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TRANSCRIPT - GR 08 05 22 ***"Immune Checkpoint Blockade for Cancer Therapy: The UVA Experience"*** – Elizabeth Gaughan, MD from the University of Virginia

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- Good afternoon, everyone.
- 00:20:22Today we have the privilege of hosting our very own Dr Elizabeth Gaughan and for our internal medicine grand rounds.
- 00:20:31Dr Gaughan has been a part of the uva family since 2012 after she completed her medical degree at Georgetown university before.
- 00:20:37Heading north to Boston for her medical residency and hematology oncology fellowship at beth Israel deaconess medical Center.
- 00:20:44Currently, serving as leader of uva melanoma program as well as the section had a Community oncology at uva.
- 00:20:50She focuses in her clinical work on caring for patients with melanoma and non melanoma skin cancers, she was recognized for her outstanding clinical document with the deans Award for clinical excellence in.
- 00:21:02An active member of asco and the American Association for cancer research Dr Gaughan 's research effort to focus on the treatment of advanced stage melanoma and the characterization enumeration and management of immune checkpoint inhibitors toxicities.
- 00:21:15She is here today to discuss the clinical clinical impact of immune checkpoint blockade in cancer therapy, please give a warm welcome to Dr Liz Gaughan.
- 00:21:30So good afternoon everyone, and thank you for the invitation to come and speak with you and thank you for the home cheering crowd from the chemo division over there, appreciate you all.
- 00:21:41I am see here let's get this to work.
- 00:21:47My objectives, this afternoon are to help to enhance recognition of immune checkpoint inhibitors therapy indications and treatment expectations.
- 00:21:56And to try to help facilitate early detection of checkpoint inhibitors toxicity mostly I want to share with you some clinical pearls and points that I have learned from the front lines of using these drugs for the last 10 years.
- 00:22:10So we'll go through agents and indications treatment expectations toxicity some predictors of response, I have some statistics on the nba experience with these agents, since 2011.
- 00:22:22I have a few recent cases of mine, and that I think highlight some challenging toxicity management points and then we'll end with just some final thoughts today we're going to go through three main classes of checkpoint inhibitors we have anti cla for antibodies.
- 00:22:44Anti PD one and anti lag but, as you can see, these are not the only checkpoints that work in control of the immune response against malignancy and so likely, these are just really the tip of the iceberg for these therapies.
- 00:23:02So anti UCLA for antibody ipilimumab was approved in 2011 and really ushered in this new era of agents for cancer treatments.
- 00:23:12Really uncle for does is it's a break on an activated T cell to try to turn off the activation signal eliminated blocks it from engaging and allows the T cell.
- 00:23:23activation signal to remain more active, this was originally approved as mono therapy and melanoma, which is the only.

- 00:23:30moto therapy indication that it has, you will see Evelyn and I've used in combination with anti PD one often the volume mad because they're made by the same company.
- 00:23:39In several diseases, especially in the hospital setting we now use this in melanoma kidney cancer lung cancer liver and some esophageal cancer.
- 00:23:51So the backbone of most of our checkpoint inhibitors therapy or the anti PD one and PDL one antibodies you have on the surface of the.
- 00:24:00T cell PD one is an inhibitory signal tumors get smart of regulate the login for this inhibitor the antibodies come in and present the binding.
- 00:24:12And the negative signal to the T cell, as I stand here today, there are seven.
- 00:24:16Different antibodies that fall into one of these two categories, they are basically considered equivalent drugs in regards to advocacy and toxicity when I first gave this talk here in 2016 there were only two.
- 00:24:30But we are certainly growing as a right now pamela's, which was the first one approved and September of 2014 has 27 different indications on the FDA label.
- 00:24:41i'm not going to stand here and show you 27 different survival curves but just to show you that the spectrum of diseases that these drugs are used for is really wide and growing the volume habit has 23 different indications, which includes both mono therapy and combination treatments.
- 00:24:59So just to focus here, the new kid on the block the lab three select three is right here it's another inhibitory signal with several different potential logins.
- 00:25:09The antibody comes in and blocks the inhibitor again on the T cell allowing yourself to be more active.
- 00:25:15there's a single drug called rely on the map approved in March of this year.
- 00:25:19It is administered, along with the volume out there in the same bag, so we actually don't give single agent for that limited, it will always be combination therapy when you see this drug as of right now it's only indication is an advanced melanoma.
- 00:25:34So, in general we like these drugs, because most patients do incredibly well it really changes what historically we're seeing.
- 00:25:43With patients with chemotherapy and hair loss and feeling bad and getting run down and losing weight and patients actually really have a much different experience and.
- 00:25:51What they're happy experience I often will tell my patients you'll go through your life and people are not going to look at you and say oh that patients on cancer therapy for the most part.
- 00:25:59And because of this we've been able to treat more and more and more patients patients that would historically had been considered not candidates for treatment.
- 00:26:07Because of co-morbidities or even age here at uva the youngest patient that we have treated as 15 years old.
- 00:26:14who had a bad melanoma on his face and the oldest is in the high 90s, and really have had very good luck with tolerability of these agents.
- 00:26:25Each of these treatments is given by intravenous therapy which ties our patients to infusion centers they're given every three, four or six weeks for half an hour infusion so it's pretty quick, but it really patients.
- 00:26:37really set their life around their infusion schedule and go and fill our fusion centers.
- 00:26:42The optimal duration of these therapies is really not known the original clinical trials had patients on for two years, so really long time to be on Antonio plastic therapy.
- 00:26:52We are doing clinical trials and participating and trials that are looking at a year of therapy get you the same as two years.
- 00:26:59We don't know those answers yet so right now, someone if the advanced cancer we're really signing them up for about two years of therapy, as opposed to what we used to do with six cycles of chemo and be done.

