WEBVTT

1 00:00:00.000 --> 00:00:03.822 Support for Yale Cancer Answers comes from AstraZeneca,

2 00:00:03.822 --> 00:00:14.170 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.

3 00:00:14.170 --> 00:00:17.879 Learn more at lifebeyondpink.com.

4 00:00:17.879 --> 00:00:20.550 Welcome to Yale Cancer Answers with your host

5 00:00:20.550 --> 00:00:21.969 Doctor Anees Chagpar.

6 00:00:21.969 --> 00:00:31.855 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

7 00:00:31.855 --> 00:00:36.057 it's a conversation about Melanoma research with doctor Jeffrey Ishizuka.

8 00:00:36.057 --> 00:00:41.341 Doctor Ishizuka is an Assistant Professor of Medical Oncology at Yale School of Medicine,

9 00:00:41.341 --> 00:00:45.909 where Doctor Chagpar is a Professor of Surgical Oncology.

10 00:00:45.909 --> 00:00:51.234 Jeff, maybe we could start off by you telling us a little bit about yourself and what you do.

11 00:00:51.234 --> 00:00:59.524 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

12 00:00:59.524 --> 00:01:02.189 for new treatments for those patients.

13 00:01:02.189 --> 00:01:09.043 And so tell us a little bit more about the kinds of patients that you treat and the kinds of research that you do.

14 00:01:09.043 --> 00:01:12.381 I see Melanoma patients and I'm an immunologist

15 00:01:12.381 --> 00:01:15.956 by training. And that means I study ways to

16 00:01:15.956 --> 00:01:19.174 make the patient's immune system work better,

17 00:01:19.174 --> 00:01:22.153 to attack the cancer.

18 00:01:22.153 --> 00:01:26.861 Tell us more about that, we've talked on the show a little bit about immunotherapy and so on,

19 00:01:26.861 --> 00:01:31.808 but tell us a little bit more about the broad spectrum of immunotherapy.

20 00:01:31.808 --> 00:01:35.575 How exactly does it work and then the role that it plays in Melanoma.

21 00:01:35.575 --> 00:01:38.382 There are a couple of types of immunotherapy.

22 00:01:38.382 --> 00:01:43.078 And for a long time we knew that the immune system had the potential to control cancer,

23 00:01:43.078 --> 00:01:46.906 but I'd say the two big advances that are more recent are on the one hand,

24 00:01:46.906 --> 00:01:54.662 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

25 00:01:54.662 --> 00:01:58.337 blockade. And these are drugs that cut the brakes on the immune system.

26 00:01:58.337 --> 00:02:02.114 Those brakes stop the immune system from attacking the cancer.

27 00:02:02.114 --> 00:02:03.644 And when you get rid of them,

28 00:02:03.644 --> 00:02:08.692 the cancer is vulnerable to immune attack.

29 00:02:08.692 --> 00:02:12.393 Tell us about which of these you work on, and

30 00:02:12.393 --> 00:02:15.500 how exactly they work in Melanoma.

31 00:02:15.500 --> 00:02:22.020 In Melanoma, immune checkpoint blockade has really been one of the biggest developments

32 00:02:22.020 --> 00:02:26.522 really in the last, well maybe ever in the disease.

33 00:02:26.522 --> 00:02:31.093 And I think Melanoma was the first disease where

34 00:02:31.093 --> 00:02:37.520 these drugs were developed and remains one of the ones where they work the best.

36 00:02:38.639 --> 00:02:41.776 Can you talk about this immune checkpoint blockade.

37 00:02:41.776 --> 00:02:45.025 Is there more than one molecule that needs to be blocked?

38 00:02:45.025 --> 00:02:49.169 How does that work? Why does the immune system have brakes to begin with?

39 00:02:49.169 --> 00:02:54.323 These are great questions and they're really at the forefront of the field right now,

40 00:02:54.323 --> 00:02:58.132 so there are certainly at least a few molecules that are important.

