Hello, Welcome to Smilo shares with Primary Care. I’m Karen Brown. I’m an internist in North Haven and the Medical Director of the Primary Care Service line of Northeast Medical Group. And I am joined normally to cohost this series with Ann Chang, who is not here and Kevin Billingsley, who’s here and is the CMO of Smilo. We will introduce our speaker shortly. After an orientation to this session in general, today’s topic is Melanoma.
This is a monthly series designed to focus on primary care perspectives of cancer, especially diagnosis and handoff where we are involved and the designated audience is primary care clinicians, although I think many clinicians can learn from this. And we always have at least one primary care clinician along with SMYLO clinicians and often focused in one geography. This one is is not so much focused in one of our geographies and we hope that this will help us all become better at what we do. So we will go and we’ll have a
introductions and then we have a three case presentations.

And we will learn through our case presentations and leave time for questions at the end.

So at this time, I would like to introduce my NEMG primary care colleague, Dr. Zarku Power. Zarku Power is a graduate of the University of Medicine Carol Davila in Bucharest, Romania, and she completed her internal medicine residency in New York. She initially joined the staff of Yellow Haven Hospital as a hospitalist.
before starting her practice in Milford. She’s now a practicing physician and also a managing partner of Primed, which is a PS: A within Northeast Medical Group. She’s been an active member of the Milford and Bridgeport area medical community, and she’s been on the executive medical staff committee at Bridgeport Hospital. And is completing A2 year Emerging Leaders program through the Yale School of Management. She’s an active clinical leader in Northeast Medical Group and lends her expertise to the NEMG Primary Care Steering Committee and also the
Yale New Haven Health System Care
Signature Pathway Work Doctor Zarku
Power strongly believes in a patient doctor relationship as the keystone to great health outcomes and that relational care team approach is paramount to effective care.
Kevin, I’ll turn it over to you on to introduce the members of yours Milo team.
Karen, thank you.
I’ll just say it’s really a pleasure for me to be here.
As you alluded to my associate Dr. Ann Chang generally partners with...
you in this wonderful venture.

But I'm absolutely delighted and honored to be here.

I'm a surgical oncologist and I service the Chief Medical Officer of the.

And I will say on a personal note,

And I am just delighted to see this initiative moving forward.

Those of us who are oncologists and are treating cancer patients regardless of our discipline are so indebted and tied to our primary care partners.

It is really kind of the teamwork, the collaboration and the.
The seamless flow of care between the primary care environment and the specialty environment that leads to great cancer care outcomes not only in the early diagnosis and in the support of the treatment phase, but in the survivorship phase. So I think that this is really a valuable exercise and I'm hoping that people are enjoying it and taking a lot away from it, it's an honor for me to introduce several of my Smiley colleagues, all of whom are esteemed experts in their field and I'll.
just start with Doctor Harriet Kluger.

It would not be an exaggeration to say Doctor Kluger is an international authority in Melanoma and cutaneous oncology. She is the Harvey and Kate Cushing Professor of Medicine and the leader of the Melanoma program. Here at Smilow, she sees patients with both Melanoma and renal cell cancer. She has an extensive research portfolio with an interest in developing new drug regimens and biomarkers that are predictive of response to therapy and Melanoma. She participates in a variety
NOTE Confidence: 0.943608066666667
00:05:03.370 --> 00:05:04.750 of clinical trials.
NOTE Confidence: 0.943608066666667
00:05:04.750 --> 00:05:06.770 She directs an active research
NOTE Confidence: 0.943608066666667
00:05:06.770 --> 00:05:08.790 laboratory that studies tumor and
NOTE Confidence: 0.943608066666667
00:05:08.863 --> 00:05:10.883 immune cells from patients treated
NOTE Confidence: 0.943608066666667
00:05:10.883 --> 00:05:12.903 with these novel therapies to
NOTE Confidence: 0.943608066666667
00:05:12.975 --> 00:05:15.187 determine mechanisms of resistance.
NOTE Confidence: 0.943608066666667
00:05:15.190 --> 00:05:16.830 Her laboratory also completes
NOTE Confidence: 0.943608066666667
00:05:16.830 --> 00:05:18.880 preclinical studies to improve treatment
NOTE Confidence: 0.943608066666667
00:05:18.880 --> 00:05:20.747 regimens for patients with Melanoma,
NOTE Confidence: 0.943608066666667
00:05:20.750 --> 00:05:22.148 renal cell cancer,
NOTE Confidence: 0.943608066666667
00:05:22.148 --> 00:05:23.546 and brain metestes.
NOTE Confidence: 0.87704586
00:05:25.920 --> 00:05:28.864 You know Harriet is definitely our go to
NOTE Confidence: 0.87704586
00:05:28.864 --> 00:05:31.898 expert and I think we’ll find her just
NOTE Confidence: 0.87704586
00:05:31.898 --> 00:05:34.640 a fountain of knowledge in this regard.
NOTE Confidence: 0.87704586
00:05:34.640 --> 00:05:37.340 Next it’s a pleasure for me to to introduce
NOTE Confidence: 0.87704586
one of my surgical partners, Doctor Kelly. Olino Kelly is a W Board certified surgeon who provides patients comprehensive surgical care for skin and soft tissue tumors including Melanoma, Merkel cell cancer, sarcoma, basal cell cancer and others. She's been a recipient of a number of awards including the Society Surgical Oncologist Clinical Investigator award and she has funding through the Calabresi Immune Oncology Scholar program. She currently serves as the NCCN Non Melanoma cutaneous on the cutaneous malignancy committee and she’s a great clinical surgeon.
Next doctor Twee Tran.

Twee is an assistant professor of Medicine.

She cares for patients with Melanoma and other skin cancers at our spinal cancer hospital sites.

She is a graduate of the A/B IM Physician Scientist Research Pathway, and Dr. Twee is a bit of a Yale product.

She did both her internal medicine residency and her fellowship here at Yale, although she received both of her PhD and her MD degrees from Vanderbilt.