- 00:27:11So, with the new the response rate to these drugs is actually numerically quite low and quite low in a lot of diseases.
- 00:27:17The thing to keep in mind about the responses to these drugs is that if a patient responds that response can be durable some patients go into complete respond to complete remission that last four years.
- 00:27:28What we're going for when we treat these patients is this tale of the curve we're hoping that our patients are going to fall here on this plateau where we don't they don't die from their cancer.
- 00:27:39And this is this curve is actually generated by data from ipilimumab which was generated in 2008 2009 2010 and our newer drugs and our combination approaches that curve is higher and higher and higher with more patients surviving these treatments.
- 00:27:56A quick word about response kinetics so it's really easy when you give somebody a drug and the tumor shrinks you can most of us can figure that part out.
- 00:28:06But what happens, sometimes, especially with nuance at treatment, especially the combination therapy, you can have this layer of.
- 00:28:14The of the tumor not so much just a progression, which is this a pseudo progression things are clearly worse, I mean things are a little bit worse they're a little bit more they're.
- 00:28:24A little bit more consolidation on skin on scans before things start to get better.
- 00:28:28And the reason I want to bring this up is especially patients who get hospitalized for toxicity will often have cross sectional imaging.
- 00:28:35And we've come in many times to our patients who are very upset thinking that their cancers so much worse and these drugs are not working.
- 00:28:43When that's not really likely the case so it's just important when you all are seeing these patients and seeing these scans especially early on.
- 00:28:50That it is possible that they're just a little bit worse because the full effect hasn't really happened yet, just very important when using your words to take what to talk to these patients.
- 00:29:02So in regards to side effects, basically, what I tell my patients is anything could happen at any time to any organ system.
- 00:29:08And there's no way to predict what patient will have a particular side effect there's not a classic.
- 00:29:14type of patient or tumor that always has colitis or always has new midnight, as the really anybody can have any problem.
- 00:29:21And the problems can range from very mild that we deal with in the clinic to severe when they bring we bring them into the hospital to interact with all of you.
- 00:29:29And so, some of these side effects have been really, really quickly, but really most of them take several treatments before they onset and so usually you're seeing patients those three those four and beyond.
- 00:29:44To be honest with you, when we first started using these drugs in 2011 and beyond, we used to really have anybody who had any kind of hint of a side effect was going right to the hospital.
- 00:29:53And anyone who had like one extra bellman that was having a colonoscopy.
- 00:29:56So it's not the way we do things anymore there's a lot of really good experience within our clinical teams within our fellows within our nurse coordinators, to be able to help us.
- 00:30:07triage these patients that cancer Center has invested in an outpatient urgent symptom clinic so we can try to bring these patients in avoid the er avoid the hospital as much as we can.
- 00:30:17So, for the most part we are managing these patients outpatient.
- 00:30:21That have mild toxicities But some people can get very sick and we have to just simply send them in.
- 00:30:28just goes to show, if you are seeing a patient who is on a checkpoint inhibitor who's in the hospital, they are probably sick because usually we try to try to keep them out.

- 00:30:36it's important to try to recognize some of the side effects early early recognition can get them on treatment and can help to prevent people from getting terribly ill.
- 00:30:45And one of the great things so far, at least in the three classes of drugs that I presented earlier all of those drugs are.
- 00:30:52Had the same kind of profile of side effects, so the colitis from PT one looks the same as colitis from leg three which looks the same as colitis from ipilimumab.
- 00:31:01And so you can use establish guidelines and algorithms to assess patients on any one of those drugs and they apply to all of them and same with their treat with the treatments.
- 00:31:16So a few more points on side effects PD one inhibitors in general have the lowest chance of side effects.
- 00:31:23When I talked to patients PD one inhibitors we're usually looking at about a 15% risk of severe problems.
- 00:31:30With me we're looking at about 25 30% and with combination, if you neither we're looking at somewhere in the 30 to 50% range, depending on the doses that we use.
- 00:31:40Not surprisingly, to anybody combination therapy is going to have a higher chance of side effects and mono therapy.
- 00:31:45That being said, we've had patients on single agent PT one inhibitors who have gotten terribly ill, so all of these drugs can make people very sick it's just more likely when you're including a cgi for antibody.
- 00:31:58And some patients show up with multiple toxicities at the same time, so if you're evaluating somebody in the hospital for the clear and obvious colitis should also be kind of looking for Okay, do they have a rash do they have.
- 00:32:09Any kind of liver function abnormalities the pancreas there are other things that can all happen at the same time.
- 00:32:15and any of these side effects can happen after the therapy is over the longest I have ever seen as a patient develops basically type one diabetes, one year after finishing the volume and.
- 00:32:27that's the longest i've ever seen so it's important as these patients re enter the health system in primary care and other specialty clinics in urgent care settings.
- 00:32:37to at least be able to recognize hey this patient was on immunotherapy I should at least put Texas, to be on the differential.
- 00:32:44Our treatments, we when I first gave this talk, we had lots of slides about this is how you grade this, and this is how you treat that.
- 00:32:50We don't need to do that anymore, there are there, as I said very well established guidelines and algorithms on how to do this, you don't have to make it up, we just find it and follow the instructions.
- 00:32:59Basically we're starting and half a milligram to two milligrams per kilogram steroids, and that depends on the severity of the presentation.
- 00:33:07And the I usually those patients twice a day on the steroids, I found that to be a lot more effective than trying to give them one big dose so.
- 00:33:16If we're if any of you are going into oncology and you ever had a problem with trying to manage one of these twice a day dosing can sometimes.
- 00:33:22really help get a patient over the hump and that's also helped in the hospital for someone who hasn't gotten better hasn't gotten better has split the dose and give it to him twice.
- 00:33:31intravenous steroids are used when patients can't swallow, or you don't think they're going to absorb or you think they're incredibly sick and you need to get them better quickly, and I said, most of patients are treated outpatient.
- 00:33:44What happens is we use a full dose treatment until a patient reaches Grade one symptoms and then we taper over four to six weeks as an outpatient.

