New Hope For Melanoma
Webcast
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David Byrd, M.D.
Kathy Sparks

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Kathy’s Story

Andrew Schorr:
After many years with no new treatments for melanoma, the FDA has just approved a breakthrough treatment for the disease, and there are other medicines that seem quite promising that may be coming soon. Coming up, experts from the Seattle Cancer Care Alliance will discuss melanoma, clinical trials and the exciting new treatments. You’ll also meet a patient who has benefitted. It's all next on Patient Power.

Hello and welcome to Patient Power sponsored by the Seattle Cancer Care Alliance. I'm Andrew Schorr.

Well, if you're someone who had severe sunburn when you were younger you may be checking your skin as you get older for skin cancer. Many of us know now that the most serious skin cancer is melanoma. If it's detected early it can be surgically removed with good results, but if it spreads it can be deadly. Unfortunately, there are about 70,000 new cases of melanoma in the US each year and almost 9,000 deaths. Fortunately, there is now hope, as we just had one new medicine approved, and there are others that look promising, so it hopefully will change the landscape in melanoma.

We'll hear from two experts from the Seattle Cancer Care Alliance, one surgeon and one medical oncologist who specializes in melanoma, in just a minute, but first I'd like you to meet their patient. That's Kathy Sparks. Kathy is a nurse actually, and has been a nursing instructor. She's 57 years old from Issaquah, Washington, outside Seattle.

Let's go back to the end of 2005, beginning of 2006, Kathy. You had what on your left forearm?

Kathy:
Well, I had a small mole on the left side of my arm that looked like a blood blister and in fact the PA that removed it at the dermatologist's office thought that it was a blood blister. It didn't actually appear anything more significant than that.
Andrew Schorr:
But the tests showed that in fact it was melanoma. Now, you're a nurse. What was your thought then?

Kathy:
Well, it was devastating because I had worked in hospice as well, and I knew it wasn't good. The pathology report came back at that time stage II melanoma and, you know, I didn't take it very well. I became very clinically depressed, and I sort of fast forwarded at what I thought would be the end result, and it didn't look good for me.

Andrew Schorr:
Well, we should happily say that we're, what now, more than five years later, and the end result you worried about, and we'll talk more about that, fortunately has not happened. So that's the happy story, and we'll talk about medical science and melanoma specialists helping you along the way. But the journey wasn't easy. So you had the melanoma removed, and then two years later it came back and then it was, what, a white nodule under the skin?

Kathy:
Yes. It came back just above where it was before, and I had another wide resection done at that time, however it had transferred or travelled to the lymph nodes.

Andrew Schorr:
Hmm. Well, as people recognize, travels to the lymph nodes, and then you start looking at various systemic therapies, which you had. This went over an extended time, very tough treatment sometimes, and you finally got to the point where in 2009, maybe even a little earlier than that, it seemed like there was no hope. Is that right?

Kathy:
Yes. It gradually kept coming back in my arm further up and finally into my shoulder, and then all of a sudden it jumped to my right breast, and I was stage IV at that point and told that surgery was no longer an option. Of course I had had the interferon therapy and lymph profusion at MD Anderson prior to that. Nothing seemed to be stopping it, despite the good medical care that I had prior to that time. And I was given essentially about a year, you know, based on the history of other patients that were in a similar situation.

Andrew Schorr:
Well, we should mention that actually there's a public television documentary coming out. You're in it as someone interviewed who did not have long to live, and the bright spot here is that while that documentary is out there you have a brighter future at this point. Let's talk about that. So you spoke to your doctor. You were being treated at the Seattle Cancer Care Alliance, which is a research center, and there is always a discussion of could there be a clinical trial that would benefit you.
Apparently one in 2009 opened up, and you chose to be in it.

**Kathy:**
Yes. Yes. At that point I really wasn't interested in feeling bad for--without a good success rate, and of course that's not anything anyone can promise me, but I wanted to take my time. I was kind of selfish with it, to use it to optimize my--if I only had a year left to optimize it. So the notion of getting involved with a study that just might make me sick and not go anywhere was not something I was looking forward to. And Dr. Margolin, my medical oncologist, encouraged me that this particular study was very promising, and so I decided for go for it, and I'm so glad that she encouraged me.