She’s also very involved in research,
including novel therapeutics and drug combinations, and is a participant in the Yale skin Cancer spore. She’s a principal investigator of several clinical trials. Last and certainly not least, Dr. Jonathan Leventhal is an associate professor of dermatology. And is the director of the SMILO Onco Dermatology Program. Doctor Leventhal received his bachelor’s degree and medical degree at the NYU at NYU and then came here to Yale for additional training, where he served as a chief resident.
His specialty is in providing care to skin cancer patients who develop cutaneous toxicities from their treatments, as well as diagnosing and treating skin cancers. Like many of the other panelists this evening, he leads clinical trials, studying new treatments for managing dermatologic toxicities. And he’s actively involved in residency in medical education as well as serving as an editor for the textbook self-assessment in dermatology. So do you really have an outstanding cast of experts here?
And I’ll turn it back to you, Karen.

Great. Let’s get started. Florida, you want to present the first case.

Karen, thank you for the warm introduction.

I want to say your work and really ursalable. I’m probably then honored also to have the support of our colleagues. It’s Milo.

This is a 59 year old healthy white female with a past mental history of hypertension hyperlipidemia.
She has a history of having used tanning beds a few decades ago. She wasn’t seen for about 3 years due to a COVID pandemic. She reported a skin lesion about a year ago and notably enlarging her family history, is remarkable for her mother with a history of Melanoma. So I just wanted one more second probably to take a look at the lesions, so my colleagues could pay attention to some of the features that associate to this lesion.
the warning signs of Melanoma.
So this would be sort of a
a good picture to remember.
We could move on to the next slide.
So talking about moles and early signs
of skin cancer, couple of specifics,
we're looking for anything new or changing
we're looking for anything new or changing
on both sun exposed and sun protected areas.

Typically Melanoma appear in women
on both sun exposed and sun protected areas.

Typically Melanoma appear in women

Typically Melanoma appear in women

Typically Melanoma appear in women

Typically Melanoma appear in women

They could arise though anywhere on the skin,
even in the areas where sun doesn’t shine,
so beware.
Generally speaking, most moles, brown spots and growths on the skin are harmless, but not always. Here’s the ABCDI was talking about. This is a simple guide to recognize the warning signs of Melanoma. A is for asymmetry, and if you draw a line through the middle of the lesion, the two halves don’t match. B is for border. Typically they tend to be uneven. They may be scalloped or notched. C is for color. Multiple colors are a warning sign and melanomas may have different
shades of brown, tan, or black.

D is for diameter.

It is a warning sign if a lesion is larger than 6 millimeters or quarter of an inch, and any lesion that’s darker than others not to be overlooked.

One exception is the amylanotic melanomas, which are colorless,

is for evolving any change in size, shape, color, or elevation of a spot.

Any new symptoms of itching, crusting, bleeding, maybe warning signs?

Also, look for an ugly duckling.

The strategy is based on most malls resembling one another, while melanomas stand out
like an ugly duckling.

Jonathan, do you want to take over?

Absolutely. It’s a pleasure to be here, really happy to participate in Smile Shares Primary care.

So I’m going to briefly highlight some of the main subtypes of a Melanoma, so superficial spreading as you can see on the top left, these are the most common types of Melanoma. You can see a lot of the features of the Abcd’s from the last slide. And they tend to grow radially pretty slowly over the course of months to sometimes even years before then growing.
vertically and penetrating more deeply.

Now this is in contrast to the nodular type of Melanoma, which tends to be far more aggressive and that these can grow quite rapidly and they tend to present more deeply in the dermis at a higher stage.

So these are important.

You know, it's talking to patients about any recent change or rapidly growing skin lesion.

The lentigo and malignant subtype tends to occur in elderly patients.

Often looks like an atypical lentigo or a sunspot that elderly patients might develop in sun exposed
areas but with atypical features. Probably the most challenging one for anyone to diagnose are the amylonotic types of Melanoma, and these tend not to have pigment, they’re often pink and. Patient history can be very important here with a new amylonotic lesion that’s either rapidly growing or symptomatic in some way such as being painful or bleeding. And then finally the acryl, intigenous and subungal types are important particularly in patients with darker skin types.
They might have a higher risk of developing this type and if that’s why it’s important when examining patients to look at the palms and soles. And regarding subungal Melanoma, these typically present with Melaninicia, which as you can see is a melanotic band that grows from the proxable nail upwards. I think it’s important to have a differential diagnosis anytime you approached pigmented lesions. So I highlighted here on this slide what I think of as the most clinically important, the most common presenting diagnosis.
NOTE Confidence: 0.941930833333333
00:13:49.960 --> 00:13:53.704 that that comes in with concern for
NOTE Confidence: 0.941930833333333
00:13:53.704 --> 00:13:56.180 Melanoma are seborrheic keratoses,
NOTE Confidence: 0.941930833333333
00:13:56.180 --> 00:13:58.574 which are on the the top left.
NOTE Confidence: 0.941930833333333
00:13:58.580 --> 00:14:01.068 These are stuck on waxy tan to brown
NOTE Confidence: 0.941930833333333
00:14:01.068 --> 00:14:03.442 or even darker brown black papules
NOTE Confidence: 0.941930833333333
00:14:03.442 --> 00:14:05.950 and plaques that tend to develop
NOTE Confidence: 0.941930833333333
00:14:06.023 --> 00:14:08.219 and patients as they get older,
NOTE Confidence: 0.941930833333333
00:14:08.220 --> 00:14:10.516 and sometimes they can be very challenging
NOTE Confidence: 0.941930833333333
00:14:10.516 --> 00:14:12.139 to distinguish from a Melanoma.
NOTE Confidence: 0.941930833333333
00:14:12.140 --> 00:14:13.996 So dermatologists use dermatoscopes.
NOTE Confidence: 0.941930833333333
00:14:13.996 --> 00:14:16.316 And if we are unsure,
NOTE Confidence: 0.941930833333333
00:14:16.320 --> 00:14:18.440 we’ll perform a skin biopsy,
NOTE Confidence: 0.941930833333333
00:14:18.440 --> 00:14:19.920 certainly on the top right,
NOTE Confidence: 0.941930833333333
00:14:19.920 --> 00:14:22.344 we always consider normal appearing nevi
NOTE Confidence: 0.941930833333333
00:14:22.344 --> 00:14:25.400 and those that are slightly dysplastic.
NOTE Confidence: 0.941930833333333
So they’re not fully normal appearing. They might be slightly asymmetrical, borders are irregular, but these don’t meet criteria for Melanoma. And when these are biopsied, they’re not Melanoma then on the bottom left. Illustrates the fact that even non Melanoma skin cancers can be pigmented. So this is an example of a pigmented basal cell carcinoma noted as a slightly more pearly appearance to it and with a dermatoscope you might see other features of a basal cell on the the bottom. Middle picture is an example of vascular lesions such as angiokeratomas or angiomas. Sometimes they can have
a really dark purplish, even blackish hue and can be challenging. As dermatologists, we can use a dermatoscope which you can see in the top right corner highlighting those vascular lacunae and that’s reassuring. And then on the bottom right is a picture of a blue Nevis. And so these moles can also appear in as differential diagnosis of Melanoma, but they are benign. Everyone here is familiar with Melanoma.
I wanted to highlight that most cases actually occur on de Novo, although some might develop from a precursor lesion and these are typically either a congenital Nevis or an atypical Nevis that the patient has that then changes. It can occur in anybody, but tends to tend to predominant in white men over age 50. And then interestingly, underage 50 women outnumber men, likely due to tanning habits. It also is a diagnosis of young patients. And regarding survival, some factors associated with poor
00:16:10.434 --> 00:16:12.930 outcomes include elderly male patients,
00:16:12.930 --> 00:16:14.448 those who have darker skin types,
00:16:14.450 --> 00:16:16.575 likely because of the more
00:16:16.575 --> 00:16:18.275 aggressive biology and presentation
00:16:18.275 --> 00:16:20.728 of the equal indigenous Melanoma,
00:16:20.730 --> 00:16:22.809 as well as patients who are immunosuppressed.
00:16:25.460 --> 00:16:27.196 I very want, I very briefly wanted
00:16:27.196 --> 00:16:28.901 to provide an overview of the
00:16:28.901 --> 00:16:30.416 main risk factors for Melanoma.
00:16:30.420 --> 00:16:32.765 So like any cancer we can consider
00:16:32.765 --> 00:16:35.352 those that are environmental and those
00:16:35.352 --> 00:16:38.620 that are hereditary. Next slide.
00:16:38.620 --> 00:16:40.786 So for the environmental risk factors
00:16:40.786 --> 00:16:42.697 it’s it’s really all ultraviolet
00:16:42.697 --> 00:16:45.525 exposure and so we know that intermittent
intense sun exposure throughout life and increase the risk of Melanoma.
As well as sunburns, but also sunburns that occur cumulatively through adolescence and adulthood. And finally, especially in young women, tanning beds have been associated with increased odds of Melanoma.
And now I'll discuss some of the hereditary risk factors. So having decreased melanin and increased tendency to burn such as fair skin,
light eyes are all associated with Melanoma.