- 00:33:51And usually that gets patients better most people if they have a problem we are expecting them to get completely better all the way back to baseline without lingering issues.
- 00:34:01The one exception to that is endocrine dysfunction if one of the endocrine organ stops working it doesn't usually restart working.
- 00:34:11So these are some examples of some of those algorithms that we typically use this is our ncc and guidelines.
- 00:34:17Which markets through all of the major side effects, this is our guidelines from the American society of clinical oncology and then from the society of them, you know therapy for cancer.
- 00:34:30alrighty so just to walk through kind of some patients of mine, this is a 33 year old male who has widely metastatic melanoma you got one dose of ipilimumab in the volume and then presented with this rash y'all can see.
- 00:34:45That happened a week or two after starting the therapy it, this is a very classic rash it tends to be on the anterior and posterior torso for most people occasionally involves the extremities as I clearly didn't this patient.
- 00:34:57Most of the time, this is achieved some of the time, and for this patient, it was not.
- 00:35:03Just a very classic rash it's not hurting him we don't necessarily need to do anything about it, we can do topical steroids for itch and other symptoms, but this is just showing us oh hey we hit the target, and so we usually kind of happy to see a little bit of rash.
- 00:35:18This is another patient of mine, a 71 year old male who has metastatic melanoma who had received two doses that they've been EVO and presented with fecal incontinence.
- 00:35:28And over 20 bowel movements per day, he was hospitalized and put on intravenous steroids and didn't completely improve, as you can see his colonoscopy looks rather angry and he actually required secondary measures with remicade to infliximab to overcome this issue with a Kaleidoscope.
- 00:35:51So next this is.
- 00:35:54Another patient of mine who ended up having new midnight of font imaging, this is a pretty classic Newman is tight picture.
- 00:36:01But the problem is that ground glass capacities and a patient with advanced cancer is not always clear this is drug induced new rhinitis is usually a differential diagnosis.
- 00:36:10we've been very fortunate to have some of our colleagues in the pulmonary service, who have really helped us try to manage these patients new midnight is can be quite tricky.
- 00:36:20Typically, presents as a dry cough and that you can tell, in your exam room because they're just cough.
- 00:36:26all the way through the history, all the way through the exam doesn't really bring anything up and they tend to have shortness of breath with exertion, and so we do a lot of ambulatory stats in our clinic.
- 00:36:35And you can usually you can usually watch the hypoxia develop in front of you, and you put them on steroids, and they get better very quickly.
- 00:36:43This is a classic hypothesis this links with.
- 00:36:46Anti cta like for treatment, so when it blew the map is on board patients present with symptoms and hormone deficiency typically of cortisol deficiency and low thyroid as well as the headache from the pressure in the brain and these patients usually have permanent hormone.
- 00:37:02hormone replacement requirements.
- 00:37:05So in my clinic I use these drugs pretty much every day i'm in clinic, and these are the side effects and issues that I deal with on a daily basis.
- 00:37:13So we are seeing a lot of issues with skin aches and pains people feeling tired, we see it, a lot of the Lego i'm a melanoma doctor, I think that a Lego is great.
- 00:37:23But you see it, and anybody who's getting 51 inhibitors we see some mild GI upset some mild laboratory abnormalities and red eyes and coffin fever.

