Welcome to Yale Cancer Answers with your host Dr. Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it’s a conversation about Melanoma with Doctor Harriet Kluger.

Sure, when we think about oncologic treatments, there are three major categories. You can take a cancer out with surgery, or you can do radiation, or you can...
give what we call systemic therapy, which is therapy that’s given by mouth. But I feel the vast majority of melanomas are actually discovered really early on when people see a changing mole or a dermatologist might find one on a routine skin exam. Most of the melanomas are then excised, in other words, taken out and nothing further needs to be done, and patients are simply observed. Every so often patients come in without ever knowing that they had a Melanoma in the skin. So it’s a Melanoma that has spread beyond the primary site. Or they might have had a primary Melanoma that was removed years ago, but a few cells escaped and are now developing into tumors in other locations in the body. What I do in my clinic is treat with systemic therapy so things that are administered by mouth or by IV so they go all over the body and that’s what we’re going to talk about primarily today. One of the questions that a lot of patients have is when they have that phenomenon of metastatic Melanoma, so the Melanoma has escaped.
It’s gone to other parts of the body where surgery really can’t remove the Melanoma itself and where you’re treating with systemic therapy people wonder about the prognosis and whether in fact they can never be quote cancer free. Can you talk a little bit about that?

When I started treating patients with metastatic Melanoma in 2001, if somebody had cancer that had spread beyond the skin and into the internal organs, we would have a frank conversation with the patient and say we’re really sorry, this is an incurable disease, and on average people live between 6 and 12 months. You should start getting your affairs in order and we will do what we can and hope for the best. At the time we had a chemotherapy called Dacarbazine and an immunotherapy called high dose interleukin two which was very difficult to administer. The Dacarbazine might have shrunk the tumors temporarily for a few weeks, and the high dose interleukin two would result in actual cure.
but in a very small percentage of patients, perhaps 4 or 5%.

Newer therapies were then developed after that, and by 2005 or 2006 we were seeing that the median survival was actually in the order of one year. At present we don’t actually even know what the median survival is, and when a patient comes in and asks what the prognosis is, I say at least 50% chance that we’re going to have prolonged survival and if prolonged, disease free. But I can’t actually tell people if the cancer is ever going to come back. We do believe that we are actually curing a subset of patients who have metastatic Melanoma, including people who’ve had a lot of disease and disease that’s gone to vital organs such as the liver, the lungs, and the brain. When you say prolonged disease free survival, I’m assuming that you mean more than days or weeks and maybe even more than a few years. Is that right? Absolutely. So when we started using the first of the newer immune therapies,
a drug called ipilimumab
we still have patients who were
treated in those years who have never
required additional treatment and are
disease free and living their lives.
Now I can’t say for sure that
it’s never going to be a problem,
but the chances are that it’s not going
to be a problem over a decade later.
So yes, we’re talking about years.
We’ve talked a little
bit on this show about immune
therapy for a variety of cancers,
but it seems that in metastatic
Melanoma it really seems to
be incredibly effective,
especially when you look
at how far we’ve come
in 2001 telling people that
they had less than a year,
and to get their affairs in order,
why is it that immunotherapy seems
to work so well in Melanoma but may
not work as well in other cancers?
That’s an excellent question.
Melanoma by nature tends to have
more mutations than many other tumors.
It’s for the most part a
sun exposed malignancy.
So the sun will cause damage in many,
mutations there are a lot of immune cells that recognize these cancer cells as foreign or bad and with time they get exhausted and these newer drugs will stimulate them. But we probably have a larger repertoire of immune cells in Melanoma than most other cancers, and that’s why they respond better. And I think another interesting point to make is that there are two other types of skin cancers. There’s a fairly rare skin cancer called Merkel cell carcinoma, which also has a fair number of metastatic squamous cell carcinomas and also will respond very well to immunotherapy, better than many other tumor types where we might see response but not for many years as we see in Melanoma.

