Julian Hong: Thank you to all of you guys for joining us today. Carissa put it very elegantly, but so I'm not quite as eloquent as she is. But, you guys are why we do all of this. Thank you for being here. I'm leading off for the radiation talks. I'm excited to have Joe joining me this year, that's great. Then you'll hear from a couple of our other colleagues later today. But I usually start off by trying to explain radiation. It can be a very scary thing to hear about. But it's commonly used across different cancers, number of patients with different types of cancers. When we receive radiation, it's a curative treatment for many of these cancers, including prostate cancer. It's often used in conjunction either with surgery. Sometimes after surgery can be used with systemic therapies, in our case, hormone therapy, or it can be used by itself. Radiation oncologists, we're like these nerds that hide out in the basement of the hospital. We get really excited about this random physics stuff. But the way that radiation works is commonly through photon therapy. Essentially what it does is it creates DNA damage through a couple of different primary mechanisms. The idea is that normal human tissues have the ability to recover damage that's caused by radiation. That's why you frequently hear about radiation that's being given over several weeks, extended periods of time because that allows your body to recover from radiation while the cancer cells themselves have difficulty repairing DNA damage. I often describe cancer cells as being dumb. They have been messed up to the point where they're really just trying to proliferate, try to grow, multiply, and so they don't quite have their act together when it comes to DNA repair. We take advantage of that biologically with radiation. In prostate cancer, specifically, there are a number of places where radiation can play a role. I think Joe and my job today is to talk about localized prostate cancer and specifically in the definitive setting. I think you'll hear from Dr. Sadin and Dr. Chen later today, and they'll be talking a little bit about some of these other domains. But it's a broad range of areas where we do apply radiation in prostate cancer. We treat after surgery, we treat different scenarios when there are lymph nodes involved, other types of metastases, so a number of different indications. There are a lot of different types of radiation, and some of this can be very intimidating. We love acronyms in radiation oncology, so you'll notice a bunch of them end in RT. We're not terribly creative with our naming. The most common thing that you'll hear about and what I'm primarily covering today is external beam radiation. Within that subset, there's 22 main forms. The predominant despite how this chart is organized, the predominant form is what we call photon radiation therapy, which is primarily what we do here. You'll also hear about proton therapy, which is available at some institutions across the country. You probably have heard that we're building a proton center here down the street as well. Functionally speaking, I'm happy to discuss this more when we get to the panel questions. But so far the data suggests that protons and photons for prostate cancer specifically are essentially equivalent options. This is a little bit of insider information, but there's actually a major study that's going to get presented within the next few months that's confirming that as well. Within photon therapy, the current state of the art is what we call IMRT. There's a variant of that that's referred to as VMAT. Essentially, I'll show you guys some pictures about how IMRT works, but it's a way to essentially take a target and work backwards from the target through computer algorithms to design the radiation so you're able to focus the radiation to the shape of the target. Then within that, essentially, we've broken down radiation into different treatment types of schedules. There's conventional fractionation, which is slow radiation. You've probably heard about people who have gotten radiation over the course of eight or nine weeks. That's when we give little bits of radiation each day. Then the natural question that was asked a couple of decades ago was can you guys do this a little bit faster? There have been a number of trials demonstrating that we can do this with the same rate of cure and the same rate of side effects, shortening those courses down to roughly somewhere between four and 5.5 weeks. Then ultra-hypofractionation, which is also very commonly referred to as SBRT. Is a way to deliver high doses of radiation over very few treatments. Anywhere between 1-5 treatments for prostate cancer, we're treating in the localized setting. It's usually five treatments, and we usually space that out over a course of a week and a half. Similarly, it's a little bit more of the new kid on the block, but it's still been around for over a decade at this point. There are actually a few clinical trials that have similarly comparable efficacy and side effects. That's actually become an increasingly

popular option for patients. Then Joe is going to talk to you a little bit later today or I guess next about brachytherapy. He'll cover the bottom part of the graph. Chris I mentioned earlier, pluvicto. There are a number of radionuclides which go across the whole body. I threw a bunch acronyms at you already. I like to describe the way that radiation works is essentially focusing beams from different directions, and they essentially all focus in one area. I use the death star analogy a lot, and how the lasers come together and focus into one big laser. You can tell I'm a nerd, but In the graphs that you see over on the right hand side, these are different types of radiation plans. 3DCRT or conformal radiations, basically 3D radiation was what we used to do decades ago. Doctors, we're not, I guess I'll speak for all the doctors, but I don't think we're terribly creative. 