- 00:37:34I tend to send patients in for severe fatigue and severe headache these tend to be patients who have.
- 00:37:41issue hormone related hormonal deficiencies patients who I don't think are going to be able to tolerate oral pregnant zone.
- 00:37:48I don't see a lot of abdominal pain for these patients and so when I see it, it always kind of gets my attention and grade three diarrhea has over seven bowel movements per day.
- 00:37:59People who have clear presentations of decay and acute kidney injury the hypoxia on exertion clearly altered mental status, you go in.
- 00:38:08And then I grew up these last four together we've had about 10 patients here at uva who had combination of my car diagnosis minus the India and my situs.
- 00:38:18And each one of them died and each one of them had at least one of these four issues when they presented so I remember doing a lot of pre syncope work up in the er when I was a resident when I actually see precinct could be It makes me very nervous for our patients in the clinic.
- 00:38:37So.
- 00:38:41One of my favorite lines in the notes oncology console to the prognosis So these are all examples of my patients can see soft tissue metastases.
- 00:38:51You can see Liverpool the metastasis here in our brain metastases.
- 00:38:56These drugs have really changed prognosis for patients with cancer and really complicated the discussion of prognosis.
- 00:39:04because some of these patients can go on to have their cancer go into complete remission and go on to live, what would be considered normal or their normal natural life.
- 00:39:13or they could die from the cancer, where they could die from the treatment and so that's a really wide spectrum of things that could happen, and so the discussions with the patients have to become quite nuanced and quite careful especially early on.
- 00:39:29All three of these patients are long in long term remission all three of these patients are alive many over five years out.
- 00:39:37From their initial therapy and the reality is we don't know who's going to respond, we can't look at a patient we can't look.
- 00:39:44At any factors related to the tumor reliably at this point in time and sick, you are absolutely going to be one that's going to respond, we should give this to you.
- 00:39:52Or you are not going to respond, we should not give this to you, we just do not have that right now, and so we really use these drugs not really knowing what the role that what is going to happen.
- 00:40:03prognosis in these patients is really related to that response, it is you have to get into response in order to get these kind of durable.
- 00:40:11remissions there are multiple patient and tumor related factors, there are lots of smart people across the world, trying to learn, who the right people to treat are at this point in time and it's just nothing that's really been perfect or really usable in every situation.
- 00:40:29I put in here that the durable response can be salvaged in some patients with progressive disease so patients coming into you all, and because they.
- 00:40:37Had abdominal pain, they have a CT scan and it shows balance that's though some of the times those things can be completely respected, and we can salvage.
- 00:40:48complete response with surgery or with radiation so again, it all goes into scan interpretation you'll see things that the radiologists will say it really takes interpretation and talking well to patients.
- 00:41:00Because there's a lot of uncertainty and unpredictable nature of the immune response and how we manage our patients on these drugs.
- 00:41:07So these are some of the.
- 00:41:11Current factors tumor factors which seem to correlate with a higher chance of response higher tumor mutation burden.

- 00:41:20That generates neo antigens higher chance of having a response patients who have DNA mismatch repair deficiency and microsatellite instability.
- 00:41:28More neo antigens more chance of response there's a lot of controversy over PDL one expression in some diseases higher PDL one expression is linked.
- 00:41:39With higher chance of response to immunotherapy and so say in non small cell lung cancer, if you have over 50% expression of PDL one you can get single agent pemberley ISM and you don't need chemo.
- 00:41:52But if you have lower you need the chemo and the immunotherapy, this is not as well borne out and other diseases so say had melanoma.
- 00:42:01I don't know what to make of appeal one expression, because it doesn't really correlate necessarily the treatment, some of my best responders have been patients with no PDL one expression.
- 00:42:10And I have patients who have PDL one and 80 and 90 even 100% we don't respond at all so it's just not perfect, but you'll often see it in our notes.
- 00:42:19A lot of interest in the tumor micro-environment in particular.
- 00:42:23That idea of a hot tumor and a cold tumor so tumors that are not responding some of what we are doing now is trying to aggravate those tumors with.
- 00:42:31Radiation with focus ultrasound with international injection to try to create.
- 00:42:37Hot tumors from cold tumors to change the immune cells that are getting into the micro environment there's a lot of interest and the microbiome colon microbiome and people who are studying.
- 00:42:48fecal transplants and ways of changing the microbiome to make people more likely a responder or and that that is work that's just.
- 00:42:57still being done, and hopefully we'll know more in the years to come, and there are likely multiple patient characteristics.
- 00:43:04That also factor into how people how people respond to these drugs, so the bottom line is we just really don't know who's going to respond at this point, and who is not.
- 00:43:16I thought this side was really kind of interesting on.
- 00:43:20The y axis here, this is your response rates and on X axis, this is your tumor mutation burden and so these are your two how tumors.
- 00:43:30cutaneous Weymouth cell carcinoma has a very high rate of somatic mutations and very high response rate to PT one.
- 00:43:37And so that's UV exposure same with melanoma right here UV exposure creating neo antigens and then you have your mismatch repair deficient diseases, also have very high responses to some of these drugs, but you can see that response is 50% that's a 50 that's not 100.
- 00:44:00there's also a intricate relationship between response to therapy, the side effects and the use of steroids.
- 00:44:08Patients who have side effects, especially once we get really sick and wind up in the hospital.
- 00:44:13We actually are somewhat happy to see that because, in general, some of those patients who have those bad side effects tend to be the responders.
- 00:44:22And so that's one way we try to comfort our patients who are terribly ill so hey This makes me this is working sorry that you're in the icu but the steroids.
- 00:44:31Can are used to try to manage the toxicity and so there's always a big question about once we start getting patients steroids for Texas to do we're going to blend the response.
- 00:44:41To the agents, and so the data that we have on this comes in kind of has to basic ideas we focus on A and B up here, this is patients treated with ipilimumab at sloan kettering.
- 00:44:54That up here the survival and the yellow line of patients without any side effect or and blue has no side effect and over here yellow line steroids and blue no steroids.