41 00:02:58.132 --> 00:03:02.221 And all of the ones we learned about first are on the surface of T cells,

42 00:03:02.221 --> 00:03:07.205 which we know are one of the important cells for controlling cancer.

43 00:03:07.205 --> 00:03:09.669 There are a number of molecules that target

44 00:03:09.669 --> 00:03:13.354 PD-L1 and that's a major inhibitory pathway in the T cells,

45 00:03:13.354 --> 00:03:15.453 and also molecules that target CTL A4,

46 00:03:15.453 --> 00:03:18.174 which is another inhibitory pathway in T cells.

47 00:03:18.174 --> 00:03:25.318 And what we learned is when you block either one of these and sometimes if you block them both together it works even better.

48 00:03:25.318 --> 00:03:28.378 The T cells can get supercharged to attack the cancer.

49 00:03:28.378 --> 00:03:30.039 Why is it that

50 00:03:30.039 --> 00:03:32.086 they have breaks to begin with?

51 00:03:32.086 --> 00:03:38.991 The immune system is supposed to be able to identify foreign stuff in our bodies and get rid of it.

52 00:03:38.991 --> 00:03:41.996 So why doesn't that work in cancer?

53 00:03:41.996 --> 00:03:45.128 Why is it that we need to take off these brakes?

54 00:03:45.128 --> 00:03:47.622 Why do they have breaks to begin with?

55 00:03:47.622 --> 00:03:51.651 This is the foundational question of immunology,

56 00:03:51.651 --> 00:03:54.527 the distinction between self and nonself.

57 00:03:54.527 --> 00:03:59.387 All cells need to be able to get rid of foreign things just as you said,

58 00:03:59.387 --> 00:04:00.729 but at the same time

59 00:04:00.729 --> 00:04:09.909 they need to have mechanisms to avoid attacking the normal cells in the body that are healthy and so

60 00:04:09.909 --> 00:04:15.647 why is it that the immune system thinks that these cancer cells are normal?

61 00:04:15.647 --> 00:04:26.511 I think it's really because cancer cells arise from normal cells as normal cells become dysregulated as they acquire genetic errors called mutations.

62 00:04:26.511 --> 00:04:29.175 And eventually you develop cancer.

63 00:04:29.175 --> 00:04:33.819 And because the cancer cell arises from a backdrop of normal cells,

64 00:04:33.819 --> 00:04:40.720 doing normal cell things, the immune system has to find specific signals of damage or mutations that

65 00:04:40.720 --> 00:04:43.007 look abnormal in order to recognize cancer.

66 00:04:43.007 --> 00:04:46.233 So you're telling me that normally it won't do that?

68 00:04:48.156 --> 00:04:54.451 Some tumors are recognized by the immune system and the immune system can actually get rid of them,

69 00:04:54.451 --> 00:05:02.615 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

70 00:05:02.615 --> 00:05:07.141 the immune system and turn them into tumors that the immune system can see and destroy?

71 00:05:07.141 --> 00:05:10.750 And so it seems to me that if you take that problem just at its face,

72 00:05:10.750 --> 00:05:13.264 there are two ways of doing that.

73 00:05:13.264 --> 00:05:18.617 One is to make the tumor look more abnormal so that the immune system

74 00:05:18.617 --> 00:05:27.904 realizes, I need to attack it and get rid of it without actually revving up the immune system or getting rid of the

75 00:05:27.904 --> 00:05:36.675 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.

76 00:05:36.675 --> 00:05:41.899 Yeah, that's right, and I think people are working at both sides of that problem.

77 00:05:41.899 --> 00:05:49.271 We and others in the lab, are thinking of strategies both to make tumors put out signs for the immune system, saying,

78 00:05:49.271 --> 00:05:55.995 come get me and also looking for new ways to charge the immune system to be more aggressive against cancer.