In addition, having an increased number of pigmented lesions,

the important one here is having over 100 nevi that really increases the risk of developing Melanoma.

And I think it’s important to have an idea of these inherent risk factors because the United States Preventative Services Task Force does not recommend screening everybody, but it’s important to keep in mind those who have phenotypic risk factors for Melanoma as well as personal or family history.
So having a history of skin cancer increases your risk of developing subsequent skin cancers, and this is true for Melanoma. As well as having a first degree relative with Melanoma, there are also genetic syndromes of kindreds who have Melanoma passed on from generation to generation. The most important one to know about clinically and the most common is the familial atypical multiple Melanoma syndrome. So these patients have hundreds of dysplastic appearing nevi and they’re at increased risk of developing Melanoma,
but also pancreatic cancer. And I think it’s important to keep in mind who to think about screening for genetics. So we shouldn’t send everyone who has a family history. So you want to keep in mind patients who have several members on one side of the family with a Melanoma or if a family member had more than one Melanoma and in particular. Anyone who comes from a family that has both Melanoma and pancreatic cancer, that should be an important clue. And we have seen many patients who have had several skin cancers,
including melanomas.

But you really want to think about those that have had over 3, especially if the first one happened when they were young.

So I'm now going to turn it over to my wonderful colleague, medical oncologist Dr. Tran.

To discuss how do we follow patients, especially those with low risk melanomas.

Thank you so much, Dr. Leventhal.
So we typically see all Melanoma patients and follow up in medical oncology. And so we typically follow these individuals for at least five years after their Melanoma surgery. Presuming that it’s an early stage Melanoma, prognosis is typically very good with close surveillance. And we see these individuals, depending on their stage either every six to 12 months for the next five years and then subsequently at that point considered handing over the reins to primary care for ongoing surveillance. And every visit we check
complete blood cell count,

metabolic panel and an LDH as a surrogate tumor marker that we can assess for early Melanoma recurrences. And depending on the stage as well, for these early stage individuals, consider getting an annual chest X-ray or CAT scans. I think what’s really important and helpful is that if the primary provider determines that there is any suspected new symptoms, is any worrisome symptoms concerning any distant recurrence, we should always keep in mind to have a low threshold for ordering additional
imaging and if possible for early diagnosis.

After five years, and during that time as well, we always have to consider age appropriate cancer screening and continue full body skin checks with the dermatologist.

We are presented here with a 76 year old male who has a right forearm lesion noted about a year ago he denied any recent change in pigmentation of the lesion or rapid recent growth.

He underwent a shave biopsy and pathology report revealed Melanoma; breast load thickness 2.3 millimeter.
He reported a history of blistering sunburns.

No history of tanning, but use.

He does not have a history of Melanoma.

His family history is also negative for Melanoma or non Melanoma, skin cancer and he retired from finance.

On physical exam, he didn’t have any evidence of lymphadenopathies and his skin exam on the biopsy site of the right forearm showed no signs of infection, no residual pigmentation, no nodularity, no satellite lesions.

Next slide please.

So this case, as you’ve heard earlier as
Jonathan presented, is actually a nodular Type A lesion Melanoma, so. But this type requires a wide local excision to treat the primary lesion. The probability of nodal micrometastasis is approximately 20%. The work up will include labs just X-ray, EKG if needed. Depending on the remainder of the history and lymphosyntography there is an indication for Sentinel node biopsy to determine staging and future therapy decision. In this case I’ll turn it on.
Our colleague to discuss further.

Hi,

I’m Kelly Olina, one of the surgical oncologists and I have the pleasure to work with doctors Kluger, Tran and Leventhal on an everyday basis.

So you know a lot of times when the patients first come in again, they come in really scared and that’s really how we meet most people. They come in very uncertain.

