AIM AT MELANOMA FOUNDATION

OPTIONS FOR STAGE II MELANOMA

Making the Decision That's Right For You.

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A DIAGNOSIS OF MELANOMA IS OFTEN SCARY AND OVERWHELMING.

If you (or someone you love) have been diagnosed with Stage II melanoma, which is a deep melanoma with or without ulceration that does not involve the lymph nodes, it will typically be managed by surgical removal. Depending on its characteristics, the melanoma may be at high risk of coming back or spreading after the surgery. Your health care provider may offer active surveillance to monitor you closely for melanoma recurrence without any specific treatment. Or you may be offered an option called adjuvant therapy. This type of therapy is called adjuvant because it is given after the surgical removal of cancer, and it is given to reduce the chance of the melanoma coming back or spreading.

"In January 2020, I was diagnosed with my first melanoma, Stage IIA. I was referred to a melanoma specialist. A wide local excision (WLE) and Sentinel Lymph Node Biopsy were recommended. Surgery showed clear margins and nodes. Five months later, two more melanomas were found in situ. WLEs were scheduled. I am now three years NED and still have my three-month skin checks because I am at a higher risk for recurrence. The journey is both mentally and physically taxing, but I am lucky."

LORNA DANKO
STAGE II MELANOMA SURVIVOR
AGE 48
CUMBERLAND, RHODE ISLAND

A DISCUSSION WITH GEOFFREY FS LIM, MD JASON J LUKE, MD, FACP

To help you or your loved one learn more about Stage II melanoma and weigh the benefits and risks of adjuvant therapy vs active surveillance, we've brought together two experts in melanoma for a discussion.

On behalf of AIM, Dr. Geoffrey Lim, a dermatologic surgeon in private practice at SkinMed Institute, in Lone Tree, Colorado, interviewed Dr. Jason Luke, Associate Professor of Medicine at the University of Pittsburgh Medical Center, a leading medical oncologist and one of the authors of a key adjuvant therapy study. They will go over the most common questions about Stage II melanoma, which Stage II patients are eligible for adjuvant therapy, and the pros and cons of adjuvant therapy vs active surveillance. This resource should help you or your loved one, in conjunction with your oncology care team, make an informed decision about steps to take after surgery.

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Dermatologist
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WHAT IS STAGE II MELANOMA?

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Dr. Geoffrey Lim: Dr. Luke, it is great to talk to you. When I have a patient with Stage II or more advanced melanoma, that's when I pick up the phone and call a colleague like yourself. Can you tell us how you define Stage II melanoma for patients?

Dr. Jason Luke: Dr. Luke, it is great to talk to you. When I have a patient with Stage II or more advanced melanoma, that's when I pick up the phone and call a colleague like yourself. Can you tell us how you define Stage II melanoma for patients? *A detailed discussion of staging is included in the Staging Overview sidebar (see page 10).*

Stage II melanoma is generally thicker than Stage I melanoma. It is a melanoma that is local, meaning it has not spread either regionally (to the nearest lymph nodes or the region between the original melanoma and the regional lymph nodes) or distally (to other parts of the body beyond the regional lymph nodes).

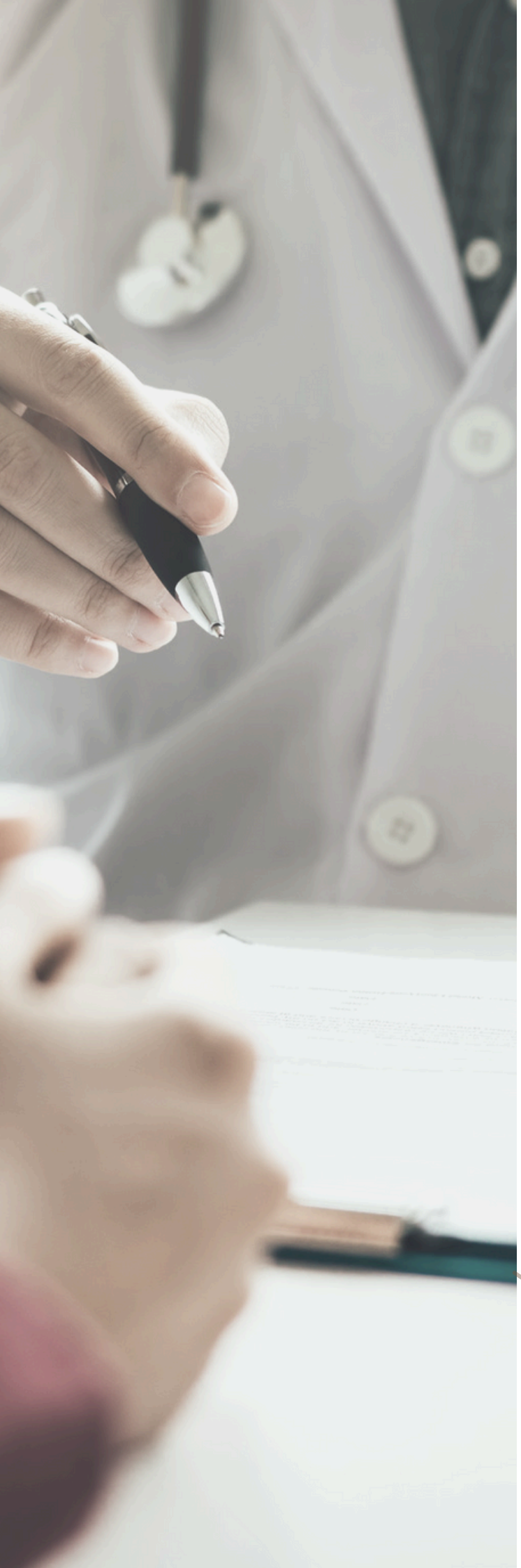
Stage II melanomas are either more than 1 mm but less than 2 mm in depth and ulcerated or they are deeper (greater than 2 mm in depth), regardless of ulceration status.

Let's look specifically at depth and ulceration status.

- ***Depth (thickness)** of the tumor means how deep within the skin did the melanoma grow? This is a little bit different than some other kinds of cancers, where the main concern is how big it is. It can be the case that a melanoma on the skin looks quite large with a splotchy appearance but in reality is not a deep lesion. So, the deeper it goes into the skin, the worse it is.*

- ***Ulceration** means if the skin covering your melanoma was intact or not, as we already have said. On visual examination, ulceration typically means the melanoma was bleeding or looked crusty. This is also a finding under the microscope that we look for and means that we might be able to see changes in the cells and skin tissue. Ulcerated is worse than non-ulcerated.*

Considerations of a primary melanoma on the skin, then, include how deep into the skin did it grow and whether it is ulcerated or not. That dictates how worried we are about it in terms of the risk that it could spread. We use these features to derive a stage for the melanoma, which in turn helps us understand what the likelihood is that the melanoma could come back somewhere else—in other words, spread somewhere else in the body. We can then have a discussion with an individual who's facing melanoma about how high risk the melanoma is for coming back.