**Andrew Schorr:**
Well, the good news is my understanding is on this therapy over time your melanoma tumors melted away?

**Kathy:**
They did. You know, I was dubious at first, as I said, and then as they started shrinking I was thrilled that I was getting bonus time. And then the lesions just started melting away. I think there were nine areas of significance they were following on the CT scans, and I was just truly blessed because before that I couldn't even think in terms of six months away for a dental cleaning, much less, you know, beyond buying clothes for the next season, or even the whole prospect of using sunscreen was preposterous when you're, you know, faced with, you know, death. It's something that's experiential. You really can't express it in words--

**Andrew Schorr:**
Right.

**Kathy:**
--unless someone has been there.

**Andrew Schorr:**
Right. Well, I'm sure. So here we are. You go through that therapy over many months, a new drug that has now been approved called Yervoy, and we're going to talk more about that, or ipilimumab, and that is an immunotherapy. We'll learn more about that, but basically helped your immune system fight the melanoma. And I think that what's so cool is as you recovered from the therapy and the melanoma melted away you went back to Florida where you had had those sunburns when you grew up on the Gulf Coast on sort of an appreciation tour. I imagine really a celebration of a new lease on life.

**Kathy:**
Oh, yes. You know, for me, grief work is very deep and personal, and it leads you to what's essential. And what it led me to was expressing my gratitude and
appreciation to all those who sent prayer my way or were nurturing me as I--all along my life that perhaps I didn't really pay attention to before. And oh, you know, so many people dread birthdays, but not me. I believe we should celebrate them all month.

Andrew Schorr:
Amen. Well, let's put all this more in perspective, but you're a great inspiration and thank you. You know, I'm so glad and you're so glad you were in the clinical trial, but the knowledge gained by you being in the clinical trial helps others, some who may be listening.

Let's meet your medical oncologist first. That's Dr. Kim Margolin, who is a medical oncologist at the Seattle Cancer Care Alliance and a melanoma specialist. Doctor, first of all, this is a big deal, I think. I know it doesn't happen with every patient, but to hear an example like this must be thrilling for you when we've really needed new medicines in melanoma.

Dr. Margolin:
Definitely.

What is Yervoy or Ipilimumab?

Andrew Schorr:
So what happened? Describe Yervoy, or ipilimumab, as a immunotherapy. My understanding is it sort of takes, breaks up the immune system so it can fight the melanoma. Did I get it right?

Dr. Margolin:
Yes, I mean, basically the discovery about agents like this, which are termed checkpoint blocking agents, is that when the T lymphocytes which help us fight against mainly virally infected cells, eradicating viruses from our body, when they finish doing their job they need to know how to turn off their power so that they don't start to proliferate and cause damage to normal tissues. Furthermore, there are T lymphocytes that can cause damage to normal tissues not in the infection setting but because they may recognize some antigens on our normal tissue material.

The control of both those types of lymphocytes is by the movement within the cell of a molecule that tells the cell to stop being so activated and stop secreting toxins into its atmosphere that may damage the surrounding cells or the surrounding tissues. In normal physiology that's an important control that prevents us from getting diseases like lupus and colitis and rheumatoid arthritis and multiple sclerosis and also prevents us from overreacting against virus infections. So when we recover from the flu we're only sick for a few days.

This power can be harnessed in a way that will treat malignancy if there are T lymphocytes in the body that can recognize an antigen on the malignant cells that
is not supposed to be there and is perceived by the body to be foreign. So if you can get the T-cells, which are normally kind of calmed down, the ones that may recognize the tumor's antigen, and you can stimulate them by blocking this negative regulator or this checkpoint on their activity, then you can stimulate a T-cell response that may have been there all along. You can get it going, and you may eradicate tumor.

Unfortunately, you may also cause now the T-cells to recognize and potentially damage normal tissues, so we do see instead of the typical chemotherapy side effects, we sometimes see autoimmune reactions as a consequence of this form of therapy.