So again part of this is also to empower the primary care doctors on the line who know these patients inside and out and you know are more.

More than just their doctors,
00:22:51.670 --> 00:22:53.420 you know, I think you guys really know the the person just as well as any doctor can know their patients.

00:22:53.420 --> 00:22:55.535 So, you know,

00:22:55.535 --> 00:22:57.390 when patients come in to see me, the first thing that we do is we explain to them how the depth of their Melanoma really impacts.

00:22:57.390 --> 00:22:59.550 But there’s certain principles that we stick to no matter what.

00:22:59.550 --> 00:23:01.190 we’re not just removing the skin, we remove also the fatty tissue

00:23:01.190 --> 00:23:01.710 you know,

00:23:01.710 --> 00:23:03.530 So we talked about removing the Melanoma.

00:23:03.530 --> 00:23:05.589 of their Melanoma really impacts.

00:23:05.590 --> 00:23:06.762 But there’s certain principles that we stick to no matter what.

00:23:06.762 --> 00:23:08.830 We’re not just removing the skin, we’re removing the skin.

00:23:08.830 --> 00:23:11.224 We remove also the fatty tissue

00:23:11.230 --> 00:23:13.666 We’re not just removing the skin,
that carries the lymphatics through which Melanoma cells. Can escape and it’s actually based upon doing multiple trials that have been actually honed down studying thousands of patients over the year. Interestingly, in our attempts to make sure that the surgery becomes less and less morbid, we actually are now part of an international trial called the Melmark trial. So if any of your patients are coming in to see myself or Doctor Clune in our program, you may hear this, the mention of this trial. But again we’re down to taking
out about 1 to 2 centimeter.

And that's really directly proportional to the depth of the Melanoma next,

so you know. Laura had alluded to this patient, you know we would strongly recommend you know this patient within the criterion of who benefits from having a Sentinel node.

And again in these patients we do a full lymph node exam and when we do not detect any palpable disease, we then say do they have microscopic disease.

Now just with any test that we would order if the patient isn’t medically fit or if we’re not going to act upon
the additional staging information, I would never recommend that we do a procedure. Unless we’re going to do something with that result. So for patients who have no high risk features in a thin Melanoma less than .8 millimeters, their lymph node risk is actually lower than the risk of the procedure. So we don’t usually offer it in that setting. There’s a newer indication of these in between .8 and 1 millimeter where we begin to have that discussion. But again, this continues to be a Gray area, the 1 to 4 millimeter.
Range and even I would say the greater than 4 millimeter, I really do push patients because I do feel this information is incredibly important. There’s some nomograms that you can direct your patients to or can look up yourself. Out of curiosity, one more mimics the population we see in Connecticut and that was developed from Memorial Sloan Kettering is now almost 20 years old. The other one is from Australia, however. Melanoma in Australia is a little bit different than what we see.
in the United States, so again I usually have people take a look at both, but it gives them kind of an idea where their risk is next. When we talk about what a central node biopsy is, again some principles really overlap with that of breast cancer. However, each one of us is completely unique. And I tell patients all the time, if you don’t know where you’re going, you need a map to get there. So that’s what the lymphocentigraphy is. So we inject 2 dyes, one’s a blue dye and the other one.
NOTE Confidence: 0.9201268
00:25:50.858 --> 00:25:52.568 has a little bit of technetium.
NOTE Confidence: 0.9201268
00:25:52.570 --> 00:25:54.712 So it’s got a little bit of
NOTE Confidence: 0.9201268
00:25:54.712 --> 00:25:55.948 radioactivity that’s completely saved
NOTE Confidence: 0.9201268
00:25:55.948 --> 00:25:57.803 out of the system within six hours.
NOTE Confidence: 0.9201268
00:25:57.810 --> 00:25:59.642 And what that does is it tells me
NOTE Confidence: 0.9201268
00:25:59.642 --> 00:26:01.385 which nodal station to look for, so.
NOTE Confidence: 0.9201268
00:26:01.385 --> 00:26:02.030 In this case,
NOTE Confidence: 0.9201268
00:26:02.030 --> 00:26:03.849 it’s right in the middle of the belly.
NOTE Confidence: 0.9201268
00:26:03.850 --> 00:26:05.860 And again,
NOTE Confidence: 0.9201268
00:26:05.860 --> 00:26:06.530 because we’re looking for
NOTE Confidence: 0.9201268
00:26:05.860 --> 00:26:06.530 microscopic disease,
NOTE Confidence: 0.9201268
00:26:06.530 --> 00:26:08.250 we have to figure out where to go.
NOTE Confidence: 0.9201268
00:26:08.250 --> 00:26:09.866 And then what we do in the operating
NOTE Confidence: 0.9201268
00:26:09.866 --> 00:26:11.606 room is we have a little handheld
NOTE Confidence: 0.9201268
00:26:11.606 --> 00:26:12.891 Geiger counter and that really
NOTE Confidence: 0.9201268

45
helps me hone in on which of the lymph nodes to remove next and why is that so important click. That’s because it is still our best prognostic value in. Looking at recurrence and death from Melanoma and this was one of the most remarkable trials that’s been done in the field of surgery for Melanoma. So even though it’s an additional surgery, it gives us still more valuable information than that of some of these gene expression profile arrays that you may also have patients come in with next. And we used to actually take out all of the lymph nodes when we had patients who
would even have microscopic disease.

However, there were two trials, one in Germany and 1 multicenter in the United States that showed that doing this additional surgery did not improve a patient’s survival specifically with their Melanoma survival.

So what we do is we. We remove lymph nodes only if someone comes in and we can actually feel the lymph nodes and then there’s some more selection criterion that would be a little bit more unusual.

And again, the important thing is we actually
now have effective treatments.

So I’ll next slide, so Doctor Tran will talk a little bit about this about what we call adjuvant immune therapy, which is a conversation that many of our patients now have.

