



## Advances in Melanoma Treatment

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*Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. 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 is a conversation about advances in the treatment of melanoma with Dr. Mario Sznol. Dr. Sznol is a Professor of Medicine and Medical Oncology at Yale School of Medicine and Co-Director of the Cancer Immunology Program at Yale Cancer Center. Dr. Chagpar is a Professor of Surgery at Yale and the Assistant Director for Global Oncology at Yale Comprehensive Cancer Center.*

Chagpar Mario, maybe we can start off by refreshing our memories and educating our listeners on what exactly melanoma is, and how many people get it, how many people die from it and how do we recognize it?

Sznol Melanoma is a cancer of melanocytes. Those are the cells in your body that give you pigment. So, you have them everywhere. Most people get melanoma of the skin, but some people get melanoma in their eyes, behind the eyes and some in mucosal membranes - that means inside the mouth, inside the nose or in the vaginal or rectal areas. Some people even get it underneath their fingernails. It is not a common malignancy. I would guess in the US 70 or 80,000 people will get a primary melanoma per year, and I think the statistics show that about 8000 people die per year from melanoma, somewhere in that range.

Chagpar When we think about melanoma, many of us think of it primarily as a skin cancer, we think of it primarily being related to sun exposure. Is that right?

Sznol That's correct.

Chagpar What can we do to reduce our risk of getting melanoma?

Sznol Primarily, reduce the number of sunburns and excessive sun exposure. Clearly, sun exposure is related to the development of melanoma, but not all melanomas. Remember, melanoma that forms behind the eye or in the mucosal membranes or non-sun exposed areas are not related to sun exposure, but most melanomas are related to sun exposure. So, limiting sunburns, not using tanning beds for example could reduce your risk of developing melanoma. And of course, some people have more risks – those who have light skin and light eyes are at greater risk for developing melanoma than those that have darker skin.

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- Chagpar Why is that? If melanocytes are the cells that give you pigment, they would presumably have less melanocytes right?
- Sznol I am not sure I know the answer to that question, but obviously the darker your skin is, the more you are protected from excessive sun exposure, but I actually don't know the answer to that question.
- Chagpar I was just curious. Let's talk a little bit about sunscreen. Does it actually work?
- Sznol I am not an expert on this. This is mostly an area of a dermatologist and I treat mostly people with advanced disease. But the answer is probably it does and I think SPF of 30 or higher is probably adequate. There are certain kinds of sunscreens that are targeted to UVB radiation rather than UVA, and I think UVB is actually more important for damage than UVA radiation. So, at least dermatologists recommend using these sunscreens to reduce your risk.
- Chagpar And the other question that I have with regards to just melanoma in general is, how do people get melanoma in these non-sun exposed areas -- in the mucosal membranes, behind the eye and so on? If we think about melanoma, I mean I think of it really in a very simplistic fashion that the sunlight is radiation, the radiation kind of screws up your DNA in your skin cells and aberrant DNA causes cancer. What are the sources, the mutagenic sources that cause melanoma in other places?
- Sznol No one really knows. There are cancers for which we do not know the inciting causes and melanomas that occur in the acral regions for example underneath the fingernails and the bottom of the foot, in the mucosal areas, in the vaginal and rectal areas are clearly not sun exposed, but the factors that cause DNA damage that leads to mutations that lead to cancer is not clear. It is also important to remember that the biology of melanomas that start in nonexposed areas is very different than melanomas that start in the skin. The mutations that drive those melanomas and the altered pathways are different in melanomas from mucosal areas, acral lentiginous which means underneath the fingernail or under the foot, those mutations are different than mutations that occur in sun-exposed melanomas.
- Chagpar That's interesting. And similarly, the melanomas that occur in the back of the eye might be different?
- Sznol That's correct.
- Chagpar How does one actually figure out that one has a melanoma, say in the back of the eye. We know the ABCDEs of melanoma of the skin that these tend to be asymmetric

lesions, they have ragged borders, the color is variegated, the diameter is more than 6 mm and they are on exposed areas of the skin, but how do we really clue in to whether or not we might have a melanoma in the back of our eye?