79 00:05:55.995 --> 00:05:57.940 Tell us more about the first,

80 00:05:57.940 --> 00:06:04.721 because I think that we've heard a little bit about checkpoint inhibitors,

81 00:06:04.721 --> 00:06:11.267 but we really haven't heard a lot about the work that's going on to have tumor cells put out those signs that

82 00:06:11.267 --> 00:06:22.262 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

83 00:06:22.262 --> 00:06:24.663 get rid of these cancer cells,

84 00:06:24.663 --> 00:06:26.910 because one of the problems,

85 00:06:26.910 --> 00:06:35.040 as you point out, of having a supercharged immune system is that it can then attack its own cells.

86 00:06:35.040 --> 00:06:37.966 Yeah, that's a great point and

87 00:06:37.966 --> 00:06:42.720 we've been thinking, and others as well,

88 00:06:42.720 --> 00:06:49.041 that it comes down to tricking the tumor cell into making inflammatory signals,

89 00:06:49.041 --> 00:06:56.002 tricking it into making kind of an antiviral response that recruits anti tumor immune cells into the micro environment,

90 00:06:56.002 --> 00:06:57.336 and I think

91 00:06:57.336 --> 00:07:06.963 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

92 00:07:06.963 --> 00:07:10.675 directly around the tumor.

93 00:07:10.675 --> 00:07:15.610 Tell us more about that work, is that actually something that's being done?

94 00:07:15.610 --> 00:07:19.267 Is it in clinical practice?

95 00:07:19.267 --> 00:07:20.778 How do we do that?

96 00:07:20.778 --> 00:07:29.605 There are a number of clinical trials now using stimulators of viral pathways that look like DNA or RNA,

97 00:07:29.605 --> 00:07:36.523 things that viruses make and that ourselves have dedicated sensors in order to detect,

98 00:07:36.523 --> 00:07:42.485 and I think none of them has proven to be the Magic bullet for cancer yet.

99 00:07:42.485 --> 00:07:46.779 But there are still some technical hurdles to workout.

100 00:07:46.779 --> 00:07:49.764 And I think we're getting there though.

101 00:07:49.764 --> 00:07:56.178 Why has that not proven to be as successful as supercharging the immune system?

102 00:07:56.178 --> 00:08:03.264 I think one of the challenges is that cancer in many cases can spread to many locations,

103 00:08:03.264 --> 00:08:09.158 and when you think about triggering an inflammatory response in the tumor bed,

104 00:08:09.158 --> 00:08:12.439 you're really thinking about triggering it,

105 00:08:12.439 --> 00:08:14.081 not just at one site,

106 00:08:14.081 --> 00:08:16.394 but at many sites all at once,

107 00:08:16.394 --> 00:08:18.930 and so finding ways to send drugs

108 00:08:18.930 --> 00:08:26.410 to all of the different sites that cancer occupies in the body is one of the major challenges to getting this approach to work.

109 00:08:26.410 --> 00:08:33.524 The other approach then is the one that is the mainstay of immunotherapy,

110 00:08:33.524 --> 00:08:38.844 which is to quote supercharge the immune system to get rid of the blocks.

111 00:08:38.844 --> 00:08:43.157 I always think of it like Harry Potters invisibility cloak,

112 00:08:43.157 --> 00:08:48.403 right. The tumor has kind of made itself invisible to the immune system,

113 00:08:48.403 --> 00:08:57.100 and it's getting rid of that that cloak and getting the immune system to recognize it and to go after it and two,

114 00:08:57.100 --> 00:08:59.630 to be quote supercharged now.

115 00:08:59.630 --> 00:09:09.755 You mentioned two molecules, in particular CTL A4 and PDL1, tell us a little bit about the differences between the two.

116 00:09:09.755 --> 00:09:14.227 I mean we have drugs that will block either pathway.

117 00:09:14.227 --> 00:09:17.602 How do you figure out which one to use?

118 00:09:17.602 --> 00:09:20.556 Tell us more about that interplay.

119 00:09:20.556 --> 00:09:29.019 I think we still don't fully understand the mechanism of either drug and either pathway.