So as Doctor Alina had already discussed, whether to pursue Sentinel lymph node biopsy. And so my next part is kind of talking about what how can we move the needle further decrease recurrence risk in these patients who may have a positive lymph node or otherwise thickened melanomas or ulcerated melanomas which
have a higher risk for recurrence. And so this chart just kind of displays for the five year Melanoma specific survival for the higher risk stage twos which are included two B’s and two C’s as well as the stage 3 melanomas. And as you can see there are actually some subsets of stage 3 melanomas that do much better than the higher risk stage two events. So for stage 3A melanomas, the five year Melanoma specific survival is 93%. And so compare that to a stage 2C where the survival decreases to 82%.
adjuvant immune therapy,

we're always talking about one additional year of some sort of systemic treatment either in the form of immune therapy or targeted therapy with the goal of trying to decrease recurrence risk.

So in terms of adjuvant, oh, I'm sorry, if you could go back. In terms of adjuvant immune therapy options, there are two FDA approved drugs, temporalismab also known as Keytruda which is given every three to six weeks versus new volume M also known as Opdiva which is given every two to four weeks. Again these are all intravenous, they have similar side effect profiles.
and they both target the PD1 protein.

To help stimulate the immune response against Melanoma.

Both of these drugs are considered interchangeable in stage 2 Melanoma and as well as stage 3 melanomas. In general, it’s been known to have a decrease of 40%. In terms of the recurrence, however, there is no impact upon improving survival to date.

As an alternative to immune therapy for individuals with a B RAF mutation, mainly V600E or V600K mutations, which are present in about.
half of cutaneous melanomas,

there is additional alternative

adjuvant therapy in the form of B,

RAF and MECH inhibitors,

so drabraf nib and tremet NIB,

which are both oral medications.

Either given BID or daily respectively.

And these medications are approved

not in the stage 22 setting,

but in the stage 3 setting for individuals

with lymph node positive Melanoma,

where it’s been shown to

reduce recurrence risk by half.

But unlike immune therapy,

it has been demonstrated to

impact overall survival as well.
So for these individuals with higher risk melanomas, we typically again follow them closely for five years, but because of our higher risk for recurrences, we see them more frequently and we also do imaging more frequently as well. And these imaging can typically include a CAT scan of the chest, abdomen, and pelvis. And I think the main point very similar to early stage melanomas.
is that as a primary care physician, it's always very helpful to screen these patients for any atypical symptoms, red new red flag symptoms because again if we can detect these, if we can diagnose these earlier outcomes are much better potentially if it's localized recurrences, they can still undergo a potentially curative resection. The most important thing even after five years is that these individuals still see the dermatologist still have age appropriate cancer screening. And while we only see these individuals
for five years in medical oncology, it’s so important to keep a low threshold for additional work up if there’s any concern. And so the graph at the bottom here is just a representative graph from the adjuvant trials of Jabrachno Ventremett showing that at 60 months which is equivalent to five years although the recurrences plateau. There is still a few recurrences afterwards and so even despite completing 5 years without any recurrence of disease, there’s still a possibility and so that has to be something that is factored in,
particularly if a patient develops new symptoms, New lymph adenopathy next. So when we talk about individuals with high risk disease, adjuvant therapy isn’t the correct answer for everyone. We have to individualize the and personalize these decisions based on age, comorbidities, what stage they are, going back to the fact that some stage threes act even better than some stage twos. Also the risk of toxicities as well immune therapies can often lead to permanent toxicities, endocrinopathies that require lifelong.
hormone replacement or steroid replacement for example versus reversible toxicities, more so in the case of oral targeted therapies with B raft neck inhibitors. We also have to factor in quality of life as well with some of these side effects. And then whether or not all of this is and what we’re doing makes any impact in terms of how long people live, which is our ultimate endpoint. We have some interesting upcoming clinical trials here that many of you might have heard in the news. We will be opening the phase three portion of our personalized mRNA.
vaccine for Merck in combination with pembrolizumab that has been shown to reduce further the recurrence risk. In high risk melanomas. And so that it will be something that would be opening up in the next few months. And we also have additional trials of antitigit antibodies in the adjuvant setting as well. So really potentially interesting clinical trials coming down the pipeline. Next I'll take over from here and we'll talk about another case. This is a 73 year old male presented who with a left sided cervical lymphadenopathy.
A CAT scan of the neck was ordered to further work this up and it showed 4 enlarged centrally necrotic lymphadenopathies lymph nodes. Biopsy of the left scalp lesion revealed a Melanoma. An ultrasound guided biopsy of the left cervical node was positive for metastatic Melanoma. He subsequently underwent white local excision of the left parietal scalp lesion and the patch revealed metanoma and cyto and scar with negative margins. Left neck lymph nodes were excised and three out of 10 are positive.
for metastatic Melanoma.

Next line he subsequently presented to ER with generalized abdominal pain, nausea, vomiting and diarrhea for three days.

The CT of the other men and pelvis show liver metastasis, peritoneal carcinomatosis and bowel obstruction with antisusception and mass of the transition point.

He underwent surgery ilial bowel resuction of metastatic Melanoma and anastomosis.

Subsequently he developed symptoms of dizziness.

MRI of the brain performed showed 49 to predatorial and
00:35:29.155 --> 00:35:31.127 14 in predorial lesions.

00:35:33.860 --> 00:35:34.499 Next time I'll

00:35:37.060 --> 00:35:38.100 turn it to my colleague.

00:35:39.220 --> 00:35:41.825 Thank you, Flora. So when we

00:35:41.825 --> 00:35:43.653 talk about metastatic Melanoma,

00:35:43.660 --> 00:35:46.579 people generally feel, oh, it’s stage 4,

00:35:46.580 --> 00:35:48.112 we’re actually within the last 20 years,

00:35:48.112 --> 00:36:01.252 the paradigm for how we think about.

00:36:01.260 --> 00:36:03.690 Stage 4 disease, historically 5

00:36:03.690 --> 00:36:06.780 year survival has been very dismal,

00:36:06.780 --> 00:36:10.049 but that is ongoing in terms of
00:36:10.049 --> 00:36:12.979 improvements within the last few decades.

NOTE Confidence: 0.915252465714286

00:36:12.980 --> 00:36:16.283 So in the middle here we have sort of

NOTE Confidence: 0.915252465714286

00:36:16.283 --> 00:36:20.056 an outline of the recent drug approvals

NOTE Confidence: 0.915252465714286

00:36:20.060 --> 00:36:22.900 that include now immune therapy,

NOTE Confidence: 0.915252465714286

00:36:22.900 --> 00:36:25.900 combinations of immune therapy in the

NOTE Confidence: 0.915252465714286

00:36:25.900 --> 00:36:28.560 systemic setting for metastatic disease.