- 00:45:04What I think you all can see here is that there really is no difference, these are patients who came in didn't have any steroids a baseline.
- 00:45:11got treated had a side effect went on steroids what this is saying is the steroid use of steroids did not impact their survival.
- 00:45:19And so, for patients who are coming in to the hospital are coming into our clinics and need treatment.
- 00:45:24The teaching is just treat the toxicity will get them off quickly we're not going to lose ground on the cancer and we just go and usually patients get better.
- 00:45:34that's not the case for patients who start on steroids so unless we focus on see right here.
- 00:45:41So these are patients from France and the United States, who were treated with anti PT one or anti PDL one therapy.
- 00:45:51The black line is that those patients were on prednisone at a dose less than 10 milligrams and the red line here the sort of overall survival red line here.
- 00:45:59prednisone greater than 10 mil greater than or equal to 10 milligrams So these are patients coming in to the immunotherapy starting the immunotherapy on steroids.
- 00:46:08And as you can see here the patients who were on steroids did worse my patients who were on a lower dose of steroids.
- 00:46:16Typically, people who needed steroids before we treat them our patients with severe pain patients who have they have some kind of cancer related obstruction or brain metastases patients who have more aggressive disease, to begin with.
- 00:46:30But if we try to avoid or less than the amount of steroids patients are on before we treat them the best that we can.
- 00:46:36And this was data within 30 days of starting the immunotherapy they were on that prednisone.
- 00:46:41So we don't usually wait 30 days before we start people on treatment, but we do try to bring the steroids down as much as we can, and it just something to think about when we're dosing patients in the hospital about how much do they really need and for their issues.
- 00:46:57So it can't do a talk in 20 2022 and without mentioning it 19 right and so as this audience knows very well they're concerned about patients with cancer and unmute and immunosuppressive Antonio plastic therapy and potential for adverse outcomes from.
- 00:47:16That literature on these on this correlation is really not that strong but all of it highlights this this central question which is.
- 00:47:24checkpoint inhibitors may strengthen the clearance of the virus or may worsen immune mediated consequences of the infection basically we don't really know what's going to happen when patients on these therapies get infected.
- 00:47:36We we did recommend, at least through my clinic and I imagine for my colleagues as well, that all of our patients get vaccinated.
- 00:47:43I didn't really have much vaccine hesitancy and experience that for patients on.
- 00:47:47Active therapy the patients who didn't want to get vaccinated where those who are in the complete long term remission they don't want anything that's going to mess with that remission.
- 00:47:56And those are the patients that just who are five years out 10 years out, they would just they're not playing, no matter how you said you still don't want to die coven it we're not going to get vaccinated.
- 00:48:09So the only real data that I could find that this was an observational study that was from 19 different centers in nine countries, including the United States, Australia and several countries in Europe.
- 00:48:25It was a retrospective cohort study of 110 patients who were on checkpoint inhibitors therapy and tested positive for coded while, on the checkpoint inhibitors.

- 00:48:36About a third of those patients presented with covert related symptoms, including fever cough and disappear.
- 00:48:43The factors associated with hospitalization included patients who are on combination immunotherapy had code related symptoms or had a worst performance status.
- 00:48:52Over the overall cohort mortality was 7% and so just to tell you, when this was done, it was between March and may of 2020 just for perspective as to when these patients were taken care of.
- 00:49:04And the authors said that at that time when they publish this the cancer mortality was between seven and 33% So this was on the lower end for cancer patients.
- 00:49:14The overall mortality for people who ended up in hospital was about 46%.
- 00:49:18So the authors concluded that treatment with checkpoint inhibitors did not appear to be an additional risk factor for severe covert infection and patients with cancer and that's really the only data that could really find on this this question.
- 00:49:33We treat patients right on through the hope that pandemic.
- 00:49:38The new issue now is that our drugs work and patients survive and they survived for a really long time and they survive and kind of go back to close to their baseline.
- 00:49:49For a lot of people, and so they are reentering the health system in primary care and in other sub specialties and the survivorship issues are going to expand and expand and expand as more patients live.
- 00:50:01And so, these are the main survivorship components, based on our ncc and guidelines, which is focusing on healthy lifestyle for these patients not surprising.
- 00:50:11maintenance of a healthy weight activity, they should be managed with immunizations and cancer screenings as you would for any other patient in that age group that you're taking care of.
- 00:50:21I remember learning oh this person is only a 10 year life expectancy, or something you know we shouldn't do this, we shouldn't do that really you should treat them as if they're going to go on to live a normal life expectancy.
- 00:50:32And screening for depression, anxiety and distress is really quite important, I can only imagine, and I do this.
- 00:50:39i've done this for 10 years you can only imagine being told I'm going to die my kids are going to lose your parent and then oh wait no.
- 00:50:47And you're Okay, and they go on to live and have to learn how to restart and how to read how to reset there's a lot of issues with post traumatic stress, as you can imagine, and so it's important when you're seeing some of these patients that screening for these issues.
- 00:51:04come up so that proper help can be provided to the patient, a lot of people lose their employment during therapy have financial and insurance concerns.
- 00:51:13And there is still a component of fatigue that lingers and patients who've had checkpoint inhibitors.
- 00:51:18The T like you can take care of yourself, you can go out, you can exercise that people run marathons and, like their hundred mile crazy business.
- 00:51:26But it still just a little more tired than they were when they started, and I also have patients that are long term survivors that note that they can't multitask as well, their memory is not quite a sharp.
- 00:51:37And they get flustered a little more easily so it's likely there's some cognitive impairment related to these drugs a lot we're still learning.
- 00:51:46So, to talk a little bit about us we have treated about 2200 patients at uva since 2011 you can see the male female breakdown, they are a little bit more men than women and then you can see the race breakdown 88% white and 8% African American and then smaller.
- 00:52:06Other groups, I thought this was a little surprising, but breakdown seemed really heavily Caucasian to me but that's what that's what the data that I have.

