0:00:00 –> 0:00:03.822 Support for Yale Cancer Answers comes from AstraZeneca,

0:00:03.822 –> 0:00:14.17 the Beyond Pink campaign aims to empower metastatic breast cancer patients and their loved ones to learn more about their diagnosis and make informed decisions.

0:00:14.17 –> 0:00:17.879 Learn more at lifebeyondpink.com.

0:00:17.879 –> 0:00:20.55 Welcome to Yale Cancer Answers with your host

0:00:20.55 –> 0:00:21.969 Doctor Anees Chagpar.

0:00:21.969 –> 0:00:31.855 Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week

0:00:31.855 –> 0:00:36.057 it's a conversation about Melanoma research with doctor Jeffrey Ishizuka.

0:00:36.057 –> 0:00:41.341 Doctor Ishizuka is an Assistant Professor of Medical Oncology at Yale School of Medicine,

0:00:41.341 –> 0:00:45.909 where Doctor Chagpar is a Professor of Surgical Oncology.

0:00:45.909 –> 0:00:51.234 Jeff, maybe we could start off by you telling us a little bit about yourself and what you do.

0:00:51.234 –> 0:00:59.524 I'm a physician-scientist and that means that I spend part of my time treating cancer patients and part of my time in the lab looking

0:00:59.524 –> 0:01:02.189 for new treatments for those patients.

0:01:02.189 –> 0:01:09.043 And so tell us a little bit more about the kinds of patients that you treat and the kinds of research that you do.

0:01:09.043 –> 0:01:12.381 I see Melanoma patients and I'm an immunologist

0:01:12.381 –> 0:01:15.956 by training. And that means I study ways to

0:01:15.956 –> 0:01:19.174 make the patient's immune system work better,

0:01:19.174 –> 0:01:22.153 to attack the cancer.

0:01:22.153 –> 0:01:26.861 Tell us more about that, we've talked on the show a little bit about immunotherapy and so on,

0:01:26.861 –> 0:01:31.808 but tell us a little bit more about the broad spectrum of immunotherapy.

0:01:31.808 –> 0:01:35.575 How exactly does it work and then the role that it plays in Melanoma.

0:01:35.575 –> 0:01:38.382 There are a couple of types of immunotherapy.

0:01:38.382 –> 0:01:43.078 And for a long time we knew that the immune system had the potential to control cancer,

0:01:43.078 –> 0:01:46.906 but I'd say the two big advances that are more recent are on the one hand,

0:01:46.906 –> 0:01:54.662 CAR T cells. And those are cells that are taken out of the patients body and reprogrammed to go back in and attack the tumor, and immune checkpoint

0:01:54.662 –> 0:01:58.337 blockade. And these are drugs that cut the brakes on the immune system.

0:01:58.337 –> 0:02:02.114 Those brakes stop the immune system from attacking the cancer.

0:02:02.114 –> 0:02:03.644 And when you get rid of them,

0:02:03.644 –> 0:02:08.692 the cancer is vulnerable to immune attack.

0:02:08.692 –> 0:02:12.393 Tell us about which of these you work on, and

0:02:12.393 –> 0:02:15.5 how exactly they work in Melanoma.

0:02:15.5 –> 0:02:22.02 In Melanoma, immune checkpoint blockade has really been one of the biggest developments

0:02:22.02 –> 0:02:26.522 really in the last, well maybe ever in the disease.

0:02:26.522 –> 0:02:31.093 And I think Melanoma was the first disease where

0:02:31.093 –> 0:02:37.52 these drugs were developed and remains one of the ones where they work the best.

0:02:38.639 –> 0:02:41.776 Can you talk about this immune checkpoint blockade.

0:02:41.776 –> 0:02:45.025 Is there more than one molecule that needs to be blocked?

0:02:45.025 –> 0:02:49.169 How does that work? Why does the immune system have brakes to begin with?

0:02:49.169 –> 0:02:54.323 These are great questions and they're really at the forefront of the field right now,

0:02:54.323 –> 0:02:58.132 so there are certainly at least a few molecules that are important.

0:02:58.132 –> 0:03:02.221 And all of the ones we learned about first are on the surface of T cells,

0:03:02.221 –> 0:03:07.205 which we know are one of the important cells for controlling cancer.

0:03:07.205 –> 0:03:09.669 There are a number of molecules that target

0:03:09.669 –> 0:03:13.354 PD-L1 and that's a major inhibitory pathway in the T cells,

0:03:13.354 –> 0:03:15.453 and also molecules that target CTL A4,

0:03:15.453 –> 0:03:18.174 which is another inhibitory pathway in T cells.

0:03:18.174 –> 0:03:25.318 And what we learned is when you block either one of these and sometimes if you block them both together it works even better.