NOTE Confidence: 0.915252465714286

00:36:28.560 --> 00:36:30.786 Which is which are all labeled

NOTE Confidence: 0.915252465714286

00:36:30.786 --> 00:36:33.040 above the the timeline bar there.

NOTE Confidence: 0.915252465714286

00:36:33.040 --> 00:36:36.262 And to even add on to this and give

NOTE Confidence: 0.915252465714286

00:36:36.262 --> 00:36:39.444 give a quick update within the last

NOTE Confidence: 0.915252465714286

00:36:39.444 --> 00:36:41.554 year two additional new treatments

NOTE Confidence: 0.915252465714286

00:36:41.554 --> 00:36:44.160 were are also approved as well.

NOTE Confidence: 0.915252465714286

00:36:44.160 --> 00:36:46.920 So when we talk about metastatic

NOTE Confidence: 0.915252465714286

00:36:46.920 --> 00:36:48.760 Melanoma combinations of the

NOTE Confidence: 0.915252465714286

00:36:48.841 --> 00:36:52.147 Lumumab and Volumeab are now having

NOTE Confidence: 0.915252465714286

00:36:52.147 --> 00:36:53.800 demonstrated objective responses
rate response rates of around 58%. Which is astounding. So this means patients that respond have stable disease or even complete responses as well. There are multiple treatment options that we can try for these individuals, some of them more tailored to certain subtypes of Melanoma such as UVL melanomas, but overall, really kind of changing the paradigm here. When we talk about immune therapy, which is intravenous versus targeted therapy, which is oral, really the individuals that can only
benefit from the targeted therapies are

And so that’s only a smaller subset of individuals.

And when we talk about sort of what is the correct sequence of therapies,

And we now know that frontline immune therapy is superior to targeted therapy in terms of multiple factors including overall survival, progression free survival and the duration of response to treatment as well.
cause multiple different types of immune related toxicities, which my colleague Dr. Kluger will detail for us now. Thank you Doctor Tran. So everything comes with the price unfortunately. So these immune therapies are wonderful in that not only do they induce response, but these response can be durable and last for many, many years. We have many patients who are alive and well over a decade after stopping the immunotherapy. The other advantage to the immuno?
Therapies that you can treat for a certain period of time and then stop, they’re not on continuous therapy, but the price to pay is the immune related adverse events.

So if you think about the mechanism by which these drugs work, it’s not really specifically targeting the cancer cells. So we stimulate the immune system in a nonspecific way, but we also have T cells that recognize our normal organs that are quiescent. By various mechanisms and they are, they remain that way during our
our lifetime but they live as resident memory cells. So these cells actually live in almost all organs in our body. And when we inhibit the breaks on these cells with immunotherapies that we administer, you then can get inflammation in almost any organ in the body. The common ones are the hormonal side effects, colitis and respiratory problems. Now some of them are quite reversible with very responsive to immune suppression.
specifically steroids and sometimes they resolve quite quickly when we give steroids, others may remain permanent.

So for reasons that we still don’t quite understand the endocrine toxicities are never reversible.

Diabetes or type one diabetes can be fulminant, less than 1% but very difficult to control and certainly a life altering event.

Hyperpituitism occurs in around 15%, less than 1% but very difficult to control and certainly a life altering event.

And if you think about a patient who might be cured with surgery alone, receiving immunotherapy in the adjuvant...
setting causing pituitary insufficiency
as a lifelong toxicity certainly
can affect them for decades to come.
And these patients are at risk when they
when they get sepsis or undergo surgery.
So if you have any of those in your practice,
please keep in mind that they need stress,
those steroids if they ever get sick.
Sometimes the neurotoxicities and the
cardiac toxicities are also irreversible.
The death rate from the immunotherapy
is quite a bit less than 1%,
but sadly we’ve all had a death
and it’s something that does occur
regardless of how careful we are.
The other problem that we have is that we have no means by which we can predict who’s going to develop the toxicities and who won’t. There are a number of immune suppression approaches that we use. They listed over here on the right primarily steroids, but I think this field is undergoing rapid evolution and I believe that in the next 5 to 10 years we’ll be using an array of different immune suppressants that might be more specific. To the the resident memory cells rather than the anti cancer immune cells.
So more to come on that as we go as we proceed into the next decade.

Next slide please.

So the next question is what do we do about patients who have underlying autoimmune disorders.

So I think all primary care folks have many patients in their practice who carry a diagnosis of RA, Polymyalgia, Rheumatica and the like. Disease can possibly burn out with time. But we have been successful in treating...
some of these patients with immune therapy.

It’s often challenging to pay extra attention to these folks, but certainly if they have an underlying autoimmunity that’s not life threatening, the immunotherapy can be administered quite safely.