- 00:52:19We have treated 45 different diagnoses and pretty much every diagnosis, you can think of, has been likely treated with a check went ahead with her at uva it runs across every team.
- 00:52:30That, I am not the 19 solid tumors malignant hematology brain tumors neuro oncology do you an oncology everybody's using them.
- 00:52:41And I'm note about cost, so this, I have a couple patients right now that are self pay so we were trying to get this information for them so they could kind of get a sense of what we were looking at.
- 00:52:52For a one single dose of embolism which is given every three weeks.
- 00:52:59$43,000 809 for the drug desta not anything else, not my time or any labs or anything else that we do $43,809 so for my admin pages for melanoma they get one year therapy $750,000 most people are getting two years of therapy at least 1.5 million and similar for Nevada man.
- 00:53:20By the time you multiply it out loud, so the patients are always quite surprised when they see the explanation of benefits, and when you look at it being EVO I hear it's about $150,000 but I couldn't get that verified in time for today, those are the charges that go to the insurance.
- 00:53:37Alright, so.
- 00:53:41A few cases, I had a 70 year old male who presented with fatigue weight loss dry cough and disappear.
- 00:53:49Now this 70 year old male is as healthy as healthy can be he bikes 30 to 40 miles multiple days per week hikes in the mountains very active very fit guy and he was to the point where he couldn't do any of those things.
- 00:54:02anymore, he ends up having a CT scan done at an outside hospital so it's kind of diffuse.
- 00:54:09infiltrated picture, he ends up having a pet scan done, which also shows mtg acidity in the lungs, which is quite a typical.
- 00:54:18And then he undergoes an open biopsy because they thought he was going to have interstitial lung disease.
- 00:54:23That turns out he had melanoma, so this is a be rafi 600 staying here, you can see in the brown highlighting the melanoma selves.
- 00:54:32So he came over to me and we treated him with it Benito and after three weeks after the first dose or they've been EVO this was the er visit.
- 00:54:44He had been on three liters oxygen and baseline he was now 84% on six liters happening over the course of two to three days and I've never seen this before, maybe you also what they said he.
- 00:54:56kind of got my attention so he came in and he has a force cta to look for pulmonary embolism which was negative, but it does show these ground glass capacities and the lungs, with increasing consolidation, you can see there.
- 00:55:11And so we were really in this position where like okay well, what is this is this melanoma that's progressing is this melanoma that's flaring on treatment is this new midnight is from it being EVO.
- 00:55:22Or is there something like infection or some even hemorrhage it was considered it wasn't popping up any blood, so he goes into the hospital.
- 00:55:31And he winds up on I don't remember exactly, but a lot of oxygen and what we decided to do is give them everything so he got all of this, all at one time.
- 00:55:39And, of course, our wonderful pulmonary colleagues came and helped us try to figure this out as well.
- 00:55:45And he was in no shape for a bronchoscopy so we had to guess, so you got steroids and antibiotics and he got new Antonio plastic therapy, he was very lucky he had to be rough mutation and he got better is the most amazing thing.
- 00:55:59He just got completely better two weeks after starting all of this, so what was it hard to know.
- 00:56:07He did well under breath and intermittent him until about a month ago, when he presented with about 30 brain metastases.

- 00:56:14So now we're challenged with can I retreat him what was that new rhinitis or was it cancer or what was the problem we're going to find out because he's on those two right now and we'll see how we do.
- 00:56:27But Newman itis is always tricky I have found.
- 00:56:31This is another patient of mine is a 71 year old female who presented in September of last year with a headache and low back pain to an outside hospital.
- 00:56:39She was found to have bone really pretty diffuse bone metastases and lung metastases you can see a representative picture here she underwent a CT guided biopsy of a right lipstick.
- 00:56:51Mass roadmap showing melanoma she completes palliative radiation therapy too painful areas of bone metastases and we started her on ipilimumab and the volume mab combination.
- 00:57:04This is also a very healthy women at baseline but her performance status had taken a market hit due to symptoms related to her cancer and she got she was getting better.
- 00:57:16And so, she came in to our clinic and time for those four of her it'd be evil combination and she reported to the team two weeks of four to six, bowel movements per day.
- 00:57:27For those of you not familiar with us grading This is great to or moderate colitis she had a low appetite and she kind of had this weird crappy lower abdominal pain.
- 00:57:37She just looked sick there was just something about her that does he look sick and of course this is like December 17 and even things are getting close to the holidays and everything's complicated so she goes to the er.
- 00:57:48She has a CT scan which shows pan colonic valois thickening and hyper enhancement and inflammatory changes consistent with colitis and thanks to the help of our GI colleagues she undergoes a flexible sigmoidoscopy and, as you can see as a pretty angry looking colon.
- 00:58:06So she gets started on.
- 00:58:09IV steroids, and she does very well in the hospital.
- 00:58:13gets Grade one symptoms frequency of bowel movements getting better she's able to transition to oral steroids she's doing the PT ot thing walking in the hallways we're going to send her out to rehab just waiting on a bed.
- 00:58:23And so we decided to let's do a CT scan and figure out where we are, from a cancer standpoint, so we can make our next plan for how we're going to treat the cancer, you can see she's responding.
- 00:58:31This is where she was to where she is and this patient clinically had gotten much, much better than she was able to walk before she came in in a wheelchair and really improving my slide.
- 00:58:42And then the team goes into car one morning during her hospitalization and she is acutely altered and just really not responsive to the team at all.
- 00:58:54And she has a very rapid couldn't believe it got all this done and $24 negative CT had negative brain MRI for metastasis lumbar puncture not showing any evidence of.
- 00:59:06meningitis and or infectious or a subject and an EG with no seizure activity so she just continues to deteriorate and deteriorate.
- 00:59:18Lots of conversations happen with the patient and the family, over the course of that time she's clearly not doing well and lots of notes suggested that this is just a natural progression of her cancer.
- 00:59:30And they decided to make her comfort measures older when she died in the hospital in January of this year, this family opted for an autopsy.
- 00:59:38To just kind of see what happened and what she had was she died from checking inhibitor pan colitis.
- 00:59:45So I talked to the pathologist she had multiple areas of new chronic bow with several areas of perforation and her bow as a side effect of treatment.