Sznol Rarely it affects vision, but most of the time these things are picked up by optometrists and ophthalmologists during routine exams and they find a macule and they follow that macule over time that is just a pigmented spot in the retina and over time, there are certain changes that occur in that spot that lead to the diagnosis of an ocular melanoma. People who present with rectal melanomas for example may present with rectal bleeding or spotty bleeding that is often attributed to hemorrhoids and then ultimately a biopsy is done and found to be melanoma. Similarly, for melanomas that occur in the nasal cavity, sometimes people present with bleeding and ultimately scans and further workup will show a mass and it is biopsied and it turns out to be a nasal mucosal melanoma. In ocular melanoma, it is probably picked up incidentally by an ophthalmologist, but in other cases, they present with symptoms.

Chagpar Could we then hypothesize that these melanomas that do not occur in the skin tend to present at a later stage simply because on the skin it is immediately visible, whereas in these other areas you are kind of waiting for it to be incidentally picked up or present with symptoms?

Sznol We do not stage melanomas of the mucosal areas exactly the same way we stage melanomas of the skin. What we can say is that most melanomas of the eye are picked up at a primary stage, so before they develop metastatic disease, which is similar to melanomas of the skin, and I think that is also true for mucosal melanomas. They are often picked up before they develop metastasis or spread to other organs. On the other hand, we have often felt that melanomas that start in the mucosal surfaces are more likely by depth, by ulceration and other factors that we use for staging are more likely to develop metastatic disease.

Chagpar I guess the key message here is that it is better to find these cancers at an early stage before they spread and the good news seems to be that ocular melanomas, skin melanomas tend to be found before they spread?

Sznol They are found before their spread, 90% of melanomas are found when they are primary lesions; in other words, before they spread beyond either the skin where they started or the closest lymph node to that primary site. And we think that catching melanomas early is better, it makes sense, but it could be that the melanomas that we catch earlier do better because they are less aggressive to begin with.

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- Chagpar Yeah, just indolent.
- Sznol That's correct. And so, I do not think we know. There is some evidence from Australian studies and again I am not an expert on this because this is primarily the realm of a dermatologist, but there is some evidence that early detection does lead to better outcomes.
- Chagpar When you said earlier that the mutational pathways of different melanomas is different, might that also play a role in terms of how aggressive these are and at what stage they present?
- Sznol It is not clear that you can tie prognosis or how they will do to the mutational status of that tumor, to the different kinds of mutations. So the BRAF mutant melanomas are different than NRAS mutant melanomas are different than c-KIT mutant melanomas on the basis of the mutation as far as we know.
- Chagpar I see. So, let's talk a little bit about these mutations. I mean, because what you have pretty much given us so far is alphabet soup. Why do we care about these mutations?
- Sznol They are really only important in the sense of whether you might have something to treat them when they develop metastatic disease or to treat them to prevent recurrence. And of all the mutations that occur in melanoma, the only one that is really reliably treatable at this point is the BRAF mutation. So, for that mutation, there is a drug and if you have that mutation, we can use these drugs to either help to prevent recurrence or to treat the disease once it becomes advanced.
- Chagpar Is it the case that all melanomas will undergo some sort of a mutational profile so that we know whether your particular melanoma has a BRAF mutation or not?
- Sznol That's correct, and in fact I left one out, there is a rare mutation in c-KIT which occurs more commonly in the mucosal and acral lentiginous in other words the non-skin melanomas that is also treatable. We often do molecular profiling when a melanoma is detected in the primary setting, especially if they have lymph node metastasis because if those melanomas have a BRAF mutation, one of the options to treat and to prevent recurrence is if they have a BRAF mutation, you can use these drugs called BRAF and MEK inhibitors, you actually use them in combination to try and prevent the recurrence of melanoma in the future.
- Chagpar How effective are those?

