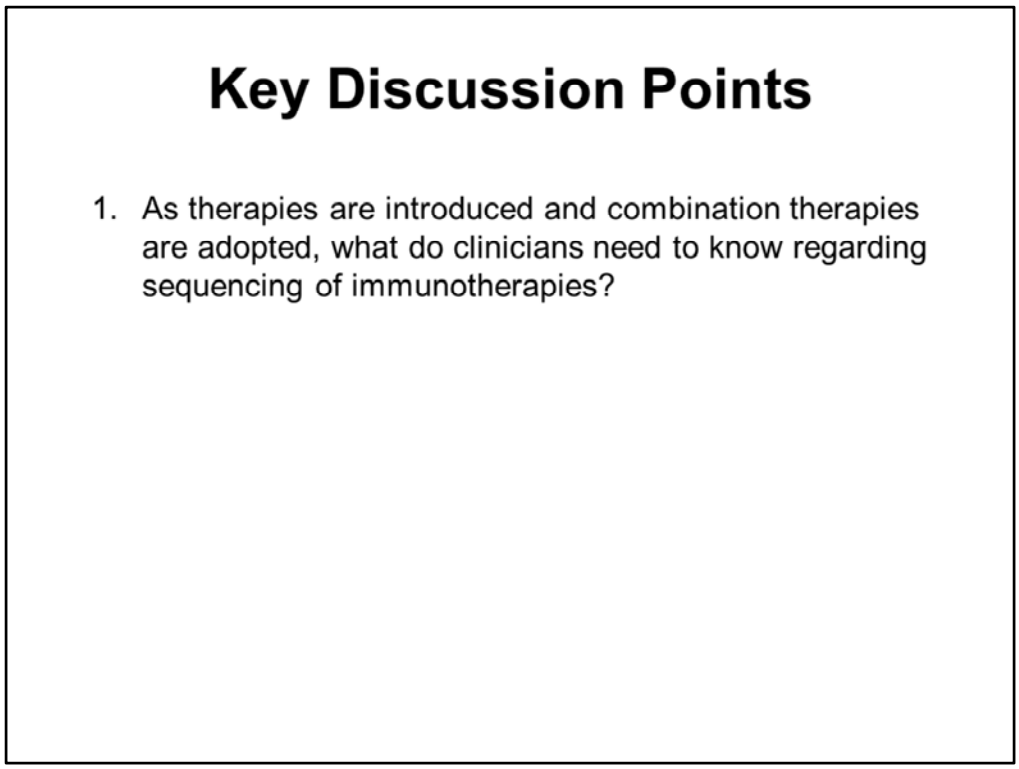
**Module 5**


So, I guess the first question is as we get these new drugs approved, people are going to start thinking about sequencing.




Dr. Weber: What are your thoughts about how quickly to give say pembrolizumab after ipilimumab?

Dr. Luke: So far we do not actually have clear guidance on this question. There are clinical trials that are ongoing to try to answer the question of which should given first, ipilimumab or nivolumab, but there is a question about whether or not you could have overlapping effects, we alluded to giving the two drugs at the same time can increase the response rate but also significantly increase the rates of adverse events. I think it is a question that we do not know the answer to. Fortunately, Dr. Weber is actually running a clinical trial that will help to answer that question, but for the meantime, I think probably the most important thing to say is to just pay attention so that if you start giving one immunotherapy after another, be aware that you may get some additive effect. The other piece to sort of keep in mind is that if a patient had an immune-related adverse event to one drug, it is theoretically possibly they could to the other. What we learned so far is that when people get anti-PD-1 second or in general they tend to have much less side effects. So, I think the likelihood of having side effects giving anti-PD 1 second is lower, but all the same if a patient is previously sort of manifested that they can have a severe immune response. You should take that into account while you are treating them. It does not mean that you should withhold the treatment. You should maybe just keep closer eye on them.

Dr. Weber: So in melanoma, we tend to be giving combination immunotherapies, but you see in renal, it is a little different because you have all these different drugs approved. So you are going end up giving a drug like MPDL3280A or pembrolizumab or nivolumab in the midst of giving someone a signal transduction inhibitor. So again, there are some pretty funky side effects with some of the STIs. So, have you seen unusual worsening or synergistic side effects from the combinations?

Dr. Carthon: You know, it is actually interesting. In our GU realm, a lot of that is actually limited to the clinical trial setting, and the most common scenarios actually looked at them in the front-line setting to avoid some of those side effects. So, for example, we received several consults a year for people you want IL-2 after they have had some of the VEGF-based therapies, imatinib, sorafenib, pazopanib. I do not know about other institutions. Based on historical data, we do not do that, largely because of very, very severe cardiac toxicities and high rates of ventricular arrhythmias. Now whether that exists with these newer agents, I do not believe that is the case. They are much better tolerated, but the clinical trials that we see have been in the front-line setting, and so I think that we are going to have to take cue from the melanoma field. Definitely IL-2 has not been an exclusion criteria for some of our PD-1 checkpoint inhibitor trials, for example, nivolumab alone, nivolumab-ipilimumab together first-line, that did not exclude patients who had IL-2 prior. So for right now, it actually has been a clinical trial-related question, but it is going to become much more of an instance that we pay attention to in standard of care approaches.