- 00:59:54But this patient presented with grey to symptoms and she got better on the treatments that we're supposed to give her.
- 00:59:59But she was but still the latest was worse than really she was manifesting all of the areas where she had had tumor.
- 01:00:08And in the past year evidence of prior tumor were all non viable so tumor basically was completely controlled and she died of the side effects of the drug, this was a tough one, this was a tough case in a tough day.
- 01:00:36yeah that's a great question so a patient like this, what I actually do is I've stopped treating them because most of the time and they've gotten a sick is this has happened.
- 01:00:45That their cancer remains controlled and as like her tumor there was no evidence of viable tumor.
- 01:00:50She would stay fine a lot of people don't need anything else, actually, so I don't restart them if I need to I would restart them on single agent.
- 01:00:59Typically forgiving somebody combination immunotherapy the thought is that the ipilimumab is driving the most of the toxicity, as opposed to the.
- 01:01:06PT one inhibitor and so you manage the toxicity you get them better if you need to retreat them we put them back on simulator PT one and they most of the time do very well.
- 01:01:18So just a few final thoughts and then I'm happy to see what else I can answer for you all.
- 01:01:23So checkpoint inhibitors therapy has a very prominent and growing role in cancer treatment.
- 01:01:29We are using these drugs and the meal adjutant and adamant setting more and more so the number and diversity of patients that are going to.
- 01:01:35be receiving these treatments is only going to increase, which means the interactions in the health system where all of you all will be practicing.
- 01:01:42Whether its primary care sub specialty medicine clinics, you will see patients on these drugs it's important that you just at least recognize that they're on these treatments.
- 01:01:52there's a lot of smart people trying to figure out how to best use these drugs, who are the patients that really are going to benefit the most.
- 01:01:59and hopefully we were going to be able to generate more reliable biomarkers of response or resistance, so we can most properly use the drugs.
- 01:02:08Just being able to identify that the patients are on this therapy is really your first step, and considering toxicity, and so I was giving a presentation to the teams on the.
- 01:02:20oncology and one of the House staff was telling me that he had a patient that came into the clinic who was on these drugs.
- 01:02:28who came in, with a severe headache just so happened that the attending in the clinic had just gone to a lecture.
- 01:02:34About checkpoint inhibitors toxicity and said oh hey we should check her hypothesizes and turned out the patient on hypothesis.
- 01:02:40So it's just it's just kind of trying to tie it all together, so you can just help get the patient to the next step.
- 01:02:46toxicity should be great in a managed according to well established guidelines and algorithms.
- 01:02:51it's all out there it's very easy, you should do this study, you should do this laboratory tests, you should give them this dose of steroids, and we go by and we go by those.
- 01:03:00And lots more issues with survivorship a lot more patients coming through and we're going to learn a lot about what happens to these people over time really the first dogs were approved in 2011 so we're not that far into this lots more to learn.
- 01:03:15And that's that.
- 01:03:28Thank you so much for that presentation, Dr Gaughan and we have a few questions from the chat So the first from cure Harrison.

- 01:03:36Are there any signs that these drugs will become more cost friendly in the future.
- 01:03:40I I imagine pembroke was approved in 2014 so you imagine us patents run out it's possible that your costs might be better.
- 01:03:50I would also say that the drug companies have been incredibly generous, so I had to go through that exercise for myself pay patients, we were able to get free drug for them through the companies so they've been very generous.
- 01:04:05And then from Dr Williams thanks for a superb review, can you also comment on the rare acute cardiac toxicity.
- 01:04:13Yes, so we had a few patients and I will never forget it first one was mine.
- 01:04:19He had metastatic melanoma and we gave them if the meebo and he was hospitalized about a weekend to treatment he kind of almost passed out while he was shaving in the morning.
- 01:04:29And he ended up seeing his primary care provider in green, who called me on a Friday night at like four o'clock like I don't know what the problem is, but it's not good.
- 01:04:38We brought him in and he had very clear discount to get gays and he had a positive proponent he was able to get a cardiac MRI on a Friday night which I've never seen before, and.
- 01:04:52showed my apart itis this is right after the New England journal paper where they published on several patients who had a very similar set of.
- 01:05:01symptoms and we like called the people who wrote those papers and call the cardiologist at vanderbilt and.
- 01:05:09Where I trained to try to get some help and we just threw everything at this guide is like we knew that this was very hot had a very high mortality.
- 01:05:17We gave him a high dose steroids atg we gave him sell said we gave them site toxin and he just got worse and worse and worse even into complete heart block.
- 01:05:27He then started having respiratory fatigue likely from them is the nia component and ultimately ended up dying and a code in the ccu.
- 01:05:36which was actually terribly terribly sad for this for all of us taking care of him.
- 01:05:43But we've actually had that happen about a total of 10 times and it's been this combination of minus the nia my car titus and Maya situs and one piece of that has been a little more prominent and each of the patients.
- 01:05:57And let all of them have had respiratory issues have had positive two opponents we've also had patients who had my card is where it was.
- 01:06:05heart failure presentation and patients we've had recurrent Am I and patients and patients who had different a rhythm he has all been hard presentations and from this it.
- 01:06:15Ever since that one early on, you know just kind of every time you worry anybody that's having anything that's happening here, makes me nervous.
- 01:06:23Thank you, and then question for me.
- 01:06:26So as we're trying to decide patient factors that make patients more or less likely to respond to immunotherapy, what is your understanding of the consensus and using immunotherapy and patients with.
- 01:06:38known history of autoimmune conditions are strong family history of autoimmune conditions, and how does that impact your decisions on therapy yeah thanks that's a great question so.
- 01:06:47I had I'm actually quite aggressive in my treatment of patients with autoimmune disease and what we have learned is for both see Chile, for an anti PD one PDL one antibodies is that you can do it successfully.
- 01:07:00You have about the same response rates to patients with underwriting autoimmune disease as compared to those who do not regard to that the chance of benefit is about the same.