120 00:09:29.019 --> 00:09:32.062 And people have done a lot of good work,

121 00:09:32.062 --> 00:09:36.102 in fact, the Nobel Prize was awarded a few years back for some of that work,

122 00:09:36.102 --> 00:09:39.042 but I wouldn't say that we completely understand which,

123 00:09:39.042 --> 00:09:41.508 even sometimes which cells are being targeted,

124 00:09:41.508 --> 00:09:44.918 but certainly which pathways within the cell are being activated.

125 00:09:44.918 --> 00:09:47.961 So a lot of how we figured this out has been empirically.

126 00:09:47.961 --> 00:09:52.369 We've done clinical trials with different drugs or different combinations of drugs,

127 00:09:52.369 --> 00:09:55.044 and we've seen what's been effective for patients,

128 00:09:55.044 --> 00:09:59.085 and the hope is going forward that as we learn more about the immune system,

129 00:09:59.085 --> 00:10:04.150 and as we learn more about the tumor that we will be able to do better

130 00:10:04.150 --> 00:10:09.876 and even predict the next set of these drugs that could be usefully combined.

131 00:10:09.876 --> 00:10:14.153 So tell us more about the differences between CTLA for an PDL1.

132 00:10:14.153 --> 00:10:24.486 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,

133 00:10:24.486 --> 00:10:26.264 and seeing that they work.

134 00:10:26.264 --> 00:10:29.620 But we must know more about these actual molecules.

135 00:10:29.620 --> 00:10:33.971 Yeah, they both play an inhibitory role in T cells.

136 00:10:33.971 --> 00:10:37.220 I think it's broadly thought

137 00:10:37.220 --> 00:10:42.621 that one of them plays more of a role in T cells initially getting primed against the tumor,

138 00:10:42.621 --> 00:10:52.032 but maybe plays more of a role in lymph nodes then generating the T cells that are capable of responding whereas the other one,

139 00:10:52.032 --> 00:11:01.325 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.

140 00:11:01.325 --> 00:11:08.470 And I'm going to steer clear of the term of exhaustion because there are a lot of debates about whether T cells

141 00:11:08.470 --> 00:11:10.476 are actually exhausted or not,

142 00:11:10.476 --> 00:11:20.903 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

143 00:11:20.903 --> 00:11:23.557 of the things that PDL1 blockade does,

146 00:11:27.120 --> 00:11:31.986 is to make the T cells that have become dysfunctional more functional.

147 00:11:31.986 --> 00:11:35.620 And so if these two pathways then are complementary,

148 00:11:35.620 --> 00:11:42.269 one being more so for priming T cells and one being more so for T cells that are already primed,

149 00:11:42.269 --> 00:11:53.511 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?

150 00:11:53.511 --> 00:11:56.664 There has, and in Melanoma combining two drugs,

151 00:11:56.664 --> 00:11:58.309 one that targets CTL A4.

152 00:11:58.309 --> 00:12:07.804 and one that targets PDL1 seems to be better than using either drug alone and potentially better than using them both in sequence,

153 00:12:07.804 --> 00:12:17.014 although the latter is a less clear conclusion.

154 00:12:17.014 --> 00:12:27.578 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.

155 00:12:27.578 --> 00:12:39.287 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

156 00:12:39.287 --> 00:12:45.355 can just be removed and surgically cut out in the early stages and really beyond Melanoma,

157 00:12:45.355 --> 00:12:53.691 it spread throughout many many solid tumor types and it's being tried in almost any tumor type you can think of.

158 00:12:53.691 --> 00:13:00.360 And so two questions. First question is one of the things you mentioned earlier as being one of the

159 00:13:00.360 --> 00:13:08.214 downfalls of some therapies is that it can't always get to all of the cells where the tumors may be hiding.

160 00:13:08.214 --> 00:13:16.735 Does immunotherapy have that problem in terms of getting to the T cells and activating them or supercharging them?

161 00:13:16.735 --> 00:13:21.847 Or is that concept, this may not work if there's a tumor,

162 00:13:21.847 --> 00:13:23.774 for example in the brain?

163 00:13:23.774 --> 00:13:27.850 Because this drug can't cross the blood brain barrier?

164 00:13:27.850 --> 00:13:31.500 Or does it affect T cells wherever they are?

