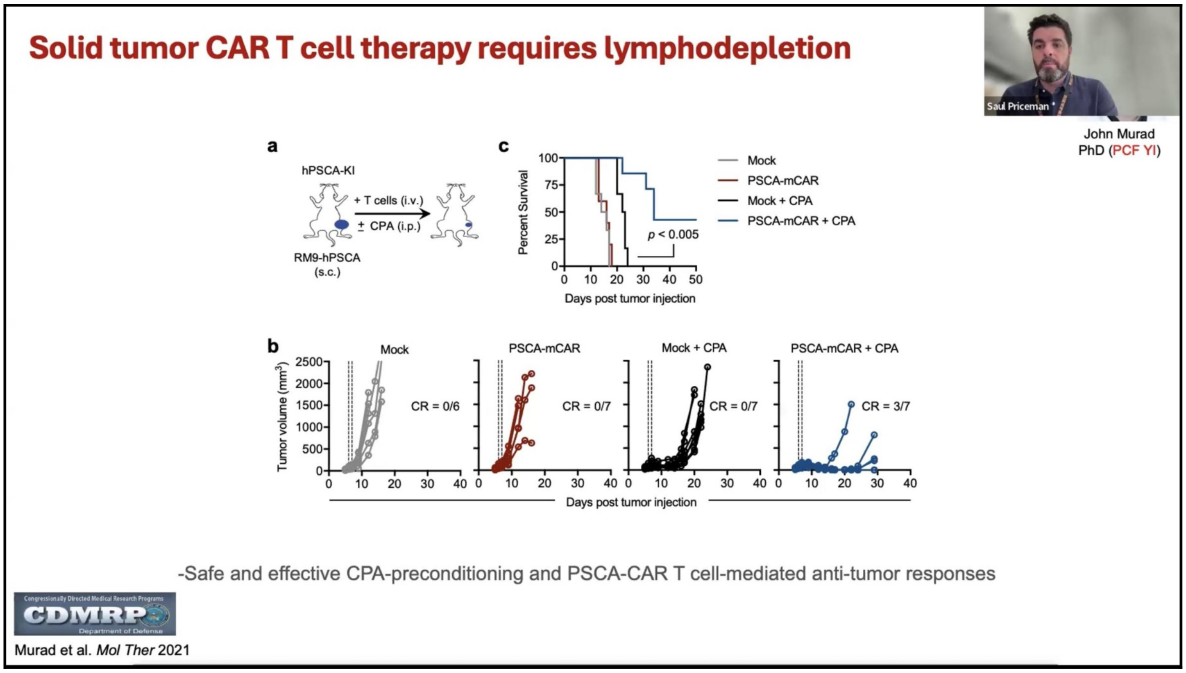
NCT#	Biological/drug name	Targets	Status	Phase
CAR-T				
NCT04227275	CART-PSMA-TGFβRDN	PSMA	Active	Phase I
NCT03873805	Autologous anti-PSCA-CAR-4-1BB/TCRzeta-CD19t-expressing T lymphocytes	PSCA	Recruiting	Phase I
NCT04053062	LIGHT-PSMA-CART	PSMA	Recruiting	Phase I
NCT01140373	Engineered autologous T cells	PSMA	Active	Phase I
NCT04249947	P-PSMA-101 CAR-T cells	PSMA	Recruiting	Phase I
NCT04107142	NKG2DL-targeting chimeric antigen receptor-grafted gamma delta T-cell	NKG2DL	Not yet recruiting	
NCT04633148	UniCAR02-T-pPSMA	PSMA	Recruiting	Phase I
NCT02744287	BPX-601	PSCA	Recruiting	Phase I
NCT04429451	4SCAR-PSMA T cells	PSMA	Recruiting	Phase I
BiTE				
NCT04104607	CC-1	PSMA x CD3	Recruiting	Phase I
NCT03406858	HER2 bi-armed activated T cells	HER2 x CD3	Recruiting	Phase II
NCT04702737	AMG 757	DLL3 x CD3	Not yet recruiting	Phase I
NCT03792841	AMG 160	PSMA x CD3	Recruiting	Phase I
NCT02262910	ES414	PSMA x CD3	Completed	Phase I
NCT00635596	MT110	EpCAM x CD3	Completed	Phase I
NCT03927573	GEM3PSCA	PSCA x CD3	Recruiting	Phase I
NCT01723475	BAY2010112	PSMA x CD3	Completed	Phase I
NCT04221542	AMG 509	STEAP-1 x CD3	Recruiting	Phase I
NCT04631601	AMG 160	PSMA x CD3	Not yet recruiting	Phase I
NCT04424641	GEN1044	5T4 x CD3	Recruiting	Phase I/II
NCT03517488	XmAb20717	PDL1 x CTLA4	Recruiting	Phase I
NCT03849469	XmAb22841	CTLA4 x LAG-3	Recruiting	Phase I

Specifically, this is a list of the trials for CAR-T cells and bispecific T cell engagers for prostate cancer. We actually started a trial several years ago targeting another antigen on prostate cancer called prostate stem cell antigen, not PSMA, but PSCA.