But we do think it’s related to the tumor mutation burden or the number of mutations that these cells have. And so as you think about immunotherapy, you mentioned that the first generation of these was actually brought into practice in 2005, 2006. Have we developed newer forms of immunotherapy since then? And what’s the prognosis?
What are some of the exciting developments that have happened over the more recent time? So there are many exciting developments, the first drug Ipilimumab was brought into clinical trials in those years. But it actually took many years to achieve FDA approval. It was only FDA approved for metastatic Melanoma in 2011, so the first Ipilimumab, results in nice tumor regression, in maybe 10% of patient’s, but the second generation drug is a drug that targets a molecule called PD1, which stands for programmed death one. There were two that were first given to patients with Melanoma. Nivolumab and pembrolizumab, also known as Opdivo and Keytruda. Subsequently, many other companies have developed drugs that inhibit PD one and this one seemed to be the better target for the immunotherapy. So when we give this to Melanoma patients, instead of seeing nice responses in maybe 10 percent of patients we will see good responses in 30 to 40% of patients.
and interestingly, this is less toxic, so the second generation was both more effective and less toxic than the first generation. Then the question asked in around 2009, when we already had a little bit of experience with these PD one inhibitors was what would happen if we give the two drugs together. So these two classes of drugs target non redundant pathways in the immune cell and its interaction with cancer cells. So if we inhibited two different places in theory we will get enhanced activation of our chief immune cell, which is called a T cell. And indeed this was the case, when we give the two together in Melanoma, we now see very nice responses in excess of 55% of patients. So the two together is better than either one alone. Just to clarify, when you say the two together you mean Ipilimumab and pembrolizumab. The studies have used Ipilimumab and nivolumab simply because both of these drugs were developed by the
same company. But yes, it’s been given with pembrolizumab as well, but not Ipilimumab and pembrolizumab, which both target pembrolizumab, which both target PD 1 correct. There’s no point in giving two drugs that inhibit the same target concurrently, so by that point, did we switch all of our patients to dual therapy? Actually no, because remember, some of the patients do very well with monotherapy. do very well with monotherapy. 30-40% will do well with the one drug, the PD one inhibitor. So we’re trying very hard to select those patients who are more likely to respond to one drug and also patients who might not be able to tolerate extensive toxicity. The toxicities are the main problem, it depends where the patient lives, how socially and economically robust they are, whether they’re associated with a health care system that can support extensive toxicities, but when we have patients who’ve got aggressive disease and particularly young patients with no other medical problems, we do start off with the two drugs up front. There are other people in the
Melanoma field who might start with one and then add the second one if the first one alone does not work. So a lot of refinement of these regimens still needs to be done, and there are many studies looking at how much to give, when to give, what sequence, etc. It takes years to sort all of this out. I also want to add that we now have a third target that is looking very promising in Melanoma, there’s a target called LAG-3. It’s an antigen that’s expressed on these same immune cells or T cells, and when you give inhibitors of LAG-3 together with PD one inhibitors, it does appear that it’s going to be better than PD one inhibitors alone. The data are still very new and more maturity of the data is going to be required. In other words, we need to follow patients for much longer to make sure that it actually holds up. Clinical trials for that drug are currently ongoing. It’s already in a phase three study which is completed accrual and the first data do suggest that the two drugs are better than the nivolumab alone.
And has anybody thought about adding Ipilimumab?

Yes, there we again will run into problems with side effects and we have to be very careful when we mix 3 drugs and this takes a long time to work all of this out.

It sounds like with now the three kind of tiers of immunotherapy that you’re talking about, upwards of 55, maybe even close to 65-75% of patients might have prolonged disease free survival. We don’t know yet about the 65-75%. That’s what we’re shooting for, and ultimately, we’re going to shoot for 100%.

I also want to add that this is just one type of immune therapy.

We call it immune checkpoint inhibitors, so the checkpoint refers to a negative regulator of the immune cells, and that’s what these drugs target. The various other types of cellular manipulations that we can give to activate the immune system against cancer, but the immune checkpoint inhibitors specifically refers to molecules on immune cells and cancer cells that have crosstalk.
They talk to each other and the cancer cell will suppress an immune cell so that it remains alive. And so this is just one approach to immunotherapy for cancer. We certainly want to find out more about the other approaches to immune therapy. We talk a lot on this show about immune checkpoint inhibitors, but certainly thinking about other ways that we can use and manipulate the immune system to fight metastatic Melanoma will be very exciting to learn about, but first we’re going to take a short break for a medical minute, so please stay tuned to learn more about Melanoma with my guest Doctor Harriet Kluger. Funding for Yale Cancer Answers comes from Smilow Cancer Hospital. 15 care centers offer access to oncologists committed to providing individualized, innovative care. Find a Smilow Care Center near you at YaleCancerCenter.org. The American Cancer Society estimates that more than 65,000 Americans will be diagnosed with head and neck cancer this year,
making up about 4% of all cancers. When detected early, however, head and neck cancers are easily treated and highly curable.

Clinical trials are currently underway at federally designated Comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital to test innovative new treatments for head and neck cancers. Yale Cancer Center was recently awarded grants from the National Institutes of Health to fund the Yale Head and Neck Cancer Specialized Program of Research Excellence or SPORE to address critical barriers to treatment of head and neck squamous cell carcinoma due to resistance to immune DNA damage and targeted therapy.