0:03:25.318 –> 0:03:28.378 The T cells can get supercharged to attack the cancer.

0:03:28.378 –> 0:03:30.039 Why is it that

0:03:30.039 –> 0:03:32.086 they have breaks to begin with?

0:03:32.086 –> 0:03:38.991 The immune system is supposed to be able to identify foreign stuff in our bodies and get rid of it.

0:03:38.991 –> 0:03:41.996 So why doesn't that work in cancer?

0:03:41.996 –> 0:03:45.128 Why is it that we need to take off these brakes?

0:03:45.128 –> 0:03:47.622 Why do they have breaks to begin with?

0:03:47.622 –> 0:03:51.651 This is the foundational question of immunology,

0:03:51.651 –> 0:03:54.527 the distinction between self and nonself.

0:03:54.527 –> 0:03:59.387 All cells need to be able to get rid of foreign things just as you said,

0:03:59.387 –> 0:04:00.729 but at the same time

0:04:00.729 –> 0:04:09.909 they need to have mechanisms to avoid attacking the normal cells in the body that are healthy and so

0:04:09.909 –> 0:04:15.647 why is it that the immune system thinks that these cancer cells are normal?

0:04:15.647 –> 0:04:26.511 I think it's really because cancer cells arise from normal cells as normal cells become dysregulated as they acquire genetic errors called mutations.

0:04:26.511 –> 0:04:29.175 And eventually you develop cancer.

0:04:29.175 –> 0:04:33.819 And because the cancer cell arises from a backdrop of normal cells,

0:04:33.819 –> 0:04:40.72 doing normal cell things, the immune system has to find specific signals of damage or mutations that

0:04:40.72 –> 0:04:43.007 look abnormal in order to recognize cancer.

0:04:43.007 –> 0:04:46.233 So you're telling me that normally it won't do that?

0:04:48.156 –> 0:04:54.451 Some tumors are recognized by the immune system and the immune system can actually get rid of them,

0:04:54.451 –> 0:05:02.615 and other aren't. And really what we're trying to understand and at the heart of the field is how can we take tumors that are not well recognized by

0:05:02.615 –> 0:05:07.141 the immune system and turn them into tumors that the immune system can see and destroy?

0:05:07.141 –> 0:05:10.75 And so it seems to me that if you take that problem just at its face,

0:05:10.75 –> 0:05:13.264 there are two ways of doing that.

0:05:13.264 –> 0:05:18.617 One is to make the tumor look more abnormal so that the immune system

0:05:18.617 –> 0:05:27.904 realizes, I need to attack it and get rid of it without actually revving up the immune system or getting rid of the

0:05:27.904 –> 0:05:36.675 brakes and the other is to supercharge the immune system as you put it to make it more sensitive to recognizing what might be abnormal.

0:05:36.675 –> 0:05:41.899 Yeah, that's right, and I think people are working at both sides of that problem.

0:05:41.899 –> 0:05:49.271 We and others in the lab, are thinking of strategies both to make tumors put out signs for the immune system, saying,

0:05:49.271 –> 0:05:55.995 come get me and also looking for new ways to charge the immune system to be more aggressive against cancer.

0:05:55.995 –> 0:05:57.94 Tell us more about the first,

0:05:57.94 –> 0:06:04.721 because I think that we've heard a little bit about checkpoint inhibitors,

0:06:04.721 –> 0:06:11.267 but we really haven't heard a lot about the work that's going on to have tumor cells put out those signs that

0:06:11.267 –> 0:06:22.262 say, come get me. And it seems to me that might be a way to allow the immune system without getting supercharged to eat up or

0:06:22.262 –> 0:06:24.663 get rid of these cancer cells,

0:06:24.663 –> 0:06:26.91 because one of the problems,

0:06:26.91 –> 0:06:35.04 as you point out, of having a supercharged immune system is that it can then attack its own cells.

0:06:35.04 –> 0:06:37.966 Yeah, that's a great point and

0:06:37.966 –> 0:06:42.72 we've been thinking, and others as well,

0:06:42.72 –> 0:06:49.041 that it comes down to tricking the tumor cell into making inflammatory signals,

0:06:49.041 –> 0:06:56.002 tricking it into making kind of an antiviral response that recruits anti tumor immune cells into the micro environment,

0:06:56.002 –> 0:06:57.336 and I think

0:06:57.336 –> 0:07:06.963 you can go about that by infecting the tumor with a virus or making it think it's infected with a virus or triggering certain danger signals in the micro environment

0:07:06.963 –> 0:07:10.675 directly around the tumor.

0:07:10.675 –> 0:07:15.61 Tell us more about that work, is that actually something that's being done?

0:07:15.61 –> 0:07:19.267 Is it in clinical practice?

0:07:19.267 –> 0:07:20.778 How do we do that?