Higher expression of it correlates with disease progression and reduced survival in patients. Its expression is high in primary prostate cancer as well as bone metastatic disease.

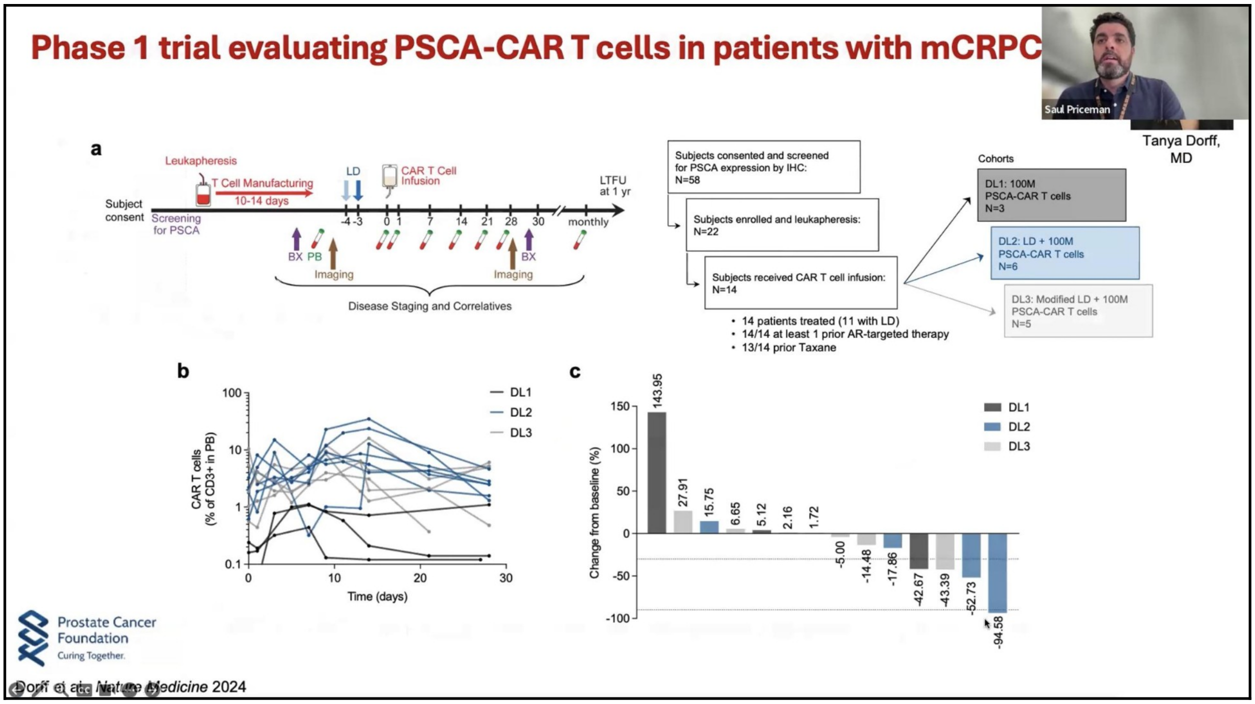
“Update on Immunotherapies (CARs and BiTEs) for Solid Tumors” (Saul Priceman, PhD) [#117]



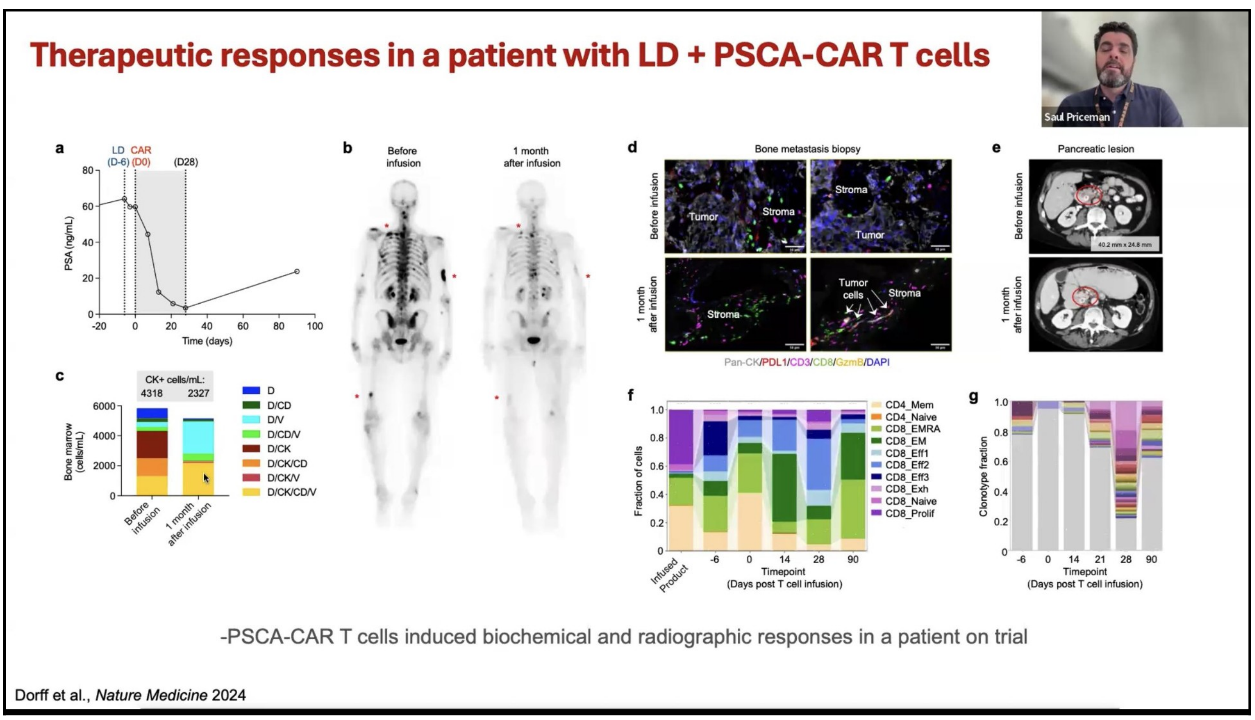
I did want to show this, which is just one set of animal studies. These are the types of lab studies that we do to try and get something into a patient. These are the types of foundational studies. We actually developed a PSCA-directed CAR-T cell—which took a lot of time to design the construct, engineer T cells, and prove it. We built a mouse model that addressed the safety issues around this type of therapy [to be prepared] once we went to trial. We were actually the first to put into a patient a PSCA-directed CAR-T cell, which could wreak havoc. Unless we predicted that [potential safety issues] in our laboratory, then we would have gone in sort of blinded. We had great therapeutic responses in very easy models.