More information is available at yalecancercenter.org. You’re listening to Connecticut Public Radio. Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar and I’m joined tonight by my guest Doctor Harriet Kluger.

We’re talking about Melanoma and T cells. We’re talking about these tremendous advances that have happened in the treatment of metastatic Melanoma.
For anyone who just joined us, Harriet was mentioning that when she started treating metastatic Melanoma back in 2001, prognosis wasn’t great. Six months, but we’ve now had a series of immune therapies, particularly with checkpoint inhibitors that have really improved the disease free survival now getting prolonged survival in over 50% of patients. But Harriet right before the break you left us with this little teaser that there may be other ways to manipulate the immune system that are now being investigated. That might hold promise in metastatic melanoma. We have a few teasers and that’s what makes this field so exciting. So one of the additional classes of therapies that we give is cellular therapies. So for Melanoma or solid tumors we know that we have these immune cells that live within the tumor but they keep trying to fight the tumor. But at some point they get exhausted and they’re no longer capable of getting rid of tumor cells.
So many years ago at the National Cancer Institute doctor Rosenberg, Steve Rosenberg pioneered a treatment modality whereby he would resect tumor and then break up all the different cellular components, and take the T cells that originated from within the tumor and grow them in a Petri dish and make billions and billions of cells. Then, in the meanwhile, he’d bring a patient back and give them high doses of chemotherapy to make space, if you will, for these newest cells that were growing in the Petri dish and actually are educated to recognize the tumor. Then he would infuse those into the patient after the chemotherapy and after the space was made and then give some growth factor called Interleukin two and then cells within patients would recover and go home and there is a subset of patients who were actually cured from this therapy as well.

It’s similar to having a bone marrow transplant you go in for a one time shot for a few weeks and then you go home and live your life. The initial response rates at the National Cancer Institute were in
the order of 50%, now with the immune checkpoint inhibitors we’re seeing lower response rates simply because many of the patients whose tumors immune sensitive are actually cured by the checkpoints that we discussed in the previous session over here, but still they work and we have patients who are cured now from the cellular therapies. After they haven’t responded to the immune checkpoint inhibitors, that gives patients another option. This treatment is now being studied in other cancers as well. Lung cancer, head neck cancer, cervical cancer, and so on, and responses are being seen there too. In the meanwhile the field has moved forward and the cellular therapy is no longer only given at the National Cancer Institute. In fact, at Yale we have a lab that can manufacture these cells. There are also companies that are trying to commercialize this modality. So you send the tumor to the company, they grow the cells for you. They send them back and we give
the treatment in the hospital. So that is something that likely will also be on the menu of options within a year or so for metastatic Melanoma and in the future, for other tumor types. So Harriet just picking up on that when we think about things like bone marrow transplant or other transplants, anytime we’re thinking about putting cells into somebody, we always worry about rejection. So do I have it correct that, what we’re actually doing in this cellular therapy is taking a patient’s own tumor? Taking finding their own T cells and getting those T cells to grow and replicate and giving the patient back their own cells, just amplified to the tune of billions of cells so that these
are the special cells that recognize the tumor and can then work against the tumor. And one would think that if some people think that your immune system is fighting off cancer all the time, and that people have quote cancer floating around in them, and that your immune system kind of fights all of these little deformed cells off so that you don't actually develop a cancer, if that was true, then why wouldn't this therapy work for everybody? Why do we need the checkpoint inhibitors? I think the problem is that when we give the cellular therapy, sometimes patients have many different tumors in different locations and we already know now that melanomas can metastasize. So it is correct that they all start from the same clone of cells within the skin, then they metastasize internally and you get subclones and daughter clones and so on. And those next generation clones might have different mutations. Now if we remove a tumor to generate the immune cells from one location, these cells might not be active against
the tumors in a different location,
so that’s one reason that it might not work.
Other reasons for failure are
inability to grow the cells in the
lab so not every cell grows.
The vast majority do,
but there’s about 10-15% that do not grow,
and sometimes they just don’t
grow enough to substantial quantities
and it’s just insufficient to overcome
the tumor cells that are actually there.
And this whole concept of
taking cells, sorting them out,
finding the T cells,
growing them up in a Petri dish,
giving them back to the patient,
it sounds really like a major production,
and so whenever we think about
major productions in medicine,
I always think about how much does that
cost and does insurance cover it?
That’s an excellent question.
So at present it’s still experimental.
So the company that’s making the
cells for us in our current clinical
trial covers the cost of it.
The National Cancer Institute,
when they used to do it,
it was free, but with some it
was covered by the government,
especially the taxpayer.
But you are right, it is very expensive. I think we also need to keep in mind that the immune checkpoint inhibitors are similarly expensive. And those can also cost hundreds of thousands of dollars per patient. So if you start adding up the hundreds of thousands and you compare it to maybe 200,000 for a one time therapy such as cellular therapy, it’s not all that different in terms of order of magnitude is actually a little bit less expensive. And so getting back to the checkpoint inhibitors, those are generally covered by insurance now aren’t they? They are yes, correct. Other than the experimental ones, the ones that are approved are covered. So it sounds to me like when you have a patient with metastatic Melanoma, your first line of therapy is the immune checkpoint inhibitors. If they fail, that cellular therapy is another option. What if they fail that? So if they fail that or sometimes by choice,
we actually have additional experimental options for patients. So I had talked about the T cells that recognize the tumor. Those are called adaptive immune cells. In other words, they've adapted to the cancer. They have special specific qualities that recognize that we also have innate immune cells. Those are generalized cells that are floating around in our bodies that have not developed receptors that recognize specific abnormalities in cancer cells. Now those innate immune cells are another whole army of cells that we can activate in order to target the cancer, and sometimes we can co-activate the innate immune cells and the adaptive cells, so we can combine additional drugs to these immune checkpoint inhibitors. There are many approaches that are being taken across the country. One of the approaches that we're doing over here is to activate a group of cells called dendritic cells, that actually present the tumor antigen to the T cells as foreign and then make them become educated or adapted.
So if we give those two together, we might have better responses than using the checkpoint inhibitors alone, so that’s one example of an approach. There are groups that are targeting a subset of cells called macrophages, which are also innate immune cells. Then we need to think about what these cells do, so they secrete substances called cytokines. Interleukin two, that early drug that I had mentioned that was approved already in the 1990s is a type of a cytokine. Many companies are now developing novel cytokines, so either better versions of interleukin two that bind to the interleukin two receptors that are more important, or that bind with a stronger affinity to the receptors. And then there are other interleukins, interleukin 12, interleukin 18, all of these are being looked at as drug targets, and in fact there’s a researcher at Yale who has developed a drug that is a mimic of interleukin 18 that doesn’t get sucked up
by decoy proteins in the body, so should be more potent and we will be excited to study that in the next month or two in the clinic.