Andrew Schorr:
And, Kathy, you did have some side effects. You told me you had itching and some skin inflammation, things like that.

Kathy:
Yes. I think the itching was the worst. I did have a skin rash and discoloration and fatigue. And brain fog, I don't know if it was from the drug itself or perhaps just from the Benadryl, it's not clear to me, that I had to take for the itching.

Andrew Schorr:
How are you doing now?

Kathy:
I'm doing great.

Andrew Schorr:
Well, you sound great.

Before we take a break I want to meet one other important player here in melanoma, such an important part of the team as we've had traditional therapies, and that is surgery, to try and surgically remove the melanoma. If you can get rid of it early where it hasn't spread, that may be the only treatment you need, and surgery certainly plays a role, and that's Dr. David Byrd, who is a very prominent surgeon at the University of Washington and Seattle Cancer Care Alliance and was also Kathy's surgeon along the way.

Dr. Byrd, I know you're not involved in systemic therapies, but as you hear about this, and we'll talk more as we go on about how surgery and drug therapies can work together, but you have been involved in melanoma a long time. Do you think this is a big deal, this medicine and the prospect of others coming?

Dr. Byrd:
I think it's an incredibly big deal, and again, being in the field for almost 20 years, I've seen trial after trial, study after study being negative for systemic treatments
of melanoma where there have been significant gains in other diseases like breast cancer, lung cancer, colon cancer and others. And it's been exceptionally disappointing that the trials have been uniformly negative.

And the really exciting part is not only do we hear about trials like this one and the acceptance of a drug that targets the immune system or the immune system breaks, but as we'll probably get to, there are other classes of small molecule targeted agents that bring the promise of going after direct pathways in cancer pathways such as melanoma but with also limiting the toxicities in normal tissues.

So I think this is the opening of the door that we've been waiting to see for melanoma that we've seen in others. It's a very exciting time. The drugs we're talking about are not homerun hits for the majority of patients, but the door is open.

Andrew Schorr:
Well said. We'll learn more about that as we continue our discussion with two leading specialists from the Seattle Cancer Care Alliance, Dr. David Byrd, who you just heard, and also Dr. Kim Margolin, and their patient who is doing great, Kathy Sparks. We'll have more right after this.

New Therapies in Development

Andrew Schorr:
Welcome back to Patient Power as we bring you a story of new hope in melanoma, our most serious skin cancer that unfortunately if it's not caught early can spread to various places around the body and greatly shorten life. You've already met Kathy Sparks, who was told almost to put her affairs in order, that she did not have that long to live, months, and you've heard that she's now been celebrating birthdays that she didn't think she would have, benefitting from the first new drug approved in a long time, Yervoy, or ipilimumab, if I get it right, that helps the immune system fight melanoma that it couldn't fight against without the drug. So that's a big change.

Now I want to go back to Dr. Margolin. Doctor, help us understand. This is one drug, but there are others that hopefully may be close to FDA approval working on different subtypes of melanoma. So they operate differently. Help us understand that.

Dr. Margolin:
The reliance of our therapy on the immune system in melanoma has been a longstanding hope, and, as we discussed earlier, the approval and availability of this checkpoint blocker, Yervoy, or ipilimumab, has been, you know, the first realization of that hope. However, in the background, predominantly based on observations in other tumor types and some success in a whole variety of other
tumor types including certain leukemias as well as solid tumors, it became possible to define some of the molecules that are abnormal in fractions of melanomas and result from mutations that are very specific to those cells.

The development of drugs that can specifically target the enzymes or proteins in the cell that are causing those cells to grow and proliferate and fail to die the way they're supposed to again was modeled after success in other diseases. So really over a very short period of time the discovery of a particular mutation in about half of melanomas that arise in the skin and very soon after that the application of one and then other drugs that are known to target that particular pathway has led to some very, very rapid and very gratifying success in a mechanism of treating melanoma that is completely different than this immune system stimulation that we talked about earlier. And what is very different is that the drugs are oral pills. They work very rapidly, and so they in a sense complement what you can get from the immune system, which works slowly.