3D radiation essentially was a radiation beam from the front, one from the back, and then from each of the sides. You ended up creating this cube, essentially. As technology improved, we were able to actually define targets better. IMRT and the bottom VMAT was the next round of evolution in radiation therapy where we basically traced out the areas that we're trying to treat, traced out the normal organs and what we're trying to avoid, and then we can run it through the computer to help us design these radiation plans. The radiation dose distribution of matches against what our goals are, and that's how we do it today. That's true for, actually both of the radiation or I guess, all of the radiation options that we're talking about today. I didn't want to belabor some of this too much because I want to talk to you guys about the process. But, as Sam and Carissa have talked about through risk stratification, this is like the general starting point for how we think about scenarios and treatments and which types of radiation we're thinking about. As you can tell, essentially, the a short version of it is that as we increase in risk status, we start thinking about treatment for one versus active surveillance, but also thinking about whether we combine external radiation with brachytherapy, which is internal radiation into combination radiation, which is a more aggressive way to treat patients with radiation. Then we also think about adding on hormone therapy. Sometimes that'll be short term over the course of about four months. Sometimes we extend that. I don't have it on this chart, but we also think about adding other medical agents with our medical oncology colleagues, which can also intensify the treatment. Now, this is just a general framework. Each patient's situation is very different. We've heard a bit about some of the newer biomarkers, there's decipher, there's Arta. All of these things sort of play into our calculus for how we make decisions, and this is just the starting point. Actually, just go to the next slide. We also have to think a lot about just how different individuals think about the pros and cons of each element of the treatment. Thinking about what you gain by adding on hormone therapy, thinking about what you gain by adding on biotherapy when we do combination, and then the risk trade offs, and we try to work together to put the calculus together to figure out. What is the right choice for the right patient. There's an extensive conversation. I think you guys have gathered that throughout the talks today. Then, importantly once we complete treatment, basically, you're stuck seeing me forever. We have extended follow up, and a big part of that is to follow for not only the cancer recurrence, but also quality of life and the potential side effects that can come as a consequence of the radiation. This is a general outline of the radiation care path. You'll meet us in the clinic. We'll do a consultation. We do a simulation, which is a little bit of an older term, but it's essentially a radiation planning scan. We'll do radiation planning, which we've called dosimetry on this chart. We'll actually test radiation on something that's like a dummy to make sure that what we program in the computer is actually happening in real life. Then you go through treatment, and then we have follow up. I'll just run through how this process works. But the first step, as I mentioned, is this planning scan. Our awesome colleagues in neurology will often help us with gold seed markers, which allow us to triangulate the target, which is the prostate in real time while we're doing the radiation treatments. Then we basically set up the system and our patient arrangement to optimize the treatments. Some of this will involve emptying the rectum, sometimes filling the bladder just to try to help protect those organs when we do the actual radiation. As I said, we had in the basement a lot. Our job is to trace things out on the computer and design the radiation plan, figure out where the radiation needs to go and where we don't want it to go. We have a team of PhD physicists that essentially back us up and help us do all of the smart person work. It's wonderful to have them on board with us. Then each treatment,

regardless of how many fractions it is, I usually describe it as like a glorified CT scan. We have this radiation machine that delivers the radiation itself, spins around you, and you don't see or hear or taste the radiation, you don't glow in the dark, no superpowers or anything like that. On a daily basis feels like you're doing an X-ray. This is just an example of the gold markers. But you can see this image is split into quadrants, and the top left, bottom right is the CT scan from the planning. Then the bottom left top right is the scan from that day. This is how we do the initial setup where we match all of the markers. Then a number of our machines actually have real time tracking to make sure that the markers are staying within target. Then the radiation gets delivered. This thing on the left is essentially what we call a collimator, and it essentially reshapes the radiation beam from each direction to make sure everything's focused and reshaped based on an individual patient's anatomy. That's what's happening as the radiation machine makes its revolutions around you. We talked quite a bit about quality of life in the first session today, which is our second session today, which is great. I think we've hit a number of these things. There are short term and long term side effects of radiation. Sometimes the timing can feel a little bit unusual. Short term side effects are things that happen during the radiation and carry through shortly afterwards. For most patients, it usually starts about halfway through and sneaks up on you and gradually increases as you go. Those typically resolve in about a month or so, and then long term side effects are things that can show up months to years down the road. Sometimes there's a little bit of separation between the short term and the long term side effects. They're all anatomically related. They're all related to what's close to where we're focusing the radiation. That you can tell many of them are focused around urine and bowel function, sexual function. The one that I think we didn't really talk about earlier today is bowel function. It's a little bit unique to radiation because the rectum sits behind the prostate. That's a little bit of a distinct side effect that can happen with radiation as opposed to surgery. One of those long term risks is bowel injury. But these are, in general the highlights of the different side effects that can occur over the long term. I'd say in general, quality of life after radiation is pretty good. But there are definitely, as we've talked about, with active surveillance, like, definitely potential side effects and risks of any treatment. It's an important part of the calculus as you're thinking about decisions. With that, I will hand things over to Peter to hand over to Joe. Thankyou.