Substages of Stage II. We can further subdivide Stage II melanoma and think about substages this way:

- ***Stage IIA: No imaging or adjuvant treatment recommended, but skin checks are recommended***
- ***Stage IIB/C: Imaging is recommended and adjuvant therapy is considered***

The reason we are going over these substages is that adjuvant therapy, which we will be going over later, is currently FDA-approved only for Stages IIB and IIC melanoma.

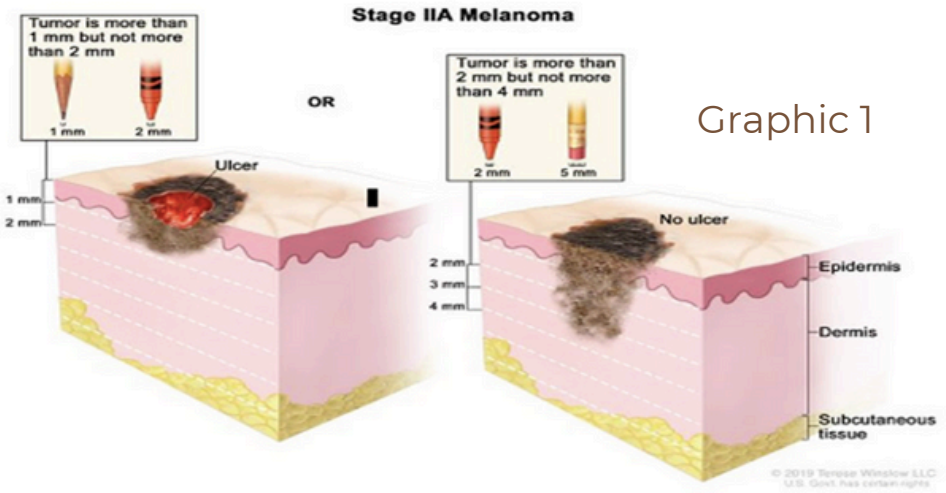
The staging system uses depth as one of the two key factors to distinguish between stages. For a more detailed discussion, you can see the sidebar, Staging Overview. The really simple way to think about invasive melanoma (melanoma that has penetrated into the dermis) is based on the following depths: less than 1 millimeter, 1 to 2 millimeters, 2 to 4 millimeters, and greater than 4 millimeters. An important difference here is noting that, when compared to other cancers where we talk about centimeters, with melanoma it's millimeters. That is similar to a tiny amount of space between your two fingers.

I've mentioned invasive melanoma when discussing these depths, so we are talking about Stage I or Stage II melanoma here. There is also an additional melanoma stage called melanoma in situ, but that type of melanoma is not invasive —it is limited to the top layer of the skin (the dermis) and does not have a measurable depth.

Dr. Geoffrey Lim: And because we define how worried we should be based on millimeters, I use a common reference point to explain that to my patients, like 5-6 millimeters being roughly the diameter of a number two pencil eraser.

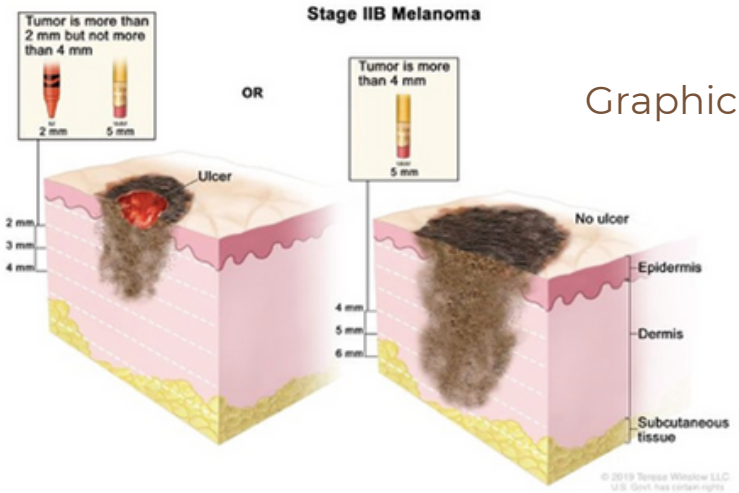
Dr. Jason Luke: *Yes, that's a helpful analogy, as shown in the diagrams. You can see how the melanoma depth generally increases with each substage of Stage II melanoma. The 3 substages of Stage II melanoma – IIA, IIB, and IIC – are shown in Graphics 1-3.*

Stage IIA Yes, that's a helpful analogy, as shown in the diagrams. You can see how the melanoma depth generally increases with each substage of Stage II melanoma. The 3 substages of Stage II melanoma – IIA, IIB, and IIC – are shown in Graphics 1-3.



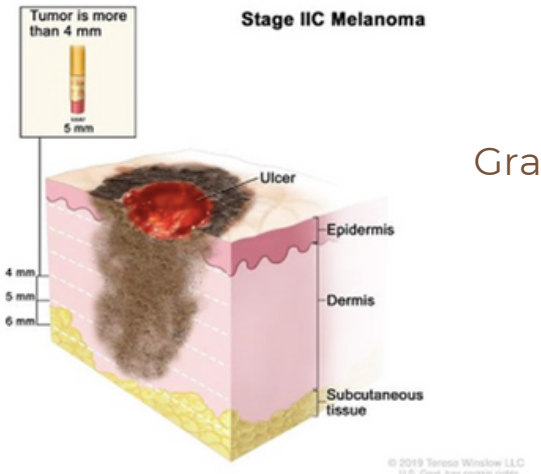
Graphic 1

Stage IIB melanoma is 2 to 4 millimeters (mm) with ulceration (Graphic 2, left panel) or more than 4 mm and not ulcerated (Graphic 2, right panel).



Graphic 2

Stage IIC melanoma is more than 4 millimeters (mm) and ulcerated, as represented by the red depression in the center of the melanoma (Graphic 3).