- Sznol            Interestingly enough, more effective than we thought they would be. There is a randomized trial for example using the dabrafenib and trametinib which are BRAF and MEK inhibitors. They target the BRAF mutation, which has shown really dramatic improvements in what is called progression-free survival, meaning the time until the melanoma develops. And there are some preliminary evidence that suggests that they may even improve overall survival in those patients. So, it does appear that using BRAF and MEK inhibitors to treat patients who have BRAF mutations is effective at reducing recurrences. At one point, we actually thought that because these are targeted drugs that they may only work while you are taking the drug, but actually the effect on progression-free survival persist even after you stop the drugs. Usually, they are given for a year.
- Chagpar        And, are they expensive, they sound expensive?
- Sznol            Yes, they are probably expensive. I don't know what the exact cost of the drug is. Sometimes, if you have to pay out of pocket for these drugs, they could cost 10 or 12,000 dollars per month and could be more.
- Chagpar        And it is given for a year?
- Sznol            And it is given for a year, but of course, as you know, many of these drugs are covered by insurance. The high co-pays that are associated with that can often be reduced through a variety of programs and so fortunately here in Connecticut, I don't think that we have ever not been able to give these drugs because of cost.
- Chagpar        So, that was going to be my other question was whether they are in general covered by insurance, but it sounds like they are, which is a good thing. You mentioned the other mutation was c-KIT and for listeners of the show, c-KIT is associated with other GI stromal tumors right?
- Sznol            That's correct. It is associated with the GI stromal tumors. That mutation and similar mutations are also seen in melanoma, and patients with advanced melanoma who have c-KIT mutations can respond to these drugs that are c-KIT inhibitors and there is a number of them on the market.
- Chagpar        We are going to take a short break for a medical minute. But I would like to learn more about all kinds of melanomas and how we can target these tumors for treatment right after we take a short break.

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Chagpar Welcome back to Yale Cancer Answers. This is Dr. Anees Chagpar, and I am joined tonight by my guest, Dr. Mario Sznol. We are talking about advances in melanoma treatment and right before the break, Mario was telling us about tumor profiling for melanomas and the fact that we now can figure out that some of these melanomas have mutations in genes like BRAF and c-KIT where we actually have drugs to target these mutations that can have a lasting impact, particularly for BRAF. Mario, just to wrap up our conversation with regard to that, do we find that c-KIT inhibitors are also very effective in c-KIT mutant melanoma?

Sznol In advanced melanoma, meaning melanoma that spread to other organs, the c-KIT inhibitors can produce in some subsets of patients very, very good responses. They are not curative agents, they do not cure the disease but as far as we can tell, they cause tumor regression, some of those regressions can last a reasonable period of time and so probably the subset of people that get c-KIT inhibitors, some of them live longer because they receive these drugs.

Chagpar In advanced disease, whereas when we talked about BRAF inhibitors, you had mentioned that the BRAF inhibitors are actually used in the treatment setting, so when you get your primary melanoma, is it to prevent recurrence?

Sznol That's correct. We have never done what is called an adjuvant trial with the c-KIT inhibitors, which means using them to try and prevent recurrence once a primary tumor is resected. But for the BRAF and MEK inhibitors which target the BRAF mutation, we know they are effective in advanced disease, they prolong survival in advanced disease and they also are effective in trying to prevent recurrences in people who have high risk primaries. Remember that, we stratify people when they have a primary tumor by certain factors which tell us what their risk is of recurrence and so we

use a BRAF and MEK inhibitors in people who have a high risk for showing up with metastatic disease in the future and those are the patients that we treat in order to prevent those recurrences.