165 00:13:31.500 --> 00:13:38.470 We know that we can get effects certainly in the brain.

166 00:13:38.470 --> 00:13:51.299 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

167 00:13:51.299 --> 00:13:53.327 I guess what I don't know for sure,

168 00:13:53.327 --> 00:13:58.621 it's hard to say is whether there is a problem activating immune cells somewhere in the body.

169 00:13:58.621 --> 00:14:07.352 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.

170 00:14:07.352 --> 00:14:14.505 We're going to learn a lot more about Melanoma immunotherapy right after we take a short break for a medical minute.

171 00:14:14.505 --> 00:14:22.730 Please stay tuned to learn more about this research with my guest doctor Jeffrey Ishizuka. Support for Yale Cancer Answers comes from AstraZeneca.

172 00:14:22.730 --> 00:14:28.499 Providing important treatment options for patients with different types of lung,

173 00:14:28.499 --> 00:14:31.631 bladder, ovarian, breast, and blood cancers.

174 00:14:31.631 --> 00:14:35.570 More information at astrazeneca-us.com.

175 00:14:35.570 --> 00:14:38.466 This is a medical minute about breast cancer,

176 00:14:38.466 --> 00:14:41.866 the most common cancer in women. In Connecticut alone,

177 00:14:41.866 --> 00:14:46.462 approximately 3000 women will be diagnosed with breast cancer this year,

178 00:14:46.462 --> 00:14:48.541 but thanks to earlier detection,

179 00:14:48.541 --> 00:14:51.312 noninvasive treatments, an novel therapies,

180 00:14:51.312 --> 00:14:56.159 there are more options for patients to fight breast cancer than ever before.

181 00:14:56.159 --> 00:15:04.408 Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast cancer.

182 00:15:04.408 --> 00:15:10.580 Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly

183 00:15:10.580 --> 00:15:17.620 reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety

184 00:15:17.620 --> 00:15:22.706 many women experience. More information is available at yalecancercenter.org.

185 00:15:22.706 --> 00:15:26.840 You're listening to Connecticut public radio.

186 00:15:26.840 --> 00:15:29.259 Welcome back to Yale Cancer Answers.

187 00:15:29.259 --> 00:15:35.341 This is doctor Anees Chagpar andnI'm joined tonight by my guest doctor Jeffrey Ishizuka.

188 00:15:35.341 --> 00:15:41.226 We're talking about Melanoma research and in particular we're talking about immunotherapy.

189 00:15:41.226 --> 00:15:47.374 Jeff, right before the break we were talking a little bit about immunotherapy in terms of,

190 00:15:47.374 --> 00:15:51.754 really getting the immune system to attack cancer cells,

191 00:15:51.754 --> 00:15:55.024 which it may not recognize because as you put it,

192 00:15:55.024 --> 00:15:58.360 these cancer cells come from normal cells and that

193 00:15:58.360 --> 00:16:07.715 may not be as foreign looking to the immune system to really trigger it and we talked a little bit about two separate pathways,

194 00:16:07.715 --> 00:16:11.692 CTL A4 and PDL1 and the fact that we now have drugs,

195 00:16:11.692 --> 00:16:20.974 this explosion of drugs in immunotherapy targeting these two pathways and how this really has become the mainstay of therapy,

196 00:16:20.974 --> 00:16:23.921 particularly for cancers like Melanoma.

197 00:16:23.921 --> 00:16:27.971 I had a few questions to kind of follow up on that.

198 00:16:27.971 --> 00:16:32.494 The first is, tell us a little bit about the side effects.

199 00:16:32.494 --> 00:16:35.000 We think about

200 00:16:35.000 --> 00:16:39.551 chemotherapy, and you know, traditionally,

201 00:16:39.551 --> 00:16:47.469 chemotherapy was therapy that kills off cancer cells and was really thought to be therapy that switches off

202 00:16:47.469 --> 00:16:55.184 rapidly dividing cells and so people ended up losing hair and maybe getting sick because it effects your GI lining,

203 00:16:55.184 --> 00:16:57.711 which are rapidly turning over cells.