Graphic 3

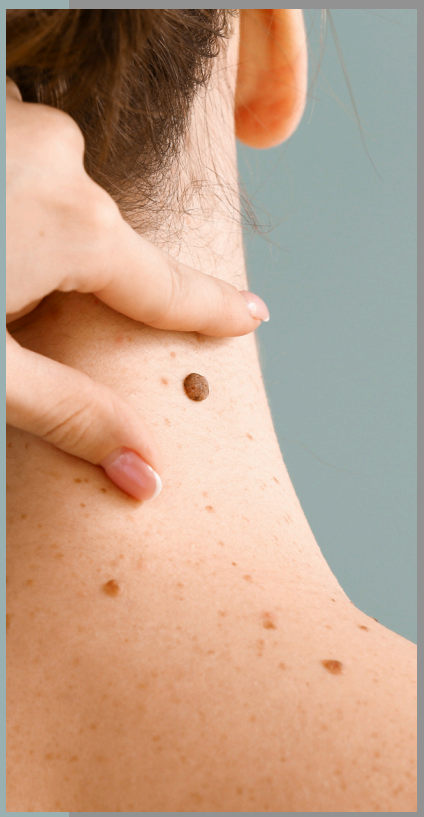
Figures adapted from Terese Winslow

STAGING *overview*

Staging is the process your health care team uses to determine how far your cancer has advanced and the chance that it could come back after initial treatment. The stage of melanoma also helps determine what treatment options should be considered. There are two ways we generally describe staging. First is the TNM staging system, which defines the extent of cancer spread from an anatomic perspective. Second is the more familiar Roman numeral staging system, which incorporates TNM criteria plus other factors. Both of these

Staging systems are maintained by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC).

The TNM system incorporates three different aspects of the melanoma into the stage designation. You will often see this information on your pathology report, with values given for T, N, and M.



T means tumor. The value is determined for the original tumor (or primary tumor) by both the depth (also called thickness) of the melanoma and whether or not it is ulcerated (a break in the skin covering the melanoma). There are 5 designations of tumor depth.

There are 5 designations of tumor depth

- **Tis** (sometimes called T0) is confined to the epidermis
- **T1** is 1 millimeter (mm) or less
- **T2** is more than 1 mm and up to 2 mm
- **T3** is more than 2 mm and up to 4 mm
- **T4** is more than 4 mm

N means node means node and refers to whether the melanoma has spread to one or more of the nearby lymph nodes (also called nodal metastases) or to the nearby skin/tissue in between the original melanoma and the regional lymph nodes

M means metastases, which is whether or not the cancer has spread to other distant sites of the body beyond the regional lymph nodes (such as the lungs, brain, etc.)

Using the TNM values, melanoma can be classified into stage groups using Roman numerals (0-IV) and then letters (A-D) for substages.

- **Stage 0**: Melanoma in situ, which is confined to the upper layer of the skin (epidermis)
- **Stage I**: Local melanoma that extends into the dermis up to 1 mm in depth regardless of ulceration status or up to 2 mm in depth if not ulcerated
- **Stage II**: Local melanoma that extends deep into the dermis; either more than 1 mm and up to 2 mm if ulcerated or more than 2 mm in depth regardless of ulceration status
- **Stage III**: Melanoma that spreads to the regional lymph nodes or to the region between the primary melanoma and those lymph nodes
- **Stage IV**: Melanoma that spreads beyond the regional lymph nodes to distant sites (e.g., to the lungs, brain, etc.)

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IS STAGE II MELANOMA AT HIGH RISK FOR COMING BACK (RECURRING)?

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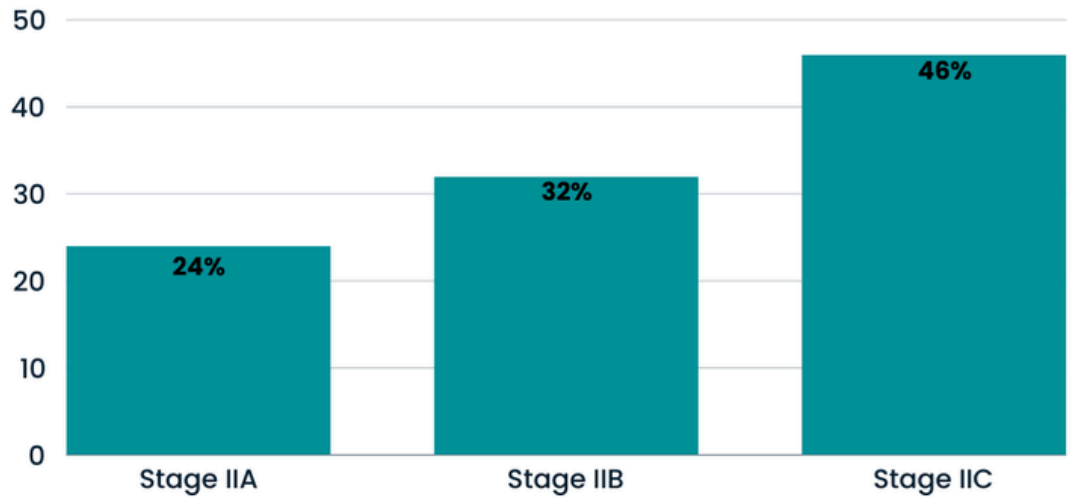
Dr. Geoffrey Lim: You've mentioned that the importance of staging is to help us predict whether the melanoma will come back. You've outlined that thickness (or depth) and ulceration of the tumor are the two main features of the primary melanoma that define the stage and substage. How does one's risk associated with each Stage II subgroup vary depending on these features?

Dr. Jason Luke: *The numbers vary a little bit, but for Stage IIA melanoma, the risk of recurrence is about 24% over five years (Graphic). But when we get to Stage IIB and Stage IIC, it increases. The five-year risk of recurrence is 32% for Stage IIB. And for Stage IIC, the risk of recurrence would be as high as 46%. And these numbers (for Stage IIB and IIC) show you that in approximately a third to almost half of cases, the melanoma will spread to somewhere else in the body just because the primary melanoma has grown very deep in the skin.*

RISK OF MELANOMA COMING BACK WITHIN FIVE YEARS



Graphic. For each melanoma substage, either IIA, IIB or IIC, the risk of melanoma coming back (recurrence) 5 years after the initial diagnosis is approximated.

"Approximately a third of Stage IIB patients and almost half of Stage IIC patients will have the melanoma come back somewhere else in the body, because the original melanoma was very deep."

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IS IT TRUE THAT STAGE II MELANOMA CAN HAVE A WORSE PROGNOSIS THAN STAGE III MELANOMA?