- Chagpar Why haven't those studies been done in people who are at high risk for developing advanced disease in the adjuvant setting using c-KIT inhibitors?
- Sznol Because it is a much rarer tumor, only a very small number of patients will have c-KIT mutations. It would require a huge effort and may even be impossible to do a randomized trial given the small number of patients that present with c-KIT mutant melanomas in the course of a year.
- Chagpar I just wonder if you are tumor profiling all of these patients with melanoma and one of the mutations that is in your panel is c-KIT and the patient has a primary melanoma where they have risk factors for developing advanced disease and they happen to be one of those few patients who has a c-KIT mutation, we would then wait until they develop advanced disease before we treat them because we do not have the randomized control trials and may never?
- Sznol In some cases, yes. There are subsets of patients where we might go ahead and treat without the data because they are at such, such high risk that it makes sense to go ahead and give them that treatment, but remember, we do not have a lot of data, it is for BRAF-MEK, it is a targeted therapy, it is not curative – we never actually thought that they would actually have such a meaningful effect or prolonged effect in the adjuvant setting even after you stop the drugs. We do not have similar data with c-KIT, although in GIST tumors, in gastrointestinal stromal tumors, there is some evidence that giving the drugs earlier can have a greater effect than giving them at the time of advanced disease. But I also want to point out that these are not our only options for treating patients in the adjuvant settings. In many of these patients, we can use immune therapies, which may even be more effective and I guess we will be going on to discuss that in the next few minutes.
- Chagpar Why don't we talk about that? Tell us more about immunotherapy, who is eligible for it, how effective is it, what are the side effects?
- Sznol For many years, people have used immune therapy to treat melanomas and they showed some evidence of benefit – for example, the drug interleukin 2 which was the only drug that we had available really for many years produced cures in a small subset of people with advanced metastatic disease. It was really remarkable, about 5-10% of people who would probably go on to die of advanced cancer could have complete



regression of their cancers, complete remissions and would be cured of their disease. But it was only a small number of patients that benefited from interleukin 2. The next drug that was developed was a drug called anti-CTLA-4, it is also called ipilimumab or YERVOY. YERVOY seemed to increase that number a little bit in patients who could be treated in the advanced disease setting and could achieve long-term remissions. In fact, the Nobel Prize was just given for the development of ipilimumab to Jim Allison just within the last 2 or 3 weeks. But what really changed the field was the introduction of drugs that targeted PD-1. PD-1. like CTLA-4. is a molecule that is expressed by activated T-cells, and it serves to actually bring down the function to inhibit the function of those T-cells. So, when you block CTLA-4, that is ipilimumab. or you block PD-1 which is a drug like nivolumab or pembrolizumab also known as Opdivo and Keytruda, you actually allow those T-cells to start working again, they are no longer being inhibited within the tumor and they can cause remarkable tumor regression, and so we went from a point where perhaps the 5-year survival for melanoma might be 10 or 15% with the introduction of a drug like anti-PD-1, we think that the 5-year survivals now for melanoma would be close to 35 to 40%, and when you combine anti-PD-1 and anti-CTLA-4, that 5-year survival might be another 10% higher, could be the 45 or 50% of patients who present with advanced melanoma could live 5 years or longer because of the use of these drugs. Comparing historically to only 5-10% who would have been alive 10 years ago. Because these drugs tend to work by releasing the immune system to attack the melanoma, they can also release the immune system to target normal tissues and so the major side effect of these drugs is called autoimmunity or the immune system attacking normal tissues and it can attack your skin, your bowel, your liver, your heart, your lungs, your endocrine organs, anything that you can think of, it can attack, and that is basis of the toxicity of these drugs. Fortunately, we know that in many patients, we can turn off those side effects with medicines that actually then suppress the immune system, but when we do that, we do not seem to lose in most patients the anti-tumor effect.

Chagpar      When we talk about this advanced survival in people who are treated with anti-PDL-1, for example, is that effect only in people who express this PDL-1 so the people whose immune system is turned off in the tumor itself or is this across the board for all melanomas?

Sznol          Let me clarify that, the thing that binds to PD-1 is PDL-1, anti-PDL-1 can work too, but in melanoma for the most part, we have used anti-PD-1. It is true that people who have PDL-1 expression in the tumor seem to do better, but for whatever reason in melanoma, people who are PDL-1 negative, whose tumors do not express PDL-1 can also derive substantial benefit from these drugs. So, if you ask why is that the case –

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we believe that the assays may be missing some of the PDL-1 expression within the tumor marker environment, so these negative results may be perhaps true-false negatives and then in fact those patients do have an active immune response in the tumor marker environment and giving anti-PD-1 or anti-PDL-1 can release those T-lymphocytes to attack the tumor.

Chagpar And so, when we talk about the survival benefit, that is across the board?