We put this into a mouse model that had an intact immune system, and the expression of PSCA, the target in the prostate cancer, is also expressed in normal bladder cells, so we worried about toxicity. Unfortunately, when we gave the CAR-T cells, we had no therapeutic response. This graph is just measuring tumor growth over time. You can see that if you left these animals untreated, their tumors grew out exponentially. And if you treated them with PSCA-CAR-T, they grew out exponentially. This contrasted data we already had in mice that don't have an immune system—the CAR-T cells had worked really well in a dish and in those mice, but in these mice, they didn't work. We had to precondition those animals with what's called lymphodepletion, which is a set of chemotherapies that are just given three times in less than a week, that primes the body to accept and receive the CAR-T cells. And that therapy alone had some delay in tumors, but all of them grew out. Now, when we combined it with our CAR-T cells, we had curative responses in our animals, in up to 40%.

“Update on Immunotherapies (CARs and BiTEs) for Solid Tumors” (Saul Priceman, PhD) [#117]



Saul Priceman 29:08
This started the trial that we undertook now many years ago, where we dose-escalated the PSCA-CAR T cells. We added, or didn't add, lymphodepletion (I'm not going to go through the details here, unfortunately). We had some PSA responses.



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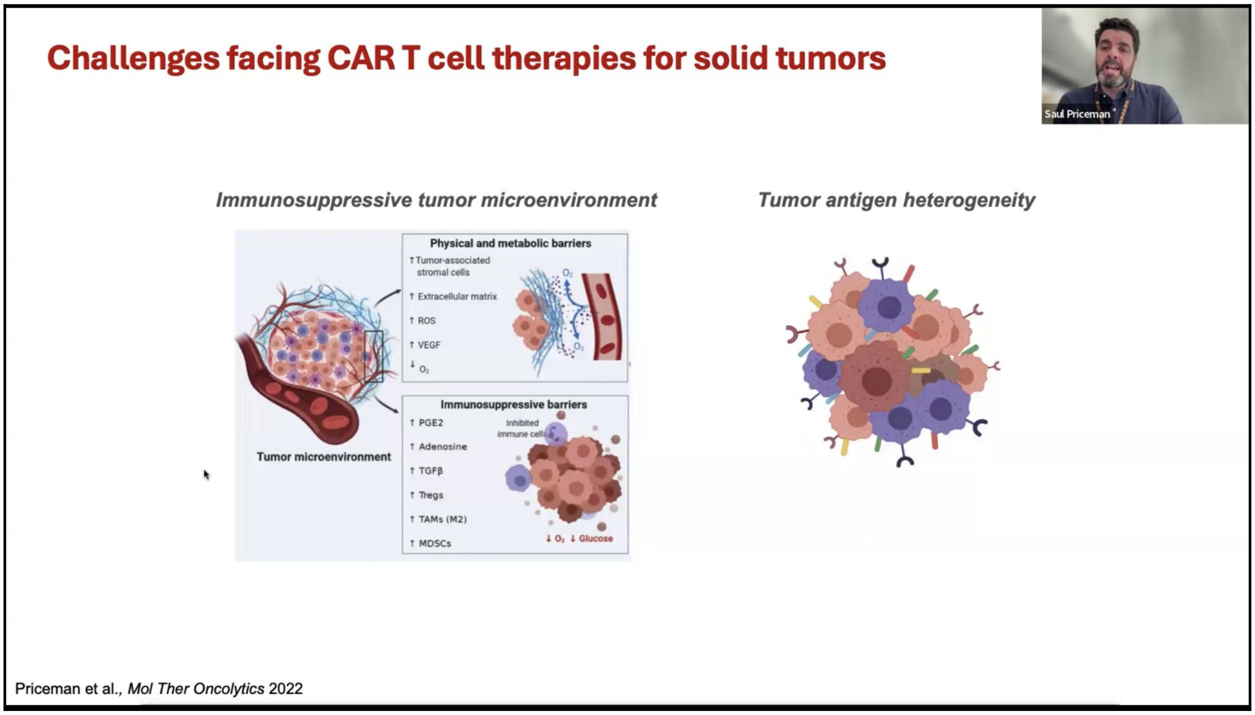
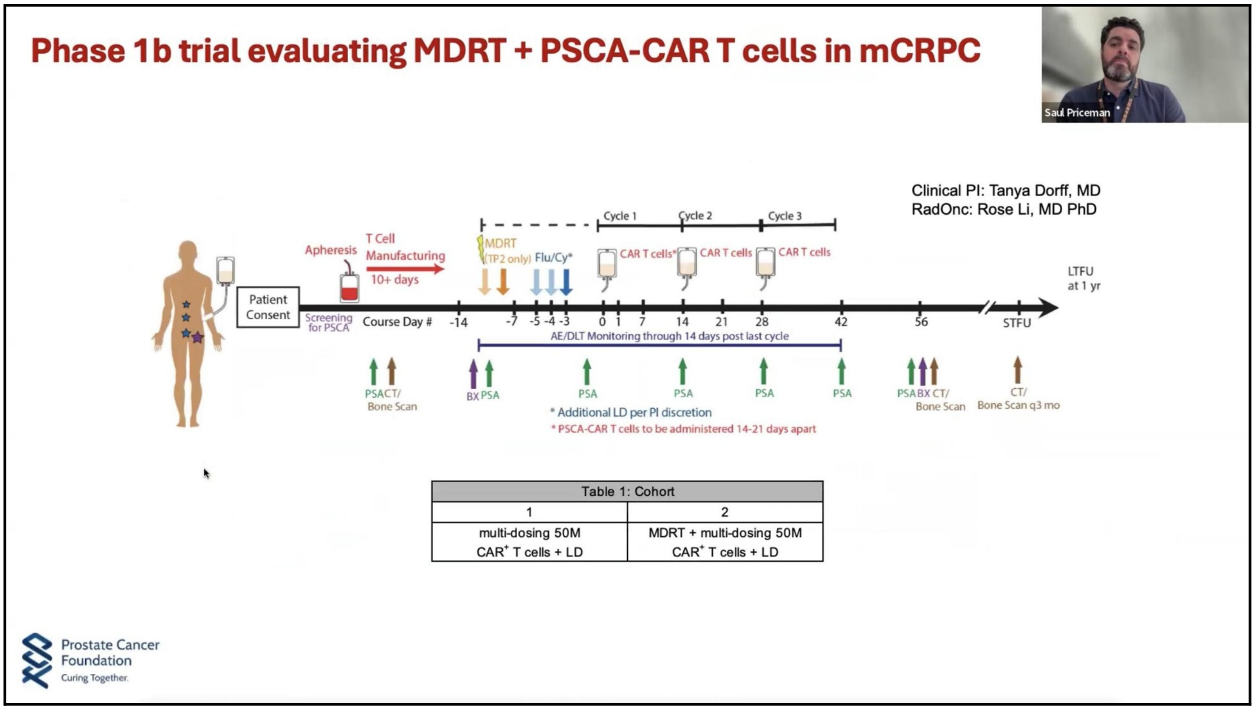