Dr. Luke: I think what I will add is that we do have some experience in melanoma combining kinase inhibitors with immunotherapy, so there was a clinical trial combining vemurafenib, the first BRAF inhibitor with ipilimumab, and that resulted in severe toxicity, so that out of the first 10 patients, at least 6 had significant rises in their LFT such that the trial was aborted. So, in standard clinical practice, we advise against the combining a BRAF inhibitor with ipilimumab. Now, whether or not that will hold for anti-PD-1 antibodies, we do not know. I think we all are hedging that that will probably be okay, but we do not actually know that difference yet. There was also at ASCO this year the report of BRAF plus MEK inhibitor plus ipilimumab which similarly had to be stopped due to severe colitis. Within that trial, it was interesting that the dabrafenib plus ipilimumab arm actually appear to be more tolerable, but I would say at the current time, it is generally speaking the case that we do not combine these kinase inhibitors with these immune checkpoint blockade agents yet. There are ongoing clinical trials of anti-PD-1, PD-L1 with BRAF and MEK kinase inhibitors with VEGF kinase inhibitors, we have a myriad of these things, but we really do not know the answer yet. So, I would say in clinical practice as it stands currently, I would not be combining across different modalities.

Dr. Weber: I will give one caution from a couple of clinical vignettes. I had occasion to take a patient who had delay in getting BRAF testing done who had pretty aggressive disease, and I just quickly got them on ipilimumab because I could get it approved quickly in frontline, off protocol. I gave him a dose or two and only then found out, my goodness, they were actually BRAF mutated as there were some equivocations over the results, and then I said okay, let's stop the ipilimumab, we are going to put him on the BRAF inhibitor and then put him on vemurafenib, and they had the most horrendous skin toxicity I have ever seen, I mean ICU level severe side effects. So that really gave me pause about giving BRAF inhibitors alone in close apposition to the use of ipilimumab. The other interesting question is giving ipilimumab, not having overt colitis and then giving high-dose IL-2 quickly in secession. There have been a few reports out of the NCI of perforations because there was occult colitis from the ipilimumab. It was low grade. They did not get scoped because they did not have much in the way of symptoms, got the IL-2. And IL-2 can induce colonic effects and then they had a perforation and did very badly and got very sick. So, I would be careful about adding things in close apposition to ipilimumab, that is all. I mean a few extra weeks off between the treatments would probably yield great dividends.

Dr. Luke: And I would just fold it up from the GU space. There was actually also a trial of sunitinib plus tremelimumab, the other anti-CTLA-4 antibody, and again that was a phase I trial that had to be stopped due to a high incidence of acute renal failure, and many of those patients ended up dialysis dependent. So, that is another one where we do not really know if that is sunitinib problem, an ipilimumab problem, or what. Sunitinib is a dirty drug. It hits a lot of things besides vascular and epithelial growth factor receptor. So, it is not clear if some of those off-target effects may have inputs, but the long and short of it is that in clinical practice off a trial, I would be careful about just sort of throwing everything all together.

Dr. Weber: So, you know the question is in the community, you now have ipilimumab approved, you have pembrolizumab approved. I have had doctors in the community in Florida, we have terrific physicians by the way, ask me why cannot I just put both together, and I said I do not think I would go that direction off protocol, and I suspect the problem with ipilimumab, which is a very good drug, is that if close to the time you give ipilimumab you give another drug, you are going to amplify the effects of the second drug, and you are going to probably amplify the effects of the ipilimumab. So, as Jason pointed out, and I will tooting my own horn a little bit, we have a very interesting trial with Steve Hodi where we randomly allocate melanoma patients to get either ipilimumab for 12 weeks, then nivolumab for 12 weeks, then nivolumab maintenance or nivolumab induction, then ipilimumab, then nivolumab maintenance just to test the idea is sequencing less toxic and just as good as giving it concurrently? We will be presenting the data at ASCO. It is looking very interesting. I have also treated patients on my nivolumab trial who failed ipilimumab and who failed ipilimumab with severe toxicity. Those patients were usually excluded from nivolumab trials or pembrolizumab trials. We did not reproduce the same toxicity with the ipilimumab toxicity patients when they then got nivolumab. So, you can have colitis with ipilimumab then get nivolumab and do well. You do not reproduce the colitis, but I think it is going to require some amount of time off because if you give ipilimumab and get colitis and just barely recover and then wham hit them with PD-1 antibody, I think you are going to have problems. If you give them time off to recover, I think you can come with the second antibody and do well either way, ipilimumab and nivolumab or nivolumab and ipilimumab, but if you give them right together, two things are going to happen. You are going to increase the toxicity to some degree, and if they had a severe toxicity to the ipilimumab which is the more toxic drug and you give the nivolumab right after, I think you would risk reproducing the toxicity. Give them 8 to 12 weeks off the ipilimumab with full recovery from the side effects. I think it will be safe to give them the other drug.

Dr. Luke: I would just throw in there as a plug. We are good friends. I trained at Memorial Sloan Kettering. We are good friends with Jedd there, and he made a comment that I thought was quite insightful when he said that with cancer immunotherapy we are at the end of the beginning, meaning that we now have learned these great things and yet this is just literally a scratch on the surface, how do you combine it, when do you do it, what sequence, etc? So, there are years and years of clinical trials that still need to be done to sort these questions out, and so I would just emphasize in places like University of Chicago here in the mid-west, that is where we are trying to do these things. So, if there are patients that are good candidates, we realize that we have not entirely figured this out yet. You know survival on anti-PD-1 looks to be about 2 years. That is still 2 years, and in a 30-year-old patient, that is not the lifespan that we are really looking for.

Dr. Weber: Not to be critical, but that is a paraphrase of a paraphrase. That was first uttered by Churchill at the time of Alamein in 1942 in a speech and then there was an editorial in *The New England Journal of Medicine* I think when ipilimumab was approved, I forget who wrote it saying it is the end of the beginning or something like that. So, it is not unreasonable.