0:07:20.778 –> 0:07:29.605 There are a number of clinical trials now using stimulators of viral pathways that look like DNA or RNA,

0:07:29.605 –> 0:07:36.523 things that viruses make and that ourselves have dedicated sensors in order to detect,

0:07:36.523 –> 0:07:42.485 and I think none of them has proven to be the Magic bullet for cancer yet.

0:07:42.485 –> 0:07:46.779 But there are still some technical hurdles to workout.

0:07:46.779 –> 0:07:49.764 And I think we're getting there though.

0:07:49.764 –> 0:07:56.178 Why has that not proven to be as successful as supercharging the immune system?

0:07:56.178 –> 0:08:03.264 I think one of the challenges is that cancer in many cases can spread to many locations,

0:08:03.264 –> 0:08:09.158 and when you think about triggering an inflammatory response in the tumor bed,

0:08:09.158 –> 0:08:12.439 you're really thinking about triggering it,

0:08:12.439 –> 0:08:14.081 not just at one site,

0:08:14.081 –> 0:08:16.394 but at many sites all at once,

0:08:16.394 –> 0:08:18.93 and so finding ways to send drugs

0:08:18.93 –> 0:08:26.41 to all of the different sites that cancer occupies in the body is one of the major challenges to getting this approach to work.

0:08:26.41 –> 0:08:33.524 The other approach then is the one that is the mainstay of immunotherapy,

0:08:33.524 –> 0:08:38.844 which is to quote supercharge the immune system to get rid of the blocks.

0:08:38.844 –> 0:08:43.157 I always think of it like Harry Potters invisibility cloak,

0:08:43.157 –> 0:08:48.403 right. The tumor has kind of made itself invisible to the immune system,

0:08:48.403 –> 0:08:57.1 and it's getting rid of that that cloak and getting the immune system to recognize it and to go after it and two,

0:08:57.1 –> 0:08:59.63 to be quote supercharged now.

0:08:59.63 –> 0:09:09.755 You mentioned two molecules, in particular CTL A4 and PDL1, tell us a little bit about the differences between the two.

0:09:09.755 –> 0:09:14.227 I mean we have drugs that will block either pathway.

0:09:14.227 –> 0:09:17.602 How do you figure out which one to use?

0:09:17.602 –> 0:09:20.556 Tell us more about that interplay.

0:09:20.556 –> 0:09:29.019 I think we still don't fully understand the mechanism of either drug and either pathway.

0:09:29.019 –> 0:09:32.062 And people have done a lot of good work,

0:09:32.062 –> 0:09:36.102 in fact, the Nobel Prize was awarded a few years back for some of that work,

0:09:36.102 –> 0:09:39.042 but I wouldn't say that we completely understand which,

0:09:39.042 –> 0:09:41.508 even sometimes which cells are being targeted,

0:09:41.508 –> 0:09:44.918 but certainly which pathways within the cell are being activated.

0:09:44.918 –> 0:09:47.961 So a lot of how we figured this out has been empirically.

0:09:47.961 –> 0:09:52.369 We've done clinical trials with different drugs or different combinations of drugs,

0:09:52.369 –> 0:09:55.044 and we've seen what's been effective for patients,

0:09:55.044 –> 0:09:59.085 and the hope is going forward that as we learn more about the immune system,

0:09:59.085 –> 0:10:04.15 and as we learn more about the tumor that we will be able to do better

0:10:04.15 –> 0:10:09.876 and even predict the next set of these drugs that could be usefully combined.

0:10:09.876 –> 0:10:14.153 So tell us more about the differences between CTLA for an PDL1.

0:10:14.153 –> 0:10:24.486 I get the fact that we've discovered these kind of fortuitously and empirically and have just made drugs that affect each of these pathways,

0:10:24.486 –> 0:10:26.264 and seeing that they work.

0:10:26.264 –> 0:10:29.62 But we must know more about these actual molecules.

0:10:29.62 –> 0:10:33.971 Yeah, they both play an inhibitory role in T cells.

0:10:33.971 –> 0:10:37.22 I think it's broadly thought

0:10:37.22 –> 0:10:42.621 that one of them plays more of a role in T cells initially getting primed against the tumor,

0:10:42.621 –> 0:10:52.032 but maybe plays more of a role in lymph nodes then generating the T cells that are capable of responding whereas the other one,

0:10:52.032 –> 0:11:01.325 that speedy one may play more of a role in activating the T cells that are already primed against the tumor that already have the capacity to attack the tumor.