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Dr. Geoffrey Lim: You mentioned that staging groups define high-risk melanoma, and Stage IIB and Stage IIC are really where we draw that line. However, for the patient who is paying attention to some of the survival curves, which measure outcomes in some of these studies, it can be confusing. Is it true that patients with Stage IIB and IIC melanomas actually fare worse than patients with Stage IIIA or Stage IIIB melanomas, where the lymph nodes are involved?

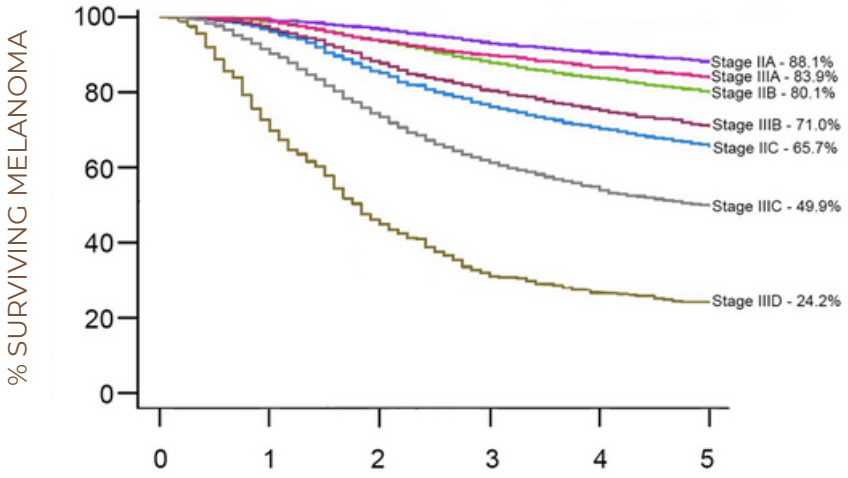
Dr. Jason Luke: *I think as patients become more aware of information around their melanoma diagnosis and read more about it, they come to this realization that some Stage II melanomas fare worse than certain Stage III melanomas, which seems paradoxical. It can be very confusing. Historically, we thought of high-risk melanoma as being melanoma that involved lymph nodes. And the reason for that was related to our surgical paradigm: We would cut the melanoma off the skin and then we'd check the lymph nodes because that's the most likely place for melanoma to go first. If melanoma was in the lymph nodes already, well, that meant that it was already spreading and was on its way to spreading to distant sites, so, therefore, that was bad.*

It turns out, however, with more long-term data, we observe that for some of the patients who have deep primary lesions without lymph node involvement, the Stage IIB and Stage IIC patients, the outcomes are as bad, possibly worse than for Stage IIIA or IIIB patients who have limited lymph node involvement combined with relatively lower risk primary melanomas, as defined by thickness and ulceration. These results are shown in the Graphic below.

And so, then you say to yourself, well wait a minute, maybe lymph node involvement is not always an indicator for high risk for distant metastatic disease. And, now that we have better follow-up on thousands and thousands of people, the biology of melanoma is becoming more obvious to us, which is to say the higher risk the melanoma on the skin (defined by depth and ulceration), the worse situation you have. The characteristics of that primary melanoma are an important driver of outcomes, even in patients who have regional disease.

Melanoma can be a systemic disease; there is a chance that it can come back even after the primary melanoma has been removed surgically.

Graphic. Differences in survival time after diagnosis between substages of Stage II and Stage III melanomas.



MELANOMA

CAN BE A SYSTEMIC DISEASE; THERE IS A CHANCE THAT IT CAN COME BACK EVEN AFTER THE PRIMARY MELANOMA HAS BEEN REMOVED SURGICALLY.

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HOW CAN I LOWER MY RISK FOR STAGE II MELANOMA COMING BACK? WHAT ADJUVANT DRUGS ARE USED?

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Dr. Geoffrey Lim: Can you please tell us about the studies you conducted looking at therapies to reduce the risk of melanoma coming back?

Dr. Jason Luke: *Yes. Now, let's go over some of the details from the clinical trials that established the use of pembrolizumab and nivolumab in Stage II melanoma. Pembrolizumab and nivolumab are immunotherapy drugs that have been approved by the FDA for many kinds of cancers for a long time, and approved for use in Stage III melanoma and Stage IV melanoma.*

Given our conversation above noting that risk of melanoma coming back after surgery is similar or perhaps worse for patients with Stage IIB and Stage IIC compared to Stage IIIA and IIIB, it made sense to study whether immunotherapy could provide a benefit in Stage IIB and IIC as well. That led us to do the clinical trials, the Keynote-716 and CheckMate-76S studies discussed below.

I also should mention that until recently, outside of clinical trials, all we had to offer these patients with Stage IIB or Stage IIC melanoma was ***active surveillance****. That typically meant looking at the skin and examining the lymph nodes on a regular basis (typically every 3 to 6 months) for up to 5 years after surgery. We were looking for any signs the melanoma had recurred. Sometimes that involved imaging tests as well, particularly if the patient had a suspicious symptom.*

KEYNOTE-716 TRIAL (PEMBROLIZUMAB)

In the KEYNOTE-716 trial, patients with Stage IIB and IIC melanoma were split into two groups. Half the patients either had standard follow-up, which would be no treatment (placebo plus an enhanced form of active surveillance), and half the patients received pembrolizumab and an enhanced form of active surveillance. Pembrolizumab was given every three weeks for a year in the same way as it is approved for Stage III melanoma.

As we predicted in designing the study, as soon as we started looking at the two groups at one year of follow-up, we already saw that there was a difference. In other words, pembrolizumab was reducing the recurrences.

To describe this numerically, at around 14 months of follow-up, 11% of pembrolizumab-treated patients had experienced a recurrence and 17% of the patients in the placebo group who had gotten no treatment had a recurrence. That calculates out to a 35% reduction if you do the math.

At a follow-up around 21 months, 15% of the patients in the pembrolizumab group and 24% in the placebo group had their disease come back or had died, which is a 38% reduction with pembrolizumab (Graphic).

We've now followed those data out past four years. We have continued to see that this reduction in melanoma recurrence has been very stable. At a follow-up of 48 months, 71% of the patients in the pembrolizumab group and 58% in the placebo group demonstrated recurrence-free survival. There was a 38% reduction in the risk of recurrence for patients treated with pembrolizumab. So, we feel confident telling patients pembrolizumab offers a potential benefit.