I do specifically want to draw your attention to inflammatory bowel disease because it’s increasing in incidence and that is actually particularly challenging for us because patients actually can die of bowel perforation if we’re not careful. It doesn’t mean we can’t do it.
We can give therapies that are active specifically in the bowel such as veto lizumab and sometimes we are very successful with that and can induce a long term cancer remission. So lastly, but certainly not least, brain metastases in Melanoma is a big problem for us. Approximately half of our patients who have metastatic disease develop brain metastases at some point in the course of their illness and they can sometimes present with brain metastases as the first site of metastatic disease.
So they’ll present with headaches, neurologic problems, et cetera. The tip off is that the headache is worse when they lie down. It gets better over the course of the day. The headaches can be severe as the tumor grows. One can have a Mass Effect midline shift and the one thing that Melanoma brain metastases. Unfortunately, do is is hemorrhage. So other than many other tumor types, these are more prone to hemorrhage. And there’s a lot of Peri lesional
00:43:30.794 --> 00:43:32.450 edema around these lesions,
00:43:32.450 --> 00:43:34.410 possibly more than in other tumor types.
00:43:34.410 --> 00:43:36.423 And it’s the edema itself that can
00:43:36.423 --> 00:43:38.815 actually cause problems and actually
00:43:38.815 --> 00:43:41.160 Doctor Tran has done a lot of.
00:43:41.160 --> 00:43:44.358 Research on this topic in particular,
00:43:44.360 --> 00:43:46.400 there are better treatments available.
00:43:46.400 --> 00:43:48.260 We’ve got effective systemic
00:43:48.260 --> 00:43:50.120 therapies for brain metastases.
00:43:50.120 --> 00:43:52.120 We believe that immune therapies,
00:43:52.120 --> 00:43:54.517 they’re going to work in the brain as well.
00:43:54.517 --> 00:43:57.432 But sometimes we have complications such as
00:43:57.432 --> 00:44:00.300 the edema and resultant symptoms from that.
00:44:00.300 --> 00:44:02.325 These lesions can be Gamma
Knife with radiation therapy, or they can simply be treated with systemic therapy. We tailor individual treatment plans to all of these patients because brain metastases are not alike. Some patients may have one big one, while others, well, they can have many small ones. Some have hemorrhagic lesions, some have lesions that cause a lot of edema. So this arena as well is an area of very active research at Yale. I’m going to turn it back to Doctor Tran to talk about the conclusions and the major takeaways.
So I think Doctor Kluwe, you highlighted on a lot of these and very important side effects that it would be important for our primary care colleagues to know about. We are typically very aggressive about treating these individuals metastatic melanoma with immune therapies. Sometimes we do seem like we push them to be able to receive. Their treatments only because we know based on experience that if they’re able to attain a response, that response can be profound and longlasting.
But unfortunately what happens during the course of the treatment is a lot of lifelong toxicities can develop which we need our primary care colleagues to be aware of and to have a low threshold about helping us to co-manage them. So things like adrenal insufficiency in patients who are presenting with URI symptoms, they need to be stressed, dosed and sometimes we can avert hospital admissions if the patient and the primary care physician are aware of this potential side effect also as Doctor Kluber alluded to.
00:45:47.500 --> 00:45:48.745 you know diabetes.

00:45:48.745 --> 00:45:51.235 These type one diabetes that can develop on immune therapy are very life changing and require multidisciplinary care with endocrinology and primary care to help manage thyroiditis is sometimes one of the side effects that we can see that perceives hypothyroidism in these patients depending on how frequently we check the the TSH levels.

00:46:17.614 Facts that as a primary care physician, if you have a patient that you know is on immune therapy presenting with extreme fatigue,
one check for the endocrine potential

side effects but also make sure that they aren’t having myocarditis too.

If you know or you suspect our toxicity, please let us know.

Reach out to us, we’re happy to be involved.

We don’t expect primary care to manage the toxicities acutely,

but just letting us know how helps us to determine what treatment,

you know,

is indicated for the individual toxicities at hand.

And a lot of the times even though patients may develop a toxicity,

it’s actually might be a good sign
that maybe their immune system is being activated and potentially will produce the anti Melanoma response.

So we’ve seen correlations between very severe toxicity toxicities and very good responses in our patients.

So in terms of treatment assessments, so going back to the case in hand, this gentleman who Doctor Lena and I treated with metastatic Melanoma. He was treated with a combination of ipilumab and uvalumab. And after the first four cycles, so looking at his scans, pretreatment on the left and then...
00:47:34.448 --> 00:47:36.630 on treatment after four cycles,
NOTE Confidence: 0.87098536
00:47:36.630 --> 00:47:38.740 there is a dramatic improvement
NOTE Confidence: 0.87098536
00:47:38.740 --> 00:47:40.998 in disease tumor burden both in
NOTE Confidence: 0.87098536
00:47:40.998 --> 00:47:43.110 the brain and in the body.
NOTE Confidence: 0.87098536
00:47:43.110 --> 00:47:45.182 Typically with immune therapies
NOTE Confidence: 0.87098536
00:47:45.182 --> 00:47:47.254 these responses are concordant
NOTE Confidence: 0.87098536
00:47:47.254 --> 00:47:49.633 because these are known to be
NOTE Confidence: 0.87098536
00:47:49.633 --> 00:47:51.608 brain active treatments as well.
NOTE Confidence: 0.87098536
00:47:51.608 --> 00:47:52.946 Early on though,
NOTE Confidence: 0.87098536
00:47:52.950 --> 00:47:55.086 if you do happen to come across a
NOTE Confidence: 0.87098536
00:47:55.086 --> 00:47:57.467 scan for a patient on immune therapy,
NOTE Confidence: 0.885067921538462
00:47:57.470 --> 00:47:59.695 just be wary that pseudoprogression
NOTE Confidence: 0.885067921538462
00:47:59.695 --> 00:48:02.659 can exist in these patients on early
NOTE Confidence: 0.885067921538462
00:48:02.659 --> 00:48:05.015 scans whereby the tumors may look
NOTE Confidence: 0.885067921538462
00:48:05.015 --> 00:48:07.682 bigger on imaging, but actually not
NOTE Confidence: 0.885067921538462
00:48:07.682 --> 00:48:10.586 be a full real tumor progression,
but actually just radiographing enlargement from the infiltration of activated immune cells. Clinically, we can sometimes determine pseudo progression because the patient otherwise is doing well, they don’t have any symptoms and if the degree of enhancement is not significant, then sometimes we will push these patients continue treatment and then confirm with restaging later on whether or not they had pseudo progression or true progression. So patients are able to eventually.
complete responses,
NOTE Confidence: 0.885067921538462
basically almost a curative response
NOTE Confidence: 0.885067921538462
to their systemic immune therapy
NOTE Confidence: 0.885067921538462
and sometimes patients are able to
NOTE Confidence: 0.885067921538462
stop and have ongoing responses
NOTE Confidence: 0.9402536
next. So just to close out the
NOTE Confidence: 0.9402536
take away points from today's
NOTE Confidence: 0.862933094444445
presentation is you know
NOTE Confidence: 0.862933094444445
early detection is critical.
NOTE Confidence: 0.862933094444445
And that’s where you know all
NOTE Confidence: 0.862933094444445
hands on deck are appreciated,
NOTE Confidence: 0.862933094444445
primary care’s involvement and
NOTE Confidence: 0.862933094444445
doing ongoing surveillance,
NOTE Confidence: 0.862933094444445
looking at the scar,
NOTE Confidence: 0.862933094444445
checking the patient’s lymph nodes,
NOTE Confidence: 0.862933094444445
assessing for any unusual atypical symptoms.
Because early detection is always important in terms of improving ultimate outcomes, and everyone plays a role in the surveillance. It’s a truly multidisciplinary, multiexpertise kind of approach here. So aggressive upfront Melanoma management and treatment, as we always said, leads to improve outcomes not only for the patient but also to help minimize potential toxicities as well. Fortunately, we’ve lucky enough to work in a field where therapeutics are always improving and we’ve
been at the forefront of helping to push that boundary forward with the ongoing clinical trials here at Yale.