0:11:01.325 –> 0:11:08.47 And I'm going to steer clear of the term of exhaustion because there are a lot of debates about whether T cells

0:11:08.47 –> 0:11:10.476 are actually exhausted or not,

0:11:10.476 –> 0:11:20.903 but there's this idea that T cells can, after seeing a lot of tumor antigen stop responding very well that they can become dysfunctional and so one

0:11:20.903 –> 0:11:23.557 of the things that PDL1 blockade does,

0:11:27.12 –> 0:11:31.986 is to make the T cells that have become dysfunctional more functional.

0:11:31.986 –> 0:11:35.62 And so if these two pathways then are complementary,

0:11:35.62 –> 0:11:42.269 one being more so for priming T cells and one being more so for T cells that are already primed,

0:11:42.269 –> 0:11:53.511 has there been any work looking into either concurrent therapy or sequential therapy of different immuno therapies that might work better than either in isolation?

0:11:53.511 –> 0:11:56.664 There has, and in Melanoma combining two drugs,

0:11:56.664 –> 0:11:58.309 one that targets CTL A4.

0:11:58.309 –> 0:12:07.804 and one that targets PDL1 seems to be better than using either drug alone and potentially better than using them both in sequence,

0:12:07.804 –> 0:12:17.014 although the latter is a less clear conclusion.

0:12:17.014 –> 0:12:27.578 And one of the exciting things in this field has been seeing the slew of approvals for immuno therapies in different cancer types in Melanoma.

0:12:27.578 –> 0:12:39.287 Certainly it's become standard of care in the frontline for most patients and it's being explored in basically every stage of care of the disease other than for disease that

0:12:39.287 –> 0:12:45.355 can just be removed and surgically cut out in the early stages and really beyond Melanoma,

0:12:45.355 –> 0:12:53.691 it spread throughout many many solid tumor types and it's being tried in almost any tumor type you can think of.

0:12:53.691 –> 0:13:00.36 And so two questions. First question is one of the things you mentioned earlier as being one of the

0:13:00.36 –> 0:13:08.214 downfalls of some therapies is that it can't always get to all of the cells where the tumors may be hiding.

0:13:08.214 –> 0:13:16.735 Does immunotherapy have that problem in terms of getting to the T cells and activating them or supercharging them?

0:13:16.735 –> 0:13:21.847 Or is that concept, this may not work if there's a tumor,

0:13:21.847 –> 0:13:23.774 for example in the brain?

0:13:23.774 –> 0:13:27.85 Because this drug can't cross the blood brain barrier?

0:13:27.85 –> 0:13:31.5 Or does it affect T cells wherever they are?

0:13:31.5 –> 0:13:38.47 We know that we can get effects certainly in the brain.

0:13:38.47 –> 0:13:51.299 So you can see effects of these drugs in what are thought of usually as sites of the body that are hard to get to or immune privilege sites but

0:13:51.299 –> 0:13:53.327 I guess what I don't know for sure,

0:13:53.327 –> 0:13:58.621 it's hard to say is whether there is a problem activating immune cells somewhere in the body.

0:13:58.621 –> 0:14:07.352 That is to say, whether we're getting these drugs as effectively as possible to all the immune cells that might be able to be mobilize against the tumor.

0:14:07.352 –> 0:14:14.505 We're going to learn a lot more about Melanoma immunotherapy right after we take a short break for a medical minute.

0:14:14.505 –> 0:14:22.73 Please stay tuned to learn more about this research with my guest doctor Jeffrey Ishizuka. Support for Yale Cancer Answers comes from AstraZeneca.

0:14:22.73 –> 0:14:28.499 Providing important treatment options for patients with different types of lung,

0:14:28.499 –> 0:14:31.631 bladder, ovarian, breast, and blood cancers.

0:14:31.631 –> 0:14:35.57 More information at astrazeneca-us.com.

0:14:35.57 –> 0:14:38.466 This is a medical minute about breast cancer,

0:14:38.466 –> 0:14:41.866 the most common cancer in women. In Connecticut alone,

0:14:41.866 –> 0:14:46.462 approximately 3000 women will be diagnosed with breast cancer this year,

0:14:46.462 –> 0:14:48.541 but thanks to earlier detection,

0:14:48.541 –> 0:14:51.312 noninvasive treatments, an novel therapies,

0:14:51.312 –> 0:14:56.159 there are more options for patients to fight breast cancer than ever before.

0:14:56.159 –> 0:15:04.408 Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast cancer.

0:15:04.408 –> 0:15:10.58 Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly

0:15:10.58 –> 0:15:17.62 reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety

0:15:17.62 –> 0:15:22.706 many women experience. More information is available at yalecancercenter.org.

0:15:22.706 –> 0:15:26.84 You're listening to Connecticut public radio.

0:15:26.84 –> 0:15:29.259 Welcome back to Yale Cancer Answers.

0:15:29.259 –> 0:15:35.341 This is doctor Anees Chagpar andnI'm joined tonight by my guest doctor Jeffrey Ishizuka.