We had a dramatic PSA response in a patient who had reductions in their bone metastatic disease all around the body. We work with a group who, I think, presented here, Peter Kuhn, who's at USC, that does circulating tumor cell analysis, which is a liquid biopsy assessment. We worked with him and showed dramatic reductions in these brown cells, which are classical prostate cancer cells that are circulating through the blood. We had reductions in that. We also had infiltration of T cells into the tumor. This is where we do our downstream analyses to understand the biology. This patient was unique, he actually had a stent in his pancreas and around the stent had pancreatic metastatic disease from his prostate. It was prostate cancer in the pancreas. He had almost complete resolution of that disease. I won't go through this data.



It highlights a bunch of challenges. The reason why we see dramatic and durable responses in blood cancers, but not in solid tumors, is really the microenvironment around the tumor, which I showed on my second slide. There's a ton of cells that are barriers to getting immunotherapies to work in solid tumors. Another reason is what's called antigen heterogeneity—we go after PSCA in prostate cancer, but the PSCA has to be expressed on 100% of the cancer [cells] if we anticipate 100% response, and they don't. So there's heterogeneity, or a mosaic of cell types that make up the prostate cancer cells or any other cancer, and it's difficult to wrap a therapy around all of that.

“Update on Immunotherapies (CARs and BiTEs) for Solid Tumors” (Saul Priceman, PhD) [#117]



I'm going to skip through this, but yeah, we have now a trial with radiation and CAR-T cells. Happy to take questions.