CHECKMATE-76K STUDY (NIVOLUMAB)

Dr. Jason Luke: *There's another medicine with a similar benefit. That drug is nivolumab, which was also Dr. Jason Luke: There's another medicine with a similar benefit. That drug is nivolumab, which was also approved for Stage III and Stage IV melanoma.*

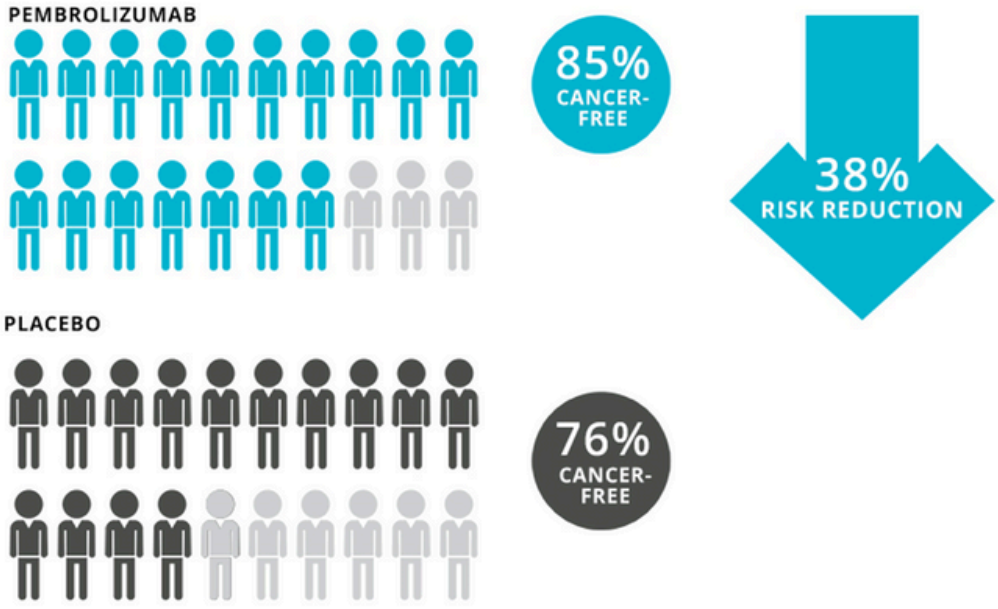
In the CheckMate-76K trial, patients with resected Stage IIB and IIC melanoma were split into two groups. Two-thirds of the patients received nivolumab every four weeks for a year and one-third of the patients had standard follow-up, which would be no treatment (placebo plus an enhanced form of active surveillance).

At a follow-up around 24 months, 22% of the patients in the nivolumab group and 34% in the placebo group had their disease come back or had died. At a follow-up around 36 months, 29% of the patients in the nivolumab group and 39% in the placebo group had their disease come back or had died. This means there is a 38% reduction in the risk of melanoma recurrence.

Functionally speaking, nivolumab shows a very similar impact on recurrence. That's what we've seen in all other settings of melanoma. They have almost identical outcomes and side effects.

Whether you receive pembrolizumab or nivolumab will be driven by how much your doctor knows about each drug, not by the perceived difference in how well the drugs work. But both of these, I think, are worth discussing with patients who are facing Stage IIB or Stage IIC melanoma to try to understand, again, the pros and the cons of whether a treatment would be useful to them.

Graphic: Results of the trial of adjuvant pembrolizumab vs placebo in patients with Stage IIB or Stage IIC melanoma at 2 years. data, click here.



"Any patient who has a deep primary with or without ulceration deserves to have a conversation about the pros and the cons of adjuvant treatment after surgery to try to reduce the risk that melanoma could come back."

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WHAT ARE THE SIDE EFFECTS OF ADJUVANT THERAPY?

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Dr. Geoffrey Lim: Can you please go over the side effects of adjuvant therapy used in patients with Stage II melanoma?

Dr. Jason Luke: *No treatment in medicine comes without risk. The most common side effects that patients experience with immunotherapies like pembrolizumab and nivolumab are shown in the graphics. Some of these are related to the immune system being activated. For example, based on our experience with pembrolizumab overall, we commonly quote this risk of about five to ten percent of patients who can have a serious autoimmune-like problem, where their own immune system will attack their organs. And that most commonly is a problem in the organs that make hormones. So, think about the thyroid as being the predominant site affected, but we can also observe changes in the pancreas, the adrenal gland, and other organs. And the reason for that is these drugs cause the organs to not work properly, and then the hormone levels go outside the normal range. And when this happens, one's hormone levels don't always fix themselves after you come off the drug.*

People may have low thyroid (or hypothyroidism), and that's something people have for their entire lives. But it's not terribly hard to manage, because we can give oral thyroid medicine, which is a relatively easy treatment. That can happen in even up to 20% of patients. So, these drugs can cause something like that, but in more severe cases they can affect other glands, causing other hormones to get out of balance or cause other irregularities. These other hormonal side effects can be more problematic. For example, diseases like type I diabetes mellitus and pituitary problems are more challenging to manage medically and can generally affect the patient's general health to a greater extent than hypothyroidism. And so, this is a real consideration in terms of the tradeoff.

I want to emphasize that there are consequences to adjuvant treatment. There are potential side effects of giving this treatment.

Common side effects (occurring in more than 10% of cases) associated with **pembrolizumab** in the clinical trial that studied adjuvant therapy in patients with Stage IIB or Stage IIC melanoma. These side effects are listed in descending order from the most common to the least common.

You can find additional information about the side effects of pembrolizumab by clicking here.

- **Fatigue (28%)**
- **Diarrhea (26%)**
- **Rash (24%)**
- **Joint pain (23%)**
- **Nausea (21%)**
- **Itchiness (17%)**
- **Low thyroid (17%)**
- **Cough (17%)**
- **Headache (14%)**
- **Weakness (11%)**
- **Overactive thyroid (10%)**
- **Muscle pain (10%)**

Common side effects (occurring in more than 10% of cases) associated with **nivolumab** in the clinical trial, CheckMate-76K, that studied adjuvant therapy in patients with Stage IIB/C melanoma. These side effects are listed in descending order from the most common to the least common.

You can find additional information about the side effects of nivolumab by clicking here.

- **Fatigue (36%)**
- **Muscle pain (30%)**
- **Rash (28%)**
- **Diarrhea (23%)**
- **Itchiness (20%)**
- **Nausea (14%)**
- **Low thyroid (14%)**
- **Headache (12%)**

IMMUNE RELATED

IMMUNE-RELATED SIDE EFFECTS ARE RELATED TO THE IMMUNE SYSTEM BEING OVERLY ACTIVATED AND ATTACKING THE BODY. SOME OF THESE SIDE EFFECTS CAN'T BE REVERSED. WEIGHING THE POTENTIAL SIDE EFFECTS AGAINST THE BENEFIT IS A CHALLENGE BECAUSE YOU ARE TAKING AN OTHERWISE RELATIVELY HEALTHY PERSON AND EXPOSING THEM TO THESE SIDE EFFECTS TO PREVENT SOMETHING FROM COMING BACK. WE DON'T KNOW WHICH PATIENTS ARE GOING TO HAVE THE CANCER COME BACK.