0:15:35.341 –> 0:15:41.226 We're talking about Melanoma research and in particular we're talking about immunotherapy.

0:15:41.226 –> 0:15:47.374 Jeff, right before the break we were talking a little bit about immunotherapy in terms of,

0:15:47.374 –> 0:15:51.754 really getting the immune system to attack cancer cells,

0:15:51.754 –> 0:15:55.024 which it may not recognize because as you put it,

0:15:55.024 –> 0:15:58.36 these cancer cells come from normal cells and that

0:15:58.36 –> 0:16:07.715 may not be as foreign looking to the immune system to really trigger it and we talked a little bit about two separate pathways,

0:16:07.715 –> 0:16:11.692 CTL A4 and PDL1 and the fact that we now have drugs,

0:16:11.692 –> 0:16:20.974 this explosion of drugs in immunotherapy targeting these two pathways and how this really has become the mainstay of therapy,

0:16:20.974 –> 0:16:23.921 particularly for cancers like Melanoma.

0:16:23.921 –> 0:16:27.971 I had a few questions to kind of follow up on that.

0:16:27.971 –> 0:16:32.494 The first is, tell us a little bit about the side effects.

0:16:32.494 –> 0:16:35 We think about

0:16:35 –> 0:16:39.551 chemotherapy, and you know, traditionally,

0:16:39.551 –> 0:16:47.469 chemotherapy was therapy that kills off cancer cells and was really thought to be therapy that switches off

0:16:47.469 –> 0:16:55.184 rapidly dividing cells and so people ended up losing hair and maybe getting sick because it effects your GI lining,

0:16:55.184 –> 0:16:57.711 which are rapidly turning over cells.

0:16:57.711 –> 0:17:01.171 Do you get the same kind of thing in immunotherapy,

0:17:01.171 –> 0:17:05.56 or are there other side effects that are the results of

0:17:05.56 –> 0:17:11.88 kind of supercharging this immune system and getting the immune system to attack healthy cells?

0:17:11.88 –> 0:17:13.54 So I think that's it exactly.

0:17:13.54 –> 0:17:20.13 Many of the side effects that you get from immunotherapy are actually side effects of supercharging the immune system,

0:17:20.13 –> 0:17:24.227 so the immune system can accidentally attack different areas of the body.

0:17:24.227 –> 0:17:27.383 Some of the things we see are inflammation in the lungs,

0:17:27.383 –> 0:17:31.536 inflammation in the GI system we see inflammation of the endocrine system,

0:17:31.536 –> 0:17:34.471 and when we first started seeing these side effects,

0:17:34.471 –> 0:17:37.183 there wasn't a good sense of how you treat them,

0:17:37.183 –> 0:17:39.73 how you manage them, or even how you monitor.

0:17:39.73 –> 0:17:41.89 We didn't really know what to look for.

0:17:41.89 –> 0:17:45.832 But I will say that as experience with these agents has progressed,

0:17:45.832 –> 0:17:49.715 we've gotten better at detecting these side effects as they occur,

0:17:49.715 –> 0:17:56.324 and managing them, usually using immunosuppressives and one of the questions that comes up when you start saying,

0:17:56.324 –> 0:18:02.469 well, you're using drugs to charge the immune system and at the same time to shut down the immune system,

0:18:02.469 –> 0:18:05.772 is that going to be is going to be bad for the patients.

0:18:05.772 –> 0:18:11.221 Are they going to have that outcomes and the data isn't really completely mature on this yet,

0:18:11.221 –> 0:18:14.119 but it certainly appears from the early data that

0:18:14.119 –> 0:18:22.204 you can safely give these immunosuppressives and that you don't at least don't clearly make their responses against the cancer

0:18:22.204 –> 0:18:26.121 worse.

0:18:26.121 –> 0:18:32.183 That's really interesting. Why would that be the case? I can imagine that when we think about people who are immunosuppressed,

0:18:32.183 –> 0:18:37.994 people who for example have HIV or other things that turn off their immune system,

0:18:37.994 –> 0:18:40.773 they are more at risk of developing cancer,

0:18:40.773 –> 0:18:45.321 and I guess for the same reason that you talked about before the break,

0:18:45.321 –> 0:18:47.263 which is your immune system,

0:18:47.263 –> 0:18:55.902 unbeknownst to you, might be getting rid of little cancers that you don't know you have because it recognizes them and it gets rid of them,

0:18:55.902 –> 0:19:01.9 and so if you are immuno compromised you're at increased risk of getting cancer,

0:19:01.9 –> 0:19:04.199 and that's the whole point of

0:19:04.199 –> 0:19:10.65 supercharging the immune system to get rid of these cancers.

0:19:10.65 –> 0:19:21.922 Why is it that giving people an immunosuppresant at the same time as an immuno supercharger doesn't seem to affect the cancer in a bad way?