Brian McCloskey 31:20
How do you identify cancer patients that are going to respond well versus those that aren't going to respond well to CAR-T?

Saul Priceman 31:52
Unfortunately, at this point, we don't know. I don't think there is a test now. There is not a test now that will predict whether someone will respond. When we start a trial with a PSCA-CAR or PSMA-CAR, we definitely look for that marker on the cancer cell, and that's a critical component. In the very near future, because there's a lot of research going into what makes up a responding patient versus a non responding patient, I think we will know. There are certain hints to it, but we don't use that to guide our therapies as of yet, it's just too new, relatively speaking, and it is highly specific, so I think we're trying to understand that.

Brian McCloskey 32:39
What about a multi-targeted approach? Given the fact that we've got heterogeneity, what are the possibilities of having a PSMA-targeted one and a STEAP-targeted one?

Saul Priceman 32:56
It's happening. I think it's already in trial for certain cancers, mostly blood cancers, because they were a bit ahead of the solid tumor researchers, but we are advancing those in our lab, and there's a lot of utility to that, and we can do that. I only went through T cells, but there are tons of different immune cells people are engineering—I didn't have time to go through it, I wish I did,

and I'm happy to come back and do that—but it's endless. You can engineer the CAR or the TCR, or anything with anything you can imagine. You just have to prove that it works in a lab, and you have to convince the FDA to get to trial, and we're all doing that. I think the possibilities are endless, literally.

Brian McCloskey 33:47
A few questions in the chat from Rick Davis:
What are the pros and cons of CAR-T versus bispecifics?

Saul Priceman 34:02
I had a slide on that, but I was told at a younger age not to go back to the past.

Brian McCloskey 34:09
[chuckle] Yeah, you can if you think it's illustrative.

Saul Priceman 34:13
No, I remember it all. I mean, there are a bunch of different considerations. So one is right now —and this is going to change—the way a CAR-T cell works is, you identify a patient, they go through an apheresis, which is a larger blood draw, and we call that ‘vein,’ and then they go through a manufacturing process. They have to be released, the sterility of those cells have to be checked, and a bunch of other things under quality control, and then they're infused back into the vein. That process from vein to vein right now takes about six weeks. It could be less, and I think in the next year or two or less, it will be far less, like on the order of maybe a week or two.

And maybe in that same time frame it may be a moot point, because people are looking at what's called allogeneic engineered cell therapies. To understand what that means, take the scenario where ‘Bob’ comes in to get a CAR-T cell. We make that CAR-T cell for Bob and it doesn't work for Susan. That's called autologous. Right now we're evaluating allogeneic T cells in a trial, which means Bob, who's a healthy guy, can donate his blood. We can make CAR-T cells from Bob, and we can make treatments for dozens or more people, and that will then shrink the vein-to-vein time to zero.

The ‘vein to vein’ time is zero for bispecific T cell engagers. It's a drug. It's made in a vat, and you can infuse that anytime a patient is eligible and rolled onto the trial, you don't need to wait for that ‘vein to vein’ time. The cost is a consideration, the insurance is a consideration, and the durability of response is a consideration. I showed the one graph in multiple myeloma, but we don't know it in prostate cancer or other diseases, really, as of yet, so I don't know which one's better.

Brian McCloskey 36:28
Having gone through the vein to vein process with Provenge [an immunotherapy for prostate cancer], I think that took a week or two. It's not a fun process, but it is what it is.

“Update on Immunotherapies (CARs and BiTEs) for Solid Tumors” (Saul Priceman, PhD) [#117]

Robb Owen 36:57
You talked about your glioblastoma patient, and I've been helping consult with a glioblastoma patient that had a resection in mid August. [Their cancer is IDH1, wild type four]. [They] chose not to do any chemo, radiation or immunotherapy, so we went with a more holistic approach, with diet and targeted supplements, hydration and whatnot. But what I've come across is being able to put together a combination of dopamine receptor 2 (D2) antagonist, a GABA inhibitor, and a H2 inhibitor, using the right combination, we're getting regression. We’re two-and-a-half months in, we've resolved the edema, and from what I see, the effects or the influence it has on the PI3K/AKT pathway and VEGF and transforming growth factor beta-1 (TGFβ-1). And we built up her immune system naturally, and it's allowing it to—by keeping the fibroblasts from differentiating and inhibiting angiogenesis—we're allowing the immune system to naturally resolve the cancer. I wasn't sure, since most of these antiemetics and whatnot are typically prescribed for cancer patients during their treatments, I was wondering if anyone has ever thought about looking more into those and how calculating the correct combination and dosing schedule and dosing amount would make every other treatment more effective.

Saul Priceman 38:50
One of my best friends studies GABA signaling in brain tumors, and I have no experience with these types of antiemetics, but I do appreciate the combination strategy. If you tailor it properly and understand the biology of the patients, it can work really well.

Robb Owen 39:15
It worked for my stage IV head and neck squamous cell. Two weeks into chemo/radiotherapy, my tumor was gone, and I stopped treatment a week later. It's had success with liver, non-small cell lung cancer. Got a 68% regression about halfway through treatment.