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HOW IS ADJUVANT THERAPY GIVEN?

Dr. Geoffrey Lim: How is adjuvant therapy given?

Dr. Jason Luke: *The treatment with immunotherapy is given by an intravenous (by vein) infusion. For nivolumab, the treatment is administered intravenously once per month. Pembrolizumab can be given every three weeks or every six weeks. In my practice, we usually do the every-three-weeks regimen to start. Both of these immunotherapies, pembrolizumab and nivolumab, are given for up to one year unless patients get an intolerable side effect or have a recurrence in which case we stop the drug and reevaluate what to do.*

I want to make sure people are feeling okay and they're not having any side effects. I believe it is very important to see people in person and have that interaction to make sure that we're doing okay. Like any medicine, you're more likely to get side effects at the beginning when you start it. If people are doing just fine on pembrolizumab, we sometimes stretch it to six-week intervals later on. But this varies by practice. Some people go straight to every six weeks right off the bat.

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HOW DO YOU WEIGH THE BENEFITS AND RISKS OF ADJUVANT THERAPY VS ACTIVE SURVEILLANCE?

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Dr. Geoffrey Lim: Before the FDA approval of adjuvant therapy for Stage II disease, we had nothing to offer these patients to mitigate the risk of their melanoma coming back. These are patients who do not have metastatic disease. Clinicians are used to having these adjuvant therapy conversations with patients with metastatic lymph node disease. How do you discuss the option of adjuvant therapy for patients with Stage IIB and IIC disease in terms of mitigating their risk for recurrence?

Dr. Jason Luke: : *A strange thing about adjuvant therapy, which often stretches people's usual thought process, is that you'll never know if the treatment worked after the surgery. You'll only know if it didn't work. Because if it works, the melanoma will never come back, but the melanoma might never have come back anyway. So how do you know whether the disease would not have come back anyway or if the adjuvant therapy prevented it from coming back?*

Also, right now, we don't know whether adjuvant therapy is better than waiting for metastatic disease and then providing treatment. We don't know whether adjuvant therapy helps people live longer than they would if we just treated them when the disease returned. Adjuvant therapy clearly reduces recurrence, which I believe is a good thing in and of itself because that alleviates psychological stress. But we don't know yet whether or not that's going to increase the survival rate for the average patient.

UNDERSTANDING WHAT RISK REDUCTION WITH ADJUVANT THERAPY MEANS FOR YOU

Dr. Jason Luke: *How different people accept information about their risk of recurrence and what it means to them can be very different. We will go through the actual risk recurrence data below, but it ultimately comes down to an individual person's priorities and risk tolerance. You can imagine scenarios where somebody says, "Well, I'm already sick of dealing with my melanoma and I have other problems that might be more pressing right now, and I'm not even worried about five years from now." For that person, active surveillance might make sense. Or, you may have somebody else who says, "This sounds like a really, really big deal, and I want to do whatever is possible to try to mitigate that risk." That person may be willing to accept the risk of side effects to gain potential benefit from adjuvant therapy.*

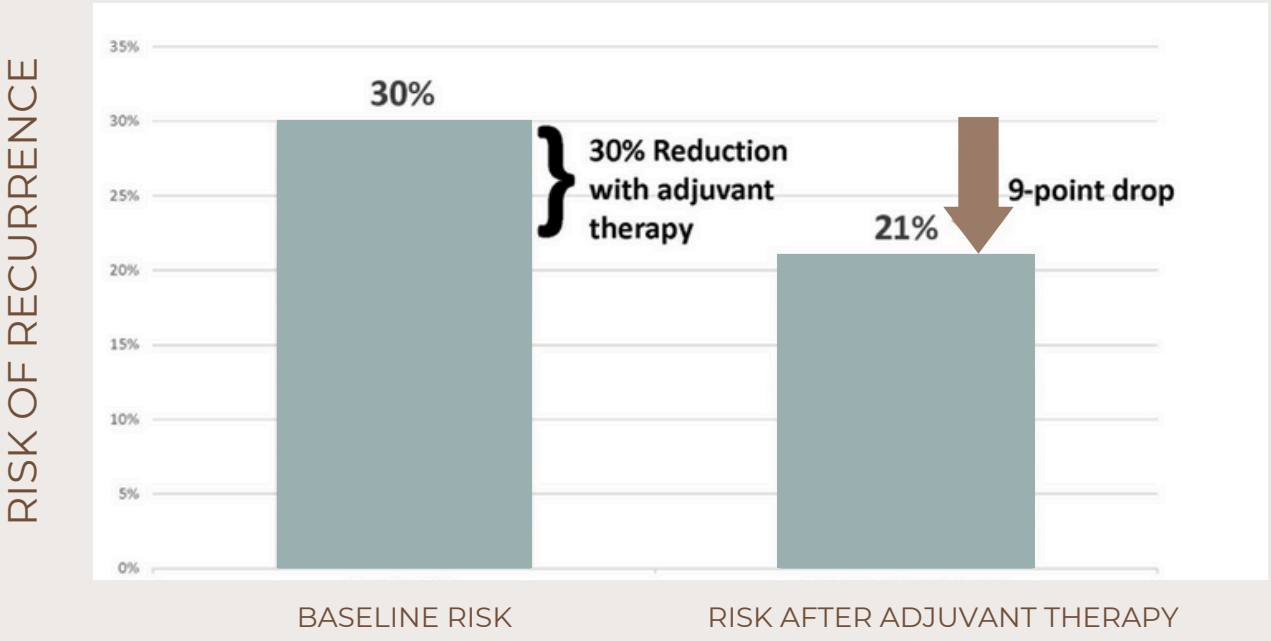
So, what we talk about is what do these numbers mean? And so, there's this percent risk that the melanoma could come back. This is called the baseline risk of recurrence. What does that number mean to you? Because people do often have a gut sense of this. They think, oh, that sounds like a lot, or that doesn't sound like a lot. And that can give you a real strong initial sense of shared decision making about what's going to be the right decision for them.

We then start to talk to them about adjuvant therapy. Here's the treatment option that we might have to offer in that case. At this time, immunotherapy that was approved for more advanced melanoma, as we mentioned before, has been studied in Stage II melanoma. And very similar to what we see in other higher stages, immunotherapy reduces the risk of the melanoma coming back by approximately 35%, 40%, somewhere around there.