Andrew Schorr:
Now, we've seen some models for this in other illnesses you both alluded to. Let's take like chronic myelogenous or myeloid leukemia, CML, where people can take a pill, they still have the leukemia, but it tamps it down to a very low level. With these so-called small molecules that you were talking about, where somebody could take a pill, is that the idea is to basically--you'd love to cure the melanoma but keep it at such a low level that you go on with your life?

Dr. Margolin:
Well, I think that's one way to look at it. These drugs have been extremely active against melanoma. They haven't had the long, long, durable remissions that have occurred in the model drugs or the parent drugs used for myelogenous leukemia, partly because the biology behind is not really the same. Nevertheless, they may be important bridges. As we get these drugs out on the market, the most exciting thing we can do is to start figuring out ways we can actually combine these treatments. And it may be possible, for example, in the not-so-distant future to take somebody with a lot of melanoma, give them one of these targeted agents orally, see a dramatic reduction of their disease over literally just a few weeks, and then come in with a drug that works on the immune system.

All of the immune system drugs work better when there's less melanoma or less tumor to take care of. They also might be able to recognize a tumor differently because it's been previously damaged by the other drugs. So there are all sorts of possibilities here.

Andrew Schorr:
Dr. Byrd, there's a term that's used, we've used it a lot in breast cancer over the last few years, adjuvant therapy, where there's what you do, surgery still plays a key role, but sometimes there's systemic therapy used first, and then there may be other therapy, drug therapy afterwards with surgery playing a role in the middle. So does it sound like that could work out that way here?
Dr. Byrd:
Well, the exciting news in the melanoma story is we've had this big middle group of patients with melanoma that we've been able to add nothing to their therapy other than surgery and a hope that they don't have microscopic disease elsewhere. Across the board, if you look at all comers, and the statistics you said at the beginning back this up, the majority of patients are actually cured with surgery alone because they come in at early-stage diagnosis. But you've got a group of patients who come in with sort of thicker melanomas, not in the thick category, but they're melanomas that are at some risk. They're node negative, meaning they've had a sentinel node or other node removal that didn't show disease, so we don't want to subject them to a drug that's very toxic unless there's likely to be benefit.

And for that group of patients there have been no clinical trials for several years now, yet a modest, moderate number of them are going to relapse either in their lymph nodes or elsewhere. And if this new set of drugs is coming along which has the promise of either reducing recurrence, killing disease or complementing other therapies and it has few side effects, it's going to open a whole new set of therapies in the adjuvant or after-surgery setting for this intermediate group of patients who have had absolutely nothing for years.

Subtypes & Treatment Decisions

Andrew Schorr:
Dr. Margolin, so we're trying to figure out who should have which therapy, whether it's an approved therapy or at a research center such as yours, be offered a clinical trial. So where are we now with tests or analysis to begin where you can recommend to someone, with what I see in your case or your subtype biologically of melanoma, we should talk about this approach?

Dr. Margolin:
Well, first of all, I think that given the imperfect and suboptimal nature of even our best therapies we still need to continue with this mantra that says at the bottom of every single page of the NCCN guidelines which the best treatment for all patients is a clinical trial. We're far from eradicating these diseases from the face of the earth, and so it's quite clear that we still need to learn more. Learning about combinations, learning best use of the available agents, finding ways to reduce toxicity and most importantly finding better ways to define each group of patients and characterize their tumor and their physiology in such a way that we can do a much better job of picking the right treatment for the right patient and avoiding the side effects in patients who cannot benefit, all of those things are further proof that we need to continue to offer clinical trials whenever possible to patients who are eligible and willing to try for their best available therapy and at the same time be moving the field forward, just as Kathy did, for the future patients.

Andrew Schorr:
But you do have tests, though, to help people understand what subtype of melanoma they may have. Like we talked about, we didn't mention the name, but
I know this type you were saying that affects about 50 percent of the cutaneous or skin melanomas, is I think called BRAF, but you might have a different type. Would that mean then that they might have a different drug if it were available?

**Dr. Margolin:**
Absolutely. So there are some what we'll call biomarkers which will clearly predict the likelihood of benefit from a particular agent, and the BRAF mutation is one that is absolutely sine qua non because essentially tumors that do not have a mutated BRAF gene and this amplified pathway will not respond to these drugs. These drugs are highly specific for that particular pathway.