0:19:21.922 –> 0:19:25.333 A couple of potential thoughts here.

0:19:25.333 –> 0:19:32.23 The first one is that I want to be careful we don't know for sure that it doesn't affect the

0:19:32.23 –> 0:19:34.575 response to therapy in a negative way.

0:19:34.575 –> 0:19:37.099 I think what we can say is that

0:19:37.099 –> 0:19:44.73 at first blush, patients who needed immunosuppressives because they had these bad immune effects and got them didn't do obviously worse,

0:19:44.73 –> 0:19:46.394 at least in the early studies

0:19:46.394 –> 0:19:55.26 then patients who didn't need them in the first place and that actually could be a kind of selection bias issue where the patients who needed the immunosuppressives

0:19:55.26 –> 0:19:58.968 actually were having the strongest immune responses to begin with,

0:19:58.968 –> 0:20:08.329 and so I think we have to do some careful experiments in a controlled setting to see whether it was really true that the immunosuppressives weren't having any effect there.

0:20:08.329 –> 0:20:14.859 And I think that's probably the main thing that I would think about for that issue.

0:20:14.859 –> 0:20:20.846 The other question that I have is, these autoimmune side effects,

0:20:20.846 –> 0:20:26.355 the side effects of people's immune system now attacking their own normal cells,

0:20:26.355 –> 0:20:28.532 are those permanent? Are

0:20:28.532 –> 0:20:37.578 they forever or are they short lived? I mean when you get chemotherapy and you lose your hair,

0:20:37.578 –> 0:20:39.319 your hair will grow back.

0:20:39.319 –> 0:20:44.597 Is it the same with immunotherapy that this is a short term thing?

0:20:44.597 –> 0:20:47.416 Or when your immune system attacks your lungs,

0:20:47.416 –> 0:20:50.776 now you've got pulmonary fibrosis forever?

0:20:50.776 –> 0:20:55.694 I think it depends on the type of immune side effect that we're talking about.

0:20:55.694 –> 0:20:57.013 I think many of them,

0:20:57.013 –> 0:20:59.833 if they're controlled with immunosuppressives,

0:20:59.833 –> 0:21:04.332 and if you take the patient off of the immunotherapy, will actually go away.

0:21:04.332 –> 0:21:06.371 So we see this in a lot of cases,

0:21:06.371 –> 0:21:09.73 inflammation in the colon, or inflammation in the lungs.

0:21:09.73 –> 0:21:16.951 I think the case in which this isn't necessarily true is when the immune system attacks the cell type

0:21:16.951 –> 0:21:26.278 that produces hormones in the body and destroys all of that cell type because in that case you may not really know what's going on until the cell type

0:21:26.278 –> 0:21:30.44 is gone, and after that there's really no bringing it back.

0:21:30.44 –> 0:21:37.403 So in most cases we actually have been able to give hormone replacement.

0:21:37.403 –> 0:21:40.398 It's extremely bad if it's not detected,

0:21:40.398 –> 0:21:45.001 but in a lot of cases it can be solved by giving a pill a day.

0:21:45.001 –> 0:21:47.413 When you talk about hormones,

0:21:47.413 –> 0:21:54.43 are you talking about thyroid are you talking about ovaries, what hormones are we talking about?

0:21:54.43 –> 0:21:57.801 Yeah, so thyroid is one that you certainly see,

0:21:57.801 –> 0:22:05.179 but you see actually a number of other hormones that are produced in the brain that can also be altered,

0:22:05.179 –> 0:22:07.356 and these can be be more rare,

0:22:07.356 –> 0:22:10.449 but can be pretty dramatic if you see them.

0:22:10.449 –> 0:22:14.289 So given the side effects of immunotherapy,

0:22:14.289 –> 0:22:17.953 is immunotherapy really better than classic chemotherapy?

0:22:17.953 –> 0:22:24.209 You had mentioned that immunotherapy has now become standard of care for Melanoma.

0:22:24.209 –> 0:22:26.925 Is it better than what we used to do?

0:22:28.758 –> 0:22:31.474 We used to give chemotherapy for Melanoma,

0:22:31.474 –> 0:22:32.991 right?

0:22:32.991 –> 0:22:36.846 And Melanoma is not particularly responsive to chemotherapy,

0:22:36.846 –> 0:22:41.268 and I think what excited everyone in the field and it's given us all

0:22:41.268 –> 0:22:44.68 a lot of excitement and a lot of hope is not even that

0:22:44.68 –> 0:22:48.277 everyone responds to these immunotherapy's because they don't,

0:22:48.277 –> 0:22:52.444 not enough patients do, and that's something we don't really understand.