There’s a trial that’s opening up and we will be administering that drug to patients who have not responded to the immune checkpoint inhibitors both with Melanoma and other diseases. So Harriet just to unpack a couple of the concepts that you mentioned. It sounds to me like the activation of both the innate and the adaptive immune system just makes intuitive sense. If you have more adaptive immune cells and you pair that with more cells that are presenting to them the antigens they need to go after, it seems like that would be a better approach. So is that something that is routinely being done or is the cellular therapies that we were talking about earlier really going after more of those adaptive cells? And wouldn’t it be better if they could also grow up in a Petri dish of patients innate T cells as well?
Well, we can grow it up in a Petri dish or in the body, so the whole concept behind giving cytokines is to grow them actually in the human. So we give more of the cytokines and we grow up both innate and the adaptive cells. So these are like growth factors for these cells. They should make them propagate. So that was going to be my next question is you talk about all of these cytokines? These interleukins with various numbers? How exactly do they work? It’s sounds now like they just stimulate the innate immune system. Is that right? Both innate and adaptive actually? So they stimulate both. So all of those different numbers reflect molecules that have different activities. So some of them will stimulate innate cells and some stimulate the adaptive cells, some stimulates suppressor cells. The biology is getting more and more complicated. Well, it’s always been complicated.
We’re just learning now how complicated it is, and every time we look, we discover that we knew nothing. And so it sounds like we’re almost coming full circle, though, because interleukin two was something that you had talked about at the very outset, which really wasn’t terribly effective back then. Why would we think that now these other interleukins will be more effective? Now we have other bullets to administer with it. And we understand better how to engineer them so that they can be more effective. So the idea is that you would use these interleukins along with cellular therapy and or checkpoint inhibitors. Yes, or if they’re so good we might be able to use them alone. Time will tell when you have a new drug you start studying it by itself, mainly because you want to look at whether it’s toxic, but you also look a little bit at the activity so some of them might end up being active on their own. We will see.
If you have questions the addresses cancer answers at yale.edu and past editions of the program are available in audio and written form at yalecancercenter.org. We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut Public radio funding for Yale Cancer Answers is provided by Smilow Cancer Hospital and AstraZeneca.