Dr. Jason Luke: *We try to make sure these discussions are straightforward for people. Another important discussion point is the concept of relative versus absolute risk reduction. If we quote a 40% risk reduction, you have to take that initial risk recurrence number (46% for Stage IIC melanoma) and reduce it by 40%. Then you have to clarify that even with adjuvant treatment, the risk of recurrence doesn't entirely go away.*

To be more granular, if we quoted you a recurrence risk of 46% and then said that we're reducing that by 40%, that's about 18.4% off the 46% (Graphic). So, then you get to a 27.6% chance of recurrence. So now the question becomes is a 46% chance of recurrence without adjuvant treatment versus a 27.6% chance of recurrence with treatment useful to you? And how do you balance that with the risk of side effects, etc.?

REPRESENTATION OF THE POTENTIAL CALCULATION OF RISK REDUCTION AND WEIGHING VS SIDE EFFECTS OF IMMUNOTHERAPY USED IN THE STAGE IIB MELANOMA ADJUVANT SETTING.



Dr. Geoffrey Lim: But there's other aspects of drug treatment to consider such as how well tolerated are these medicines? And for the patient that is really thinking about pushing the go button here, what types of things do you lay out to consider that may actually sway them the other way, whether it be toxicities or otherwise?

Dr. Jason Luke: These drugs can cause a fairly significant impact on people's quality of life. If they experience certain side effects (like low thyroid hormone), then they may have to take a medicine for the rest of their life. When you start talking about a permanent side effect, that's a big consideration. So, this is where that gut check sense from the patient really makes a big difference.

So, when you tell them their risk, do they think, "Oh my gosh, that's huge!" Or do they think, "Well, I'm not so sure, because often where we land is somewhere where we have an approximately similar risk of a long-term problem versus the amount of benefit with risk reduction of the melanoma coming back." (See Graphic) The reality is that the risks for side effects may be a little higher in healthy patients receiving adjuvant therapy vs patients with metastatic melanoma. We think this may be because patients with advanced cancer have had their immune systems beaten down by the cancer. In the earlier stages of melanoma, the immune system hasn't been beaten down, so it is more likely to get revved up and may cause collateral damage to organs. Obviously, we want to be in a place where there's more risk reduction of melanoma than potential side effects, but sometimes we aren't that far off, quite frankly.

So, the question then is how does an individual patient consider that? Do they think, "I'm going for all the risk reduction because I don't want the melanoma to come back," or is their perspective, "Well, I don't know, maybe it's not that high risk, and I really don't want the side effects." And that, in the end, often is the consideration. And that's where I think not rushing to a decision is really, really important in terms of taking the time to weigh risks and benefits. Because if you get one of the side effects, you're not going to "un-get" it, right? But similarly, if the melanoma comes back, you're not going to "un-have it" either. And so that's really the decision point for patients.

I try to keep this conversation away from the, "I'm just scared, I'm going to do this," to a real consideration of risks and benefits. We have to try to help patients stay there and think, because I think it's very easy to just defer to, "I'm scared, I'll take whatever you tell me."

"It's really important to discuss the upside and downside of potentially taking an adjuvant treatment."

Jason J Luke, MD, FACP
Associate Director for Clinical Research
Director - Immunotherapy and Drug Development Center
UPMC Hillman Cancer Center
Associate Professor of Medicine
University of Pittsburgh School of Medicine

Dr. Jason Luke: *When we think about making decisions for post-surgical adjuvant treatment, we often don't make a decision the first time we talk through everything with the patient because it can be overwhelming to think through all of this. Many people have never thought about whether a 46% risk is something that's meaningful to them. So, we really try to share the information, help people get that gut sense of things, and then often maybe take a little time to think about it because we're not in a big rush. We can chat on the phone; we can see someone back in a week or two, and we can talk through it again.*

And I fully understand that many patients start to get a little lost as we start jogging through these numbers. And that's where having support from a family member who's either taking notes or is just listening on their own can be very, very helpful.

Dr. Geoffrey Lim: And of course, you mentioned a good point about how we don't make decisions in a vacuum in the clinic. Often times it takes time to digest, bring family members into the discussion, meditate on it, whatever you need to do.

Dr. Jason Luke: *This is really a joint decision-making progress. There are a lot of numbers and percentages that get thrown all around, but in the end, we want to do something that you as a patient or that you with your family feel the most confident in. And that shouldn't necessarily be the doctor just telling you what to do. You need to absorb the information and decide. And that may mean you need to think about it for a little while. You might need to get a second opinion. You might need to reach out to resources like AIM that can give you more help maybe in a different way of presenting information. So, take advantage of all those things. There doesn't need to be a rush around the time of a diagnosis of melanoma.*

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FERTILITY AND FAMILY PLANNING

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Dr. Geoffrey Lim: There's a couple of questions that I wanted to ask you specifically about the patients thinking about fertility and how that affects them, their family planning. Are there any consequences of drug treatment on family planning? How do you have that discussion around adjuvant therapy?

Dr. Jason Luke: *Yeah, this is a great question. And it comes up in melanoma more often than in some other kinds of cancers because, unfortunately, some of our patients are younger. The answer for surgery, is that it really does not typically affect family planning. But when we're talking about medicine, drug therapy for reduction of recurrence after surgery that's going to go on for a year, then we do really need to be cognizant of this question because in reality, we just don't know the answer. There is not strong evidence that would say that if you are taking these immunotherapy medicines that you will have a problem with a pregnancy, but at the same time, it hasn't been thoroughly studied. So, in all of the clinical trials, patients were asked to take approaches that would keep them from getting pregnant.*

If fertility and family planning are at all a concern, then absolutely having a discussion with a fertility specialist and potential egg banking is a great idea. And often there's a fear factor of, "Oh my gosh, I was diagnosed, we don't have time to think about family planning." But what we have to reassure and emphasize for people, especially younger patients with melanoma, is we're thinking about your future over the next fifty, sixty, seventy years. Addressing the melanoma is not just an issue that affects the next two months. We want to make all the decisions that are going to make your life go well, which hopefully is not having melanoma, but that should not come at the expense of the other aspects of life, which obviously are so important. So that's definitely somewhere where we want to make sure we're not going too fast and we're taking into account those kinds of longer-term considerations for quality of life that people might have.

Dr. Geoffrey Lim: That's an interesting point about not rushing the decision-making process about adjuvant therapy. You've mentioned this multiple times. How much time do patients actually have after the final surgery (excision) before adjuvant therapy has to be started?