Saul Priceman 39:33
Wow. I would love to learn more about that because – Brian brought this up earlier – ‘can you combine different targets?’ I think that is an approach, and we're all evaluating that approach, but that's not the slam dunk approach. The slam dunk approach is to rewire the body and the tumor to accept these types of therapies better. So you're bringing up one example of this, which is awesome, and I love hearing about it.

Robb Owen 40:08
Yeah, we're rebooting the immune system back to its natural state. It's hard to get the patients to modify their diet and it’s harder to get supplements specifically for the mutation of that cancer. It takes a lot of work on the patient's side to stick to that. So the direction you're heading, yes, forcing it to reprogram is going to probably be beneficial for a large set, for the people that are willing to put the front end effort in. It's always going to be patient-dependent, from what I see.

Saul Priceman 40:47
It’s always going to be patient-dependent, which is tough. It's challenging. But I also think there's a question later on, which is something I ask myself all the time, ‘what are the roadblocks?’. One of the biggest roadblocks is we're scientists, like, I think of things every day. I

go to sleep and I’m like, ‘Oh, this is a good idea.’ And sometimes I wake up and I'm like, ‘that was the worst idea.’ But sometimes I wake up and I'm like, ‘Oh, my God, I gotta test that.’ So there's a time/implementation/bandwidth challenge, and the thing that you're describing is awesome, but the iterations of that are crazy.

Robb Owen 41:33
I agree, it’s patient-specific. It is going to change for every single patient.

Saul Priceman 41:38
Yes, agreed, but I don't think it has to. If we had better laboratory models and we could be better at predicting these things, we could implement that. I mean, one of the best questions was the earlier question, which is like, ‘how do you predict if the patient will respond or not respond?’ That would be the best because one size doesn't fit all, so we know that the trial that I've spent my blood, sweat, and two years on is not going to be for every patient. But if I could understand that it works for these five patients and not for the other 45 that I could treat, that's awesome, because then the other 45 have an opportunity to go elsewhere, to a different trial that might be better for them. And I think that's where our biggest roadblock is. We have tons of data emerging, and finding ways to analyze that data as quickly and as meaningfully as possible, is the next step.

Brian McCloskey 42:39
Robb's an amazing patient, as you can see. We actually did a webinar on him. If you're interested, I could send it to you.

Saul Priceman 42:49
I would love that, and Robb, I may hound you more than you would probably hound me.

Robb Owen 42:53
I would like that. I'm actually meeting with Chris Gregg from the University of Utah School of Medicine tomorrow. He's [a tenured associate professor] in neurobiology and an [adjunct] in human genetics. I just got back from the RGCC conference in Denver, speaking with integrative oncologists and oncologists. So yeah, I would love [to speak with you], I'll send you my email.

Saul Priceman 43:15
Yeah, please do.

Brian McCloskey 43:16
Thanks, Robb. So Elaine Watkins has a question about rare solid tumors, such as thymoma, and success, etc.

Saul Priceman 43:30
You know, one of the issues that we all deal with is funding as well as incidence. So, some of the rare cancers don't get a lot of attention, unfortunately, because there's limited funding for that. So I'll give you a little story. 10 years ago, I got married to my wife, who's still my wife, and

four months before we got married, her father, my father-in-law, was diagnosed with pancreatic cancer. And so we were dealing with a lot of shit at our wedding. We decided to get pregnant to make him a grandchild. We were successful at that. Donna, my wife, was one and a half months pregnant at our wedding. Her dad unfortunately died eight months later, after diagnosis, which was two months shy of meeting his grandchild. So I went into the lab and I'm like, I'm going to develop pancreatic cancer therapies, and there was no funding for pancreatic cancer. So I redirected—don't tell Prostate Cancer Foundation—I redirected some of the opportunity we got from Prostate Cancer Foundation to develop that PSCA CAR-T cell with the knowledge that it was going to be effective in prostate cancer. And we just published that phase one trial in Nature Medicine, and we're on to the next trial, and we're really working on that for prostate cancer. But in the back of my head, I was like, PSCA is even higher expressed in pancreatic cancer. So here at USC, we're moving in that direction to develop it for pancreatic cancer. And I can realize that now because fast forward 10 years from 2013, there's way more funding for pancreatic cancer now. Even though the incidence of pancreatic cancer is about 50 or 60,000 a year, versus prostate cancer, which is in the hundreds of 1000s, there's just more funding for it. For thymoma, it's really rare. There's not a lot of funding. And I don't know much about it, admittedly, and would have to look at it, but yes, I mean, technically, we could develop these types of immunotherapies for any disease if one has the indication to do so. With respect to autoimmune disease, it's like all the rage in the last year where we're applying CAR-T cells to autoimmune diseases and seeing striking, durable responses in things like systemic sclerosis and lupus and other autoimmune diseases. So I think that's the next frontier as well in treating autoimmune diseases] which is unbelievable.

Brian McCloskey 46:11
There are lots of applications. I appreciate your brain wrapped around it and having many ideas as you go to sleep and wake up in the morning.