Sznol It can be seen in both PDL-1 negative and PDL-1 positive patients, the survival effects patients who are PDL-1 positive in melanoma, but you still see the effect in the PDL-1 negative patient. But again, remember of 100 patients, maybe 35-40% are long-term benefiting.

Chagpar And the other question is, when we talk about you release the immune system and so the immune system can attack all of these other normal tissues, why is that because normally your immune system does not attack, is it that your normal cells actually have some PD-1 or PDL-1 or anti-PDL-1 that prevents your immune system from attacking them and so when you take away that, your immune system goes and attacks your normal tissues and it just is greater in the tumor, why does the immune system go and attack normal tissue? I thought your immune system knew the difference between normal and abnormal.

Sznol There are a couple of possibilities. One possibility is that some people have lymphocytes in their body that can attack their normal tissues, but the reason why they live normally and do not have any symptoms is that PDL-1, PD-1 pathway is actually keeping those cells under control. There may be other cells or other approaches to block the function of those lymphocytes that could attack normal tissues, but by releasing them using antibodies that block PDL-1 or PD-1, you may be allowing those cells to attack normal tissue. There is one other possibility, which is that the immune cells that are attacking the melanoma because melanomas have lots of mutation, some of those immune cells could cross react with normal tissues. So, when you are releasing them to attack the melanoma, perhaps they can also then attack normal tissues. But more than likely, the explanation is that some of us are just walking around with lymphocytes that could attack our normal tissues but are being controlled by this pathway.

Chagpar So, when we think about who is eligible for immunotherapy, I mean the survival advantage while not 100%, it is still 10-fold over what it was when we think about 5% versus now close to 50%, that is a big difference. So, is everybody now being treated with immunotherapy?

Sznol At our center, we prefer to treat almost everybody with immune therapy. The difference between immune therapy and targeted therapy at least in advanced disease is that you are more likely to have a durable benefit, a durable response from the immune therapy and when I say that, what I mean is that we can in patients discontinue the drugs and their disease will not come back. So, unless there are certain groups that need targeted therapy, if you start out with a lot of disease and you are very sick and the disease is progressing very rapidly, or you require steroids, which block the effect of the immune therapy, those patients probably need to be treated with targeted therapies first. Interestingly enough, there is a group of patients that have very minimal disease, just a few lymph nodes and a few skin lesions that can do very, very well with the targeted therapies. But most of the other patients probably would do better with the immune therapies. And so, we usually start with immune therapies first, either anti-PD-1 alone or at our center, we tend to prefer to give the combination of anti-PD-1 together with anti-CTLA-4, so OPDIVO together with YERVOY.

Chagpar You kind of touched on this, but I just want to clarify, can you use targeted therapies, so for example BRAF inhibitor with immunotherapy?

Sznol Those studies have been done, combining BRAF-MEK inhibitors together with anti-PD-1 or anti-PDL-1, the results were presented at ESMO, I do not know the results in detail, but the results were not nearly as promising as we had hoped. So, grouping them all in together may not be the right way to do this. There are some patients where we use the targeted therapies to debulk the tumor, to get them to a point where we think we can give them the immune therapy, but we do not necessarily give it together. Maybe those are the patients who might benefit from using all the drugs together at the same time. But at the moment, disappointingly, we do not have a lot of data that using the drugs altogether at the same time is any better than using them for example sequentially.

Chagpar Do we know whether sequential therapy is better or worse than immunotherapy alone?

Sznol If you give an immune therapy, for example, to a patient that has a BRAF mutation and they go into a complete response and you stop the therapy, you do not need it. The patients who do not respond can then get the targeted agents and they will benefit from the targeted agents. So, almost certainly sequential therapy in some patients is going to be better.

*Dr. Mario Sznol is a Professor of Medicine and Medical Oncology at Yale School of Medicine and Co-Director of the Cancer Immunology Program at Yale Cancer Center. If you have questions, the address is [canceranswers@yale.edu](mailto:canceranswers@yale.edu) and past editions of the program are available in audio and written form at [YaleCancerCenter.org](http://YaleCancerCenter.org). I am Bruce Barber, reminding you to tune in each week to learn more about the fight against cancer here on Connecticut Public Radio.*