That is quite different than the picture with the immunotherapy in the case of ipilimumab, or Yervoy, because it's a general immunostimulant or checkpoint blocker that relies very clearly on a patient having T lymphocytes that can recognize the tumor. We're not giving vaccines here. We're not giving something that causes the immune system to recognize the tumor. We're just enhancing it.

Now, some of the immune strategies that are not yet out there rely on a specific antigen, so then we'll see melanoma, become characterized--and there are many strategies that are based on our knowledge and our ability to actually identify a tumor antigen on the melanoma and then use either a vaccine or some other form of antigen-specific therapy, but those are all still in the laboratory, they're still in the testing phases, and we're not quite there yet.

**Andrew Schorr:**
Dr. Margolin, we heard from Dr. Byrd about how he feels the landscape is changing. How do you feel today? So we have a new drug, actually a couple of drugs that have been approved very lately and others that you believe may be approved before long, and you know what's in the lab, too, that seems promising. So all of the patients listen to every word you say and how you think things are going. What would you say as far as the landscape now and really reason for hope?

**Dr. Margolin:**
Well, I think that we have some new paradigms. Not only do we have some new approaches that really are based on mechanisms that have not been available so us in the not-so-distant past, but in addition to that we've got some amazing forward thinkers, people who think outside of the box, in terms of defining the mechanisms of new drugs, in terms of finding how resistance develops, helping us to understand the molecules that drive the tumors, how we pick patients, and you know getting bioengineering and getting methodologies for getting therapies into tiny particles such as nanoparticles. There's a world of progress being made in areas that may be informed even by other diseases or other fields that I have little doubt that before long we'll be able to incorporate them into effective therapies, further effective therapies for melanoma.

**Andrew Schorr:**
And latest approval of Yervoy you would say is significant?
Dr. Margolin:
Yes.

Andrew Schorr:
Okay. Well, I am so happy to tell a hopeful story here. Kathy, so you've lived it. And we know that, you know, one patient's story is not at all necessarily another's, but is there anything you'd say to people listening who are diagnosed with this very serious illness, and you went to, you know, right to the edge there and then fortunately with the help of a new medicine and expert care things turned around. What would you say to them about hope?

Kathy:
Well, I'm so glad you asked that question because, you know, I believe that hope is the most precious commodity on the planet, and none of us know when that next study is going to be the one that unlocks the secret treasure trove that might restore our DNA. And I certainly didn't know. And I know that there might be people listening who are where I was a year ago or two years ago even, and--you know, in various stages of grief, and, you know, they might even be teetering on one way or another. And I would say please engage in the research process in whatever way you feel comfortable because it is working. It might be two steps forward and one back, but we are evolving, and I'm just very hopeful for the potential of it all.

Andrew Schorr:
Right. And you, thank you and others who have played a role in helping because the fact that a new drug is approved, there were people like you in trials that moved that forward. And I know both our physicians with us are very grateful to people participating. And also if you are treated at a research center such as the Seattle Cancer Care Alliance, that's part of the discussion. Are there trials that we should be talking about, that we should consider, and that's what Dr. Margolin brought up for you. So I'm so glad it's worked out. Kathy, I wish you all the best. Many birthdays, okay?

Kathy:
Thank you.

Andrew Schorr:
Many, many birthdays. And Dr. Byrd, so surgery seems to still have a role for a while, but if the day came when somebody could take a pill or whatever and just make the disease melt away, would that be okay with you?

Dr. Byrd:
I would gladly switch my day job.

Andrew Schorr:
Okay. Dr. David Byrd, surgeon, thank you so much for being with us. And Dr. Kim Margolin, thank you so much for being with us as well.
Dr. Byrd:
Thank you, Andrew.

Dr. Margolin:
Thank you, Andrew.

Andrew Schorr:
All right. Well, a much more positive story. A lot of questions to be answered, as we heard, but progress being made in melanoma.

Thank you all for being with us. I'm Andrew Schorr. Remember, knowledge can be the best medicine of all.

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