0:22:52.444 –> 0:22:54.842 We're trying to understand it in the lab,

0:22:54.842 –> 0:22:59.238 but it's that some of the patients who respond seem to just keep responding,

0:22:59.238 –> 0:23:07.002 and some of them respond so well and for so long that we've actually started to believe that we can take the patients off of the drugs,

0:23:07.002 –> 0:23:10.371 the immunotherapy drugs, and that the cancer won't return.

0:23:10.371 –> 0:23:15.21 And this is true even in some cases for very aggressive disease.

0:23:15.21 –> 0:23:19.686 And so seeing those effects are the ones that have really made everybody excited.

0:23:19.686 –> 0:23:26.73 And you see that in clinical trials when we study how patients survive on different drugs and

0:23:26.73 –> 0:23:30.73 it was no contest between the immunotherapy's and chemotherapy.

0:23:30.73 –> 0:23:44.059 When we talk about therapy for cancer a lot of times we're talking about personalized medicine and we're talking about how we can figure out what a cancer likes to

0:23:44.059 –> 0:23:48.154 eat, what receptors cancer has,

0:23:48.154 –> 0:23:51.446 what genes are turned on and turned off,

0:23:51.446 –> 0:23:54.9 and then we target our therapy accordingly.

0:23:54.9 –> 0:24:04.34 Talk about immunotherapy. It seems to me like we're talking about a blanket turning on supercharging the immune system,

0:24:04.34 –> 0:24:09.962 is that right, or are there ways where we're actually tailoring this therapy?

0:24:09.962 –> 0:24:20.484 Are we looking at who those people are that are super responsive to immunotherapy versus the people who are not super responsive to immunotherapy?

0:24:20.484 –> 0:24:25.17 And which immunotherapy might work better in particular patients?

0:24:25.17 –> 0:24:28.638 Yeah, so this question is near and dear to my heart.

0:24:28.638 –> 0:24:39.308 We in general don't do a great job of selecting patients to get particular immunotherapy, there is one biomarker which is the expression of PDL1 in the tumor as

0:24:39.308 –> 0:24:43.237 we talked about PDL1 and PD1 is one of these key pathways,

0:24:43.237 –> 0:24:51.484 so if you have PDL1 expressed in the tumor microenvironment either by immune cells in the micro environment or by the tumor,

0:24:51.484 –> 0:24:57.809 we know that you are more likely to have a response to targeting the PD1 PDL1 axis.

0:24:57.809 –> 0:25:07.53 But basically everyone in the field spends a lot of time complaining about this biomarker because we know there are a lot of patients who will have PDL1 expression

0:25:07.53 –> 0:25:10.712 in their tumor who won't respond well to these drugs.

0:25:10.712 –> 0:25:18.018 And conversely, there are a lot of patients who won't have PDL1 expression in the tumor who will still respond to these drugs.

0:25:18.018 –> 0:25:20.257 So what's the point of the biomarker then?

0:25:20.257 –> 0:25:28.799 We know it's better than not using it in terms of you have some predictive value and in some cases you might not even be able to see

0:25:28.799 –> 0:25:32.184 a signal of the drug working in a patient population and unless,

0:25:32.184 –> 0:25:37.234 you used a biomarker, and also it's a stand in because we haven't done a good enough job yet of

0:25:37.234 –> 0:25:40.563 finding better ones.

0:25:40.563 –> 0:25:44.446 So we have this biomarker that if you have it,

0:25:44.446 –> 0:25:49.421 you won't necessarily respond to the immunotherapy, if you don't have it,

0:25:49.421 –> 0:25:52.009 you may still respond to the therapy,

0:25:52.009 –> 0:25:57.257 so either way you're likely going to get immunotherapy if you have Melanoma,

0:25:57.257 –> 0:26:01.43 regardless of whether you have the biomarker or not.

0:26:01.43 –> 0:26:06.644 That's true, and that's where I think we have the potential to do much better,

0:26:06.644 –> 0:26:10.737 particularly as we talked about these two pathways,

0:26:10.737 –> 0:26:19.978 there are a lot of other immuno regulatory pathways that can activate immune cells or can activate the tumor to recruit immune cells.

0:26:19.978 –> 0:26:23.74 And we're still at the beginning of understanding these.

0:26:23.74 –> 0:26:31.859 But as these drugs come out and as they are available we have the potential to start thinking about OK for a given patient.

0:26:31.859 –> 0:26:37.201 How can we assess that patients immune system and how can we understand the tumor,

0:26:37.201 –> 0:26:45.88 the genomics, the genetics of the tumor in such a way that we can find the best combination of drugs to work for that patient.

0:26:45.88 –> 0:26:48.942 That sounds really interesting,

0:26:48.942 –> 0:26:59.007 because that sounds like the stuff that we've been doing for awhile now in terms of cancer and looking at cancers in figuring out which therapy is going to work

0:26:59.007 –> 0:27:02.883 better. What targeted pathways are turned on versus turned off.