Roger Royse 46:32
My brother had Burkitt lymphoma, and he died last year, and he never had the opportunity for CAR-T. I always thought that might have made a big difference. And I was wondering if you know what the success rate is for that. But more importantly, it seems like this is not offered that widely, because it wasn't even available to him at the hospital, the small city hospital he was involved in.

When does this—it sounds very promising—become a little more mainstream?

Saul Priceman 47:05
One thing is appreciating the complexities of this type of therapy, and the idea is that right now, probably at a small community hospital, it's more challenging to receive this type of therapy than at a cancer center. So it gets to point of care. And those things are changing, and especially for certain diseases where without CAR-T cells, patients are dying. Like for certain lymphomas and leukemias, they should be receiving this therapy. And now some indications are saying they should be receiving this therapy before they ever see a chemotherapy. Like they should be on this therapy as frontline, because it's so effective. So I think over time, it will be more readily

available. And as I mentioned before, maybe with allogeneic cell therapies, where ‘healthy donor A’ can give to ‘patient B through Z’, or shrinking the time of manufacturing and opening sort of fully closed manufacturing systems that are like in a box you can deliver to the community hospital and they can do it there without much manual intervention.

Roger Royse
Thank you.

Saul Priceman
When was he treated?

Roger Royse 48:32
He was diagnosed in February here, and he was treated in Spokane, Washington. They told him he was in complete remission in August, [then] in October, he died. And I always wondered if he had, [like] what you said, if he'd gotten CAR-T right at the front from Fred Hutch or someplace that could do it, it might have made a difference. And it's kind of shocking, just cancer care generally, just how disparate the treatment is because we do this every week, we have these sessions, and we hear about these great new therapies and it's like, unless you're tuning in every week and hearing this, you might not know anything about it. Nobody told him about it. I didn't even know about it until it was too late.

Saul Priceman 49:19
It's been one of my biggest pet peeves and gripes around our healthcare system is that hospital A, that's on the same street as hospital B, has a very different definition of standard of care. And we should be all in the same boat, or at least sharing all of that information, so that we can funnel and come to a consensus on what those therapies should be at which stage and which patient and so on and so forth.

Brian McCloskey 49:46
So, related to that, I had a thought about who is the ideal patient, not only from a transcriptomic or a DNA level, but from a treatment perspective. Are you looking at patients that are heavily pre-treated or those that are less pre-treated? I'm sure it varies by setting. But just curious to get your thoughts on that. I'm kind of hearing that you'd rather it be earlier in the process, in the journey, which makes sense.

Saul Priceman 50:27
Yeah, I mean, I can make blanket statements, which, some of them may not be correct, or they're evolving, but I think the healthier the patient, obviously, the better to receive this type of therapy. In terms of tumor burden, which is how much disease a patient has, it could go one way or another, and I think it's context and disease dependent. But in certain diseases, it's logical that the lower the disease burden, the better chance a therapy response is. In certain tissues, where the metastatic disease is may predict whether there's a response or not. So, for instance, if you have liver metastatic disease, your likelihood to respond to certain types of immunotherapy is less than if you don't have liver metastatic disease, and that's just,

unfortunately, what we've seen. There are tons of things that we could apply, and I'm not sure they are ground truth.

Brian McCloskey 51:36
Yep. Okay, great. Rick Davis, you've got a couple questions. Your last one is about PSCA expressed in pancreatic adenocarcinoma cells. You want to jump in and ask, I think you had a couple questions. Is there anything you want to elaborate on?

Rick Davis 51:55
I'm blown away only because I have understood most of what you've presented, which is amazing, because I'm one of the less technically astute that's on this call.

Saul Priceman 52:20
Are you British?

Rick Davis 52:24
50 years ago, I was.

Saul Priceman 52:27
It’s because you’re British because I'm British too, that’s why.

Rick Davis 52:30
Oh really? But you sound less British than I do.

Saul Priceman 52:37
I was born and raised for two-and-a-half, three years in London.

Rick Davis 52:43
I've seen you before presenting, I thought it was at the Cancer Patient Lab, but it obviously wasn't, because now I remember you saying that I heard that in the last maybe it was a PCFA thing…anyway.

A couple of questions I've answered for myself in the interim, two things. One is, it's very interesting to me that PSCA is expressed on pancreatic cells. I'm wondering if we have any idea why, and it seems like there's a potential. And the other question I was going to ask you was, is your lab doing any work on trying to make cold tumors hot?

Saul Priceman 53:27
Oh my God, it’s all my lab works on. So, PSCA was a misnomer. When it was discovered as a protein, they called it prostate stem cell antigen because it was literally found in the normal prostate cells that they thought were stem-like in nature, so they just called it prostate stem cell antigen. But then a bunch of scientists come around and are like, ‘Oh, that's a cool thing. Let me see where it's expressed.’ They identified that it's expressed in some other tissues, including pancreatic cancer, they just didn't change the name. So it's called prostate stem cell antigen,

but it's also highly expressed in other tissues, including bladder cancer, which we're also very interested in treating, as USC has one of the highest rated, if not the highest rated, urologic groups around bladder cancer and treatment.