And the number of patients that are living with a history of Melanoma is ever growing and we owe that and thanks to. The drugs but also the close corroboration that we have between or specialty with in Melanoma but also with ongoing primary care physicians too.

That was absolutely terrific. Thank you for all of that. Those who are watching please submit questions using the Q&A because we we do have some time. Left over and you know I just
00:50:45.015 --> 00:50:47.837 have to say as a mature primary care physician that the change in prognosis for advanced Melanoma is one of the most miraculous things I've witnessed clinically. So it is amazing and it’s just nice to hear that whole kind of evolution outlined although not without a price as we as we’ve heard. As we wait for some questions to come in and those who are watching, please do submit questions. Flora, do you have additional questions for our Smilo panelists? So sure, a basic question.
When we are dealing with a patient in the office who we suspected toxicity, what's the shortcut? What's the easiest way and fastest way as well most effective to get in touch with the team caring for this patient.

So we have one phone number that's 203-200-6622. Someone answers that phone 24/7 during work hours. They can send a message in my chart. It goes straight to our nursing pool, but depending on the urgency,
they may decide to call.
And whether they seen in Guildford or in New Haven, they the phone calls for urgent issues such as that would come into New Haven. Thank you. And I'll just add on to that. When we have somebody, you know, with a skin lesion in primary care, we have ones that are like we can't really tell you it's normal. And then we have ones that like look like they might be a problem and then they have ones that that scream at us. This person absolutely needs this remove.
Right away and delaying care is not good.

You know within the kind of Yale system, what are some of the most efficient ways that we can kind of help to navigate and refer those type of people.

Sure. I can take this one.

Well, I think you know we have many dermatology services outpatient all all throughout New Haven and Brantford and Middlebury.

I think putting in an urgent referral. We're really worried about this one. A lot of primary care doctors will send me an epic and basket message.
Can you please get this patient in soon with you or a colleague, we're really worried about this one. I think that sort of triage is is helpful. We also have telemedicine to look for urgent lesions, but I'm more of a proponent of seeing the patient in person to examine it. So we can use a dermatoscope and biopsy and then doctors are power actually alerted me as to these. Little things I use them in the garden. When I see a weed or something that I think might be a weed or maybe the plant I planted last year and forgot about,
I use this identify thing and it tells me exactly what the plant is. Is there a software that can help us? You know, there’s a lot of new technology and iPhone apps. I think a lot of these aren’t really validated and I don’t think anything beats right now seeing a dermatologist for any evaluation, perhaps 1. Technology, we’ll get there. So immunotherapy first, technology second. So we do have a couple of questions that have come in. I’m not sure has asked when should a
PCP perform biopsy and when they when
should they refer to a dermatologist.
Now not all of our Pcp’s do biopsy,
but if it’s within the skill set what,
what do you think
so? I’m aware that you know,
primary care physicians,
certainly you know some do biopsy.
I think if you’re going to
biopsy a pigmented lesion,
it’s really important to be sure
that you sample the lesion
in its entirety because if you
only sample a small portion of it,
you might miss the Melanoma.
Further, if it is a Melanoma, but you transect it, you really won’t have an accurate stage of the true Breslow depth. I would say if it’s something that you’ve been trained in and you’re capable of doing do so. But in general, you know this is kind of what bread and butter dermatology is and we’re very happy to see those patients. And another question from Dr. Allard, what are your Melanoma screening recommendations by age despite the USPTF not recommending annual screening? Another
really good question.

I think a lot of it comes to those risk factors that I alluded to.

I don’t think somebody who has few nevi darker skin, no personal or family history needs to be screened.

If you see someone even at a young age who has a strong family history, has a lot of nevi and in particular has a lesion of concern, I think that’s the key.

If there’s a lesion of concern, that’s an automatic should be evaluated.

Those screening guidelines don’t apply to a concerning lesion.
00:56:04.410 --> 00:56:06.132 I think if it’s a young child
NOTE Confidence: 0.93857646
00:56:06.132 --> 00:56:07.968 who maybe has a parent or grant,
NOTE Confidence: 0.93857646
00:56:07.970 --> 00:56:09.400 you know, with Melanoma but
NOTE Confidence: 0.93857646
00:56:09.400 --> 00:56:11.250 certainly is a primary care doctor,
NOTE Confidence: 0.93857646
00:56:11.250 --> 00:56:12.850 you don’t see anything concerning.
NOTE Confidence: 0.93857646
00:56:12.850 --> 00:56:14.770 I don’t think it’s urgent to
NOTE Confidence: 0.93857646
00:56:14.770 --> 00:56:16.610 have that that child screened
NOTE Confidence: 0.936899133333334
00:56:20.770 --> 00:56:24.546 well. That’s the end of our questions that
NOTE Confidence: 0.936899133333334
00:56:24.546 --> 00:56:28.494 have come in and also the end of our hour.
NOTE Confidence: 0.936899133333334
00:56:28.500 --> 00:56:30.140 So again, I, you know,
NOTE Confidence: 0.936899133333334
00:56:30.140 --> 00:56:33.020 each of you spent time to prepare for this.
NOTE Confidence: 0.936899133333334
00:56:33.020 --> 00:56:35.548 It was just so well delivered and full
NOTE Confidence: 0.936899133333334
00:56:35.548 --> 00:56:37.616 of information that I think is really,
NOTE Confidence: 0.936899133333334
00:56:37.620 --> 00:56:41.213 really helpful. So these connections,
NOTE Confidence: 0.936899133333334
00:56:41.213 --> 00:56:43.497 these moments are valuable
NOTE Confidence: 0.936899133333334
00:56:43.500 --> 00:56:44.977 and and I thank you for that.
And I thank you to those who took time to listen despite a very bad, awful, horrible IT day here at the health system because we know it took special effort to get here.

And encourage your friends to watch the recording, which we’ll also send out.

Good. Thank you all.