0:27:02.883 –> 0:27:09.695 Should you be using, you know an anti HER-2 agent in somebody who's got a HER-2-positive breast cancer?

0:27:09.695 –> 0:27:12.759 Or should you be targeting KRAS in lung cancer?

0:27:12.759 –> 0:27:16.509 Sounds like you're moving in the same direction in Melanoma.

0:27:16.509 –> 0:27:19.384 But looking at it from an immune perspective,

0:27:19.384 –> 0:27:23.884 and I should say this is mostly on the research side,

0:27:23.884 –> 0:27:29.884 right now we're trying to understand the flavors of inflammation in the tumor microenvironment.

0:27:29.884 –> 0:27:35.009 The composition of the immune cells that are there and why they're there,

0:27:35.009 –> 0:27:44.134 and then once we understand that, we're simultaneously starting to look at OK if we take pieces of the tumor and study them in tissue culture,

0:27:44.134 –> 0:27:46.759 if we study them in a dish and treat them

0:27:46.759 –> 0:27:52.94 with different immunotherapy drugs, can we see patterns of response from some patients but not from others?

0:27:52.94 –> 0:27:55.515 Those are things that we're working on here,

0:27:55.515 –> 0:28:01.237 and others are working on as well that we think could lead to the development of better biomarkers.

0:28:01.237 –> 0:28:03.239 That's one kind of major approach.

0:28:03.239 –> 0:28:09.248 Another one is focusing on the technologies that have emerged to sequence patient genomes.

0:28:09.248 –> 0:28:11.479 The immune cells from patient genomes.

0:28:11.479 –> 0:28:15.141 We do technologies now to look at individual cells in sequence.

0:28:15.141 –> 0:28:17.46 Everything that that cell is expressing.

0:28:17.46 –> 0:28:24.708 Basically everything it's doing and we can do that for a bunch of cells in the micro environment all at once,

0:28:24.708 –> 0:28:33.669 and the thought is that we may find particular genetic lesions in the tumor that lead to a better response to immunotherapy A versus B.

0:28:33.669 –> 0:28:40.851 We may find particular features of the immune system that interact with the tumor as well that predict that,

0:28:40.851 –> 0:28:47.045 and so I think that in the next 5 or 10 years we're likely to see progress in this direction.

0:28:47.045 –> 0:28:50.009 Whether that will translate affectively into

0:28:50.009 –> 0:28:53.933 guiding precise therapy choice for a patients

0:28:53.933 –> 0:28:59.75 Melanoma, I'm not sure.

0:28:59.75 –> 0:29:01.787 When you talk about,

0:29:01.787 –> 0:29:09.392 essentially taking tumors and looking at the micro environment and seeing the composition of these cancer cells,

0:29:09.392 –> 0:29:13.125 and what kinds of immune therapy they may benefit from,

0:29:13.125 –> 0:29:16.656 you can also look at the immune system and see,

0:29:16.656 –> 0:29:23.922 maybe my immune system is different from your immune system in terms of attacking a particular cell.

0:29:23.922 –> 0:29:26.366 Is that on the right track?

0:29:26.366 –> 0:29:28.606 It's exactly on the right track,

0:29:28.606 –> 0:29:36.617 and you know, even taking a step back when we first started to see that these therapies could work for patients,

0:29:36.617 –> 0:29:38.384 people started to ask,

0:29:38.384 –> 0:29:41.982 why do they work for some patients but not for others?

0:29:41.982 –> 0:29:51.471 And we started to look inside patient tumors and one of the things that was clear is that some patients have a lot of attacking immune cells

0:29:51.471 –> 0:29:54.48 even prior to immunotherapy and others don't.

0:29:54.48 –> 0:29:56.509 And just unpacking that basic

0:29:56.509 –> 0:30:00.107 observation is something we're still doing,

0:30:00.107 –> 0:30:09.059 but as I was mentioning, as we start to understand it as we start to understand the chemical signals that the tumor in the immune system makes.

0:30:09.059 –> 0:30:15.05 It's giving us a lot of inputs to try to determine which drugs could be affective in each case,

0:30:15.05 –> 0:30:18.796 and what the basic flavors of immune micro environment are.

0:30:18.796 –> 0:30:25.098 Doctor Jeffrey Ishizuka is an Assistant Professor of Medical Oncology at the Yale School of Medicine.

0:30:25.098 –> 0:30:35.021 If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at Yalecancercenter.org.

0:30:35.021 –> 0:30:39.89 We hope you'll join us next week to learn more about the fight against cancer

0:30:39.89 –> 0:30:43.248 here on Connecticut Public Radio.