Dr. Jason Luke: *The pembrolizumab trial arbitrarily defined three months as the time frame within which to start adjuvant therapy after the final surgical excision. That's the time frame used in other adjuvant therapy trials in melanoma. For example, nivolumab used in the CheckMate-76K trial was the same. There's actually no biological reason why that's the time frame. From the conversations I have had, most people feel pretty comfortable about that three-month time frame, but we do have some cases where we went out to a six-month time frame, especially when pembrolizumab first became available. This was relevant to people who had their surgeries prior to the approval and still wanted to take advantage of the adjuvant therapy option. I can't speak to whether waiting past the three-month period causes any hiccups with insurance. Beyond six months, we really don't have any experience, and it's not clear how much of a benefit you would get at that point. Some experts feel that if you wait too long to start adjuvant therapy, you may just as well wait and treat if the disease comes back. Again, we do not know if adjuvant therapy provides a survival advantage vs waiting to treat the disease when it comes back.*

So there is some time to think through the decision and address issues such as family planning. Of course, we can add additional time for decision-making by obtaining the medical oncology referral early—when the pathology results come back from the biopsy. This is also an option. Some groups are now conducting multidisciplinary tumor board discussions with the dermatologist, surgeon, and medical oncologist meeting after the biopsy results are in for patients with Stage II disease. Such tumor boards make sense to make sure the care is coordinated more seamlessly, but an additional benefit is that they also give us more time to establish a relationship between the medical oncologist and the patient and facilitate shared decision making.

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WHAT DO YOU TELL PATIENTS WITH STAGE IIA MELANOMA WHO ARE WORRIED ABOUT THEIR RISK OF RECURRENCE?

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Dr. Geoffrey Lim: I want to take a step back because we've been talking about those that may qualify for adjuvant therapy. But for Stage IIA patients, for whom we currently don't have an FDA approved adjuvant therapy and surgical management is the mainstay of treatment, how do you have a discussion with those patients who may be anxious that they don't have another option even if they wanted to consider it?

Dr. Jason Luke: *So, we commonly don't think of Stage IIA as high-risk relative to Stage IIB and IIC. And that's because we see, when we look at long-term outcomes, the risk of recurrence for Stage IIA is quite a bit lower than for Stage IIB and Stage IIC.*

Now, of course, we know there are some people who will have a recurrence in Stage IIA. We just aren't really good yet at figuring out who exactly they're going to be. And there are some tests that are out there that propose to predict this, although they're not FDA-approved. So, for people who are anxious in this regard, there are some tests we can do. And then the question becomes if they are deemed to be high risk, then what do you do? Well, then we probably watch people more closely during active surveillance. We make sure that they're really following up with dermatology and medical oncology for evaluation more frequently. But we would still say that there's not clear evidence that giving a drug would help in that situation with Stage IIA. And in fact, we'd really run a high risk of causing more harm than good. And so that's the thing to chat through.

With that said, some patients with Stage IIA melanoma are being studied in the adjuvant setting. So, it may be worth keeping your eye out for additional clinical trial options if you are very motivated to reduce the risk of recurrence.

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IN CONCLUSION

We hope this interview has been helpful for you to understand the most common questions about Stage II melanoma, which Stage II patients are eligible for adjuvant therapy, and the pros and cons of adjuvant therapy vs active surveillance. Most importantly, we hope it helps you make an informed decision about steps to take after the surgical removal of your cancer.

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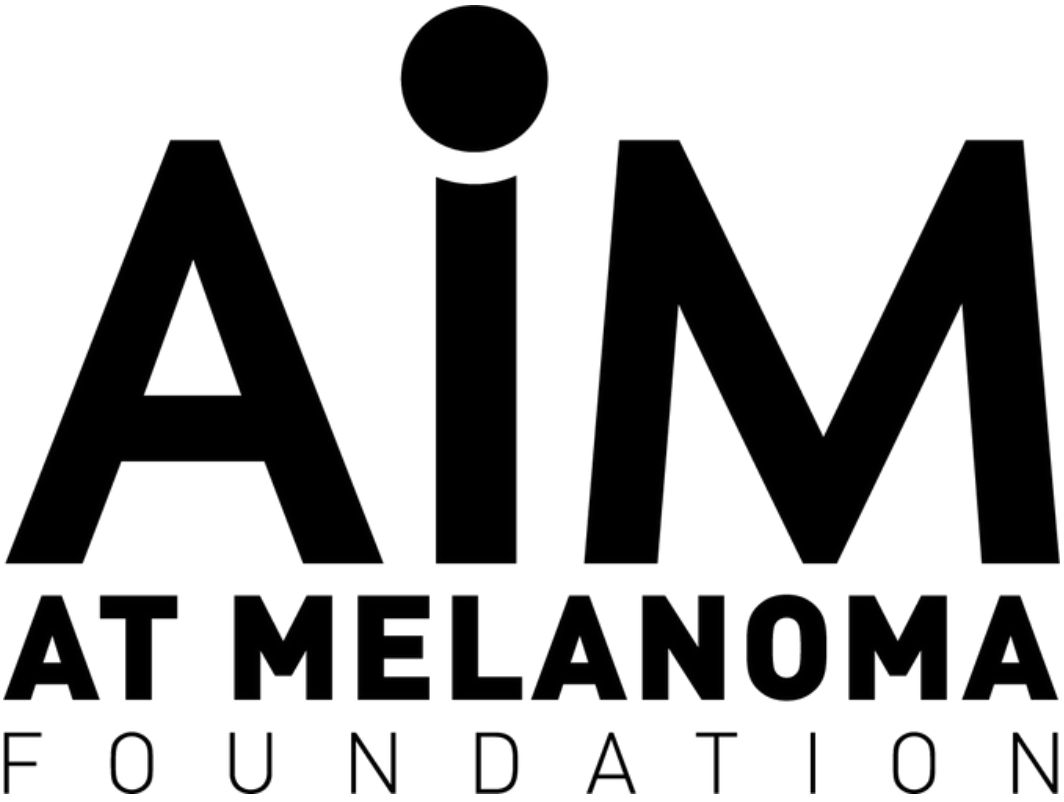
AIM's MISSION

By directing and funding paradigm-shifting research initiatives; educating patients, healthcare professionals, and the public; and advocating for survivors and their families, AIM at Melanoma's goal is to end this disease in our lifetime while improving the lives of those it affects.

Founded in 2004, AIM at Melanoma is a global foundation dedicated to finding more effective treatments and, ultimately, the cure for melanoma.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