- 01:07:09About a third of patients, you will flare the underlying autoimmune disease typically that flare looks like a typical flare for that patient it's not like a new whole new set of symptoms for that disease for that patient.
- 01:07:22And some of those patients also get different immune related adverse events, so I have been able to treat patients with ulcerative colitis and.
- 01:07:31crohn's disease, with the help of our GI colleagues who helped me try to keep control of that colitis while I'm trying to aggravate it.
- 01:07:39And then we've treated patients with either patient now with multiple sclerosis and we've been able to treat.
- 01:07:46The one patient did come into me who has active my acedia gravis That was a tough conversation we opted to give that patient chemo.
- 01:07:55Just knowing what could happen if I can make that my esteem do worse.
- 01:07:59But we are we do treat patients, and so the expectations are if they're coming in, on steroids if they're coming in, on immunosuppression they may not have the same potential benefits.
- 01:08:09But it's still not a reason to not treat them if you give the risk and benefit discussion with the patient and their family and let them decide, most people want it.

Unknown Speaker

01:08:21For A while toxicities.

UVA Internal Medicine

01:08:27There was more links to a better prognosis as far as like early activation of the immune system.

- 01:08:34Either through anecdote or data and I wouldn't say there's like they could you have a rash you're gonna respond if you have colitis you're going to respond.
- 01:08:41Like if you have a side effect usually one that tends to respond, most of that data has been generated in a non small cell lung cancer it's a little more questionable and other diseases.
- 01:08:49But I would say I worry when patients don't have something when don't have some kind of side effects, and as long as it's something I'm happy.
- 01:08:58That answer your question.
- 01:09:05Solid tumors is like an excel that is way beyond anything that I know.
- 01:09:10I didn't get a hazard a guess guess on that, but thank you for that question alright, so a few more questions from the chat and so Dr patel lives I struggle to convince patients that they can stop therapy at two years with stable disease what's your approach.
- 01:09:25I also struggled this that patients who were told they were going to die that are doing perfectly well on, and you know therapy.
- 01:09:30And so I start the conversation early and sometimes I go three years the longest i've ever gone is five years and I finally got the patient to stop.
- 01:09:40But it's very challenging for people who are doing really well like Why would I stop this is doing is doing great.
- 01:09:46Insurance forces you to stop and a lot of diseases insurance will only approved two years for non small cell lung cancer and other diseases so.
- 01:09:54you're going to stop because you have to because it's not going to be paid for.
- 01:09:57But in melanoma you have kind of an indefinite approval, so I start really early in setting the expectations and.

- 01:10:05kind of talk through it for two years before we get to the point where it's in the end it's a very hard thing for patients very, very challenging mentally to go from being on there be to not even people who've had responses, or have no evidence of disease.
- 01:10:25semi related question from Dr gensler and we all have a growing number of long term immunotherapy survivors with stage four cancer.
- 01:10:33When is it safe to say that they're cured three years, five years 10 years yeah so I'm just going to go back, I have always used because I trained at a place where they gave interleukin to go back to this one graph.
- 01:10:50i've always use this as my.
- 01:10:54slides, this is where I come up with what I expect so between 30 and 36 months is where the flattening of the PR happens here.
- 01:11:06I am usually feeling a lot better at your three if they had nothing at your three than I don't know that I can come up with anybody that has record that I can think of, in the years that I've been doing this here so.
- 01:11:21This is generated by ap as opposed to other drugs, but I think it's been pretty consistent with what we see clinically.
- 01:11:27Either see the patients that come in and the disease just goes away those patients do really, really well for the patients where you're struggling with residual findings and residual lesions.
- 01:11:37You know, those are people who are not going to do quite as well, but if I have a complete responder and we're hitting the two year mark i'm usually pretty happy I don't tell them that till five years.
- 01:11:47i'm usually happy.
- 01:11:53Right well if anyone wants to see this in real time you're welcome in my clinic and thanks so much for coming.
- 01:12:11Thank you.