“TCE” is, sorry for being confusing, but they're the same thing. The reason that that is the way that it is is because “bispecific T cell engager” stands for “BiTE”, or “BiTE” stands for “bispecific T cell engager” and “BiTE” was trademarked, I think, by Amgen, so people used it and got into trouble. So now we just call them TCE (T cell engagers).

Rick Davis 54:55
How about commenting on making cold cells hot?

Saul Priceman 55:00
Yes, that is all that I think about. We've done a lot of analysis on the trials that we've done out of my lab. So again, we're actively in clinical trial, and prostate cancer, breast-to-brain metastases and ovarian cancer, all of them are deemed immunologically cold, and so my lab really does work on—and it gets to what Robb was talking about earlier—a bunch of different therapies that, by themselves, may be ineffective, but in combination, or in advance of an immunotherapy, could prime the tumor to better receive and allow survival of those cells, survival of those adoptively transferred T cells. That's all my lab works on.

We do it across a couple of cancers, but we built awesome models—which I'll say, and I haven't presented it because we haven't matured it enough—around pancreatic cancer because the vast majority of pancreatic cancers are immunologically cold. We've built models where there are some that are cold, some that are warm, and we're literally breaking that down into the cell and the gene level to try and understand that with the idea, Rick, that we'll go back in and make those tumors immunologically warm, and can apply cellular therapy and have the responses that people are seeing in melanoma and other cancer types.

Brian McCloskey 56:35
Given what's going on with AI, how is AI getting integrated into your work? Are you seeing it accelerate the R&D efforts?

Saul Priceman 57:15
Probably guilty. I haven't gotten into it as much as I should, but we are implementing several things around machine learning to try and better analyze data in a quicker fashion. That's how we're probably implementing it the most. I think the coolest thing, which Brian, I think we learned about in Prostate Cancer Foundation, was this AI group that could take a prostate tumor that was biopsied or resected in a prostatectomy, and using AI, could predict the stage and therapy angles better than a pathologist could. I forgot what the company was called, but I think that's where we will go. There are a bunch of AI labs at USC, and we collaborate outside of USC. I think what would be really cool is getting to the question we're all asking is, how the hell do you predict that a patient will respond? And I think AI will be the best implemented in that set—

taking all the data you can get from a patient, hopefully in the most non-invasive manner, and trying to predict what therapies will be most effective.

Robb Owen 58:44
I'm using AI right now. When I get the mutation and the variants, I work backwards from that to identify what vitamin, mineral or amino acid deficiency or imbalance may drive that mutation. Then I build from that a targeted diet and supplements that will help rectify any DNA damage that's being done during nucleotide synthesis. And I use AI extensively to follow through, looking for pharmacological reactions. It's remarkable, when you ask it the right questions and fine tune this, the valuable information that AI supplies, at least from my perspective.

“Update on Immunotherapies (CARs and BiTEs) for Solid Tumors” (Saul Priceman, PhD) [#117]

CHAT DISCUSSION

00:29:03 Rick Davis, AnCan Foundation: Pros and cons of CAR-T vs Bispecific????
00:29:17 Robb Owen: Dr Priceman, have you ever considered the concurrent effective effort of typcial antiemetics (dopamine receptor 2 inhibitors, serotonin HT5 inhibitors, histamine H! & H2 inhibitors, anticholinergic agents and neurokini1 antagonists) combined with low dose anti-depressant (GABA inhibitor) and GERD meds that when used in the correct combination will have inhibitive influence on P13K/AKT signaling to VEGF & TGF beta 1 to inhibit angiogenesis and fibroblast differentiation in the TME
00:32:42 Rick Davis, AnCan Foundation: Are TCE the same as Bispecific?
00:39:46 David Plunkett: Very much looking forward to going over these slides again myself at leisure, and having them available as reference material.
00:43:32 Alane Watkins: Have these technologies been tried on more rare solid tumors such as thymoma? —And, what have you observed in patients with autoimmune disease in addition to cancer?
00:45:34 Alexander Lalov: Reacted to "Very much looking fo..." with 👍
00:46:58 Steven Merlin: What has been the main factor in limiting success of CAR-T cell therapy in pancreatic cancer?
00:48:03 Dr. Chris Apfel: Saul, what a wonderful, stimulating and thought provoking presentation and I would love to learn more about what you do.
What are your road blocks you see to get this to patients and how can we work together to overcome those challenges?
00:51:44 Robb Owen: robb.owen@hotmail.com
00:53:45 Roger Royse: what is the success rate for Burkitt lymphoma?
00:58:18 Rick Davis, AnCan Foundation: Is there an explanation as to why PSCA is expressed on pancreatic adenocarcinoma cells?
01:06:59 Dr. Chris Apfel: Thank you, Saul! Need to leave but this was great!
01:07:06 Brian McCloskey: Reacted to "Thank you, Saul! Ne..." with 👍
01:07:48 Rick Davis, AnCan Foundation: Very much appreciated a highly understandable presentation!! Tx u