204 00:16:57.711 --> 00:17:01.171 Do you get the same kind of thing in immunotherapy,

205 00:17:01.171 --> 00:17:05.560 or are there other side effects that are the results of

206 00:17:05.560 --> 00:17:11.880 kind of supercharging this immune system and getting the immune system to attack healthy cells?

207 00:17:11.880 --> 00:17:13.540 So I think that's it exactly.

208 00:17:13.540 --> 00:17:20.130 Many of the side effects that you get from immunotherapy are actually side effects of supercharging the immune system,

209 00:17:20.130 --> 00:17:24.227 so the immune system can accidentally attack different areas of the body.

210 00:17:24.227 --> 00:17:27.383 Some of the things we see are inflammation in the lungs,

211 00:17:27.383 --> 00:17:31.536 inflammation in the GI system we see inflammation of the endocrine system,

212 00:17:31.536 --> 00:17:34.471 and when we first started seeing these side effects,

213 00:17:34.471 --> 00:17:37.183 there wasn't a good sense of how you treat them,

214 00:17:37.183 --> 00:17:39.730 how you manage them, or even how you monitor.

215 00:17:39.730 --> 00:17:41.890 We didn't really know what to look for.

216 00:17:41.890 --> 00:17:45.832 But I will say that as experience with these agents has progressed,

217 00:17:45.832 --> 00:17:49.715 we've gotten better at detecting these side effects as they occur,

218 00:17:49.715 --> 00:17:56.324 and managing them, usually using immunosuppressives and one of the questions that comes up when you start saying,

219 00:17:56.324 --> 00:18:02.469 well, you're using drugs to charge the immune system and at the same time to shut down the immune system,

220 00:18:02.469 --> 00:18:05.772 is that going to be is going to be bad for the patients.

221 00:18:05.772 --> 00:18:11.221 Are they going to have that outcomes and the data isn't really completely mature on this yet,

222 00:18:11.221 --> 00:18:14.119 but it certainly appears from the early data that

223 00:18:14.119 --> 00:18:22.204 you can safely give these immunosuppressives and that you don't at least don't clearly make their responses against the cancer

224 00:18:22.204 --> 00:18:26.121 worse.

225 00:18:26.121 --> 00:18:32.183 That's really interesting. Why would that be the case? I can imagine that when we think about people who are immunosuppressed,

226 00:18:32.183 --> 00:18:37.994 people who for example have HIV or other things that turn off their immune system,

227 00:18:37.994 --> 00:18:40.773 they are more at risk of developing cancer,

228 00:18:40.773 --> 00:18:45.321 and I guess for the same reason that you talked about before the break,

229 00:18:45.321 --> 00:18:47.263 which is your immune system,

230 00:18:47.263 --> 00:18:55.902 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,

231 00:18:55.902 --> 00:19:01.900 and so if you are immuno compromised you're at increased risk of getting cancer,

232 00:19:01.900 --> 00:19:04.199 and that's the whole point of

233 00:19:04.199 --> 00:19:10.650 supercharging the immune system to get rid of these cancers.

234 00:19:10.650 --> 00:19:21.922 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?

235 00:19:21.922 --> 00:19:25.333 A couple of potential thoughts here.

236 00:19:25.333 --> 00:19:32.230 The first one is that I want to be careful we don't know for sure that it doesn't affect the

237 00:19:32.230 --> 00:19:34.575 response to therapy in a negative way.

238 00:19:34.575 --> 00:19:37.099 I think what we can say is that

239 00:19:37.099 --> 00:19:44.730 at first blush, patients who needed immunosuppressives because they had these bad immune effects and got them didn't do obviously worse,

240 00:19:44.730 --> 00:19:46.394 at least in the early studies

241 00:19:46.394 --> 00:19:55.260 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

242 00:19:55.260 --> 00:19:58.968 actually were having the strongest immune responses to begin with,

243 00:19:58.968 --> 00:20:08.329 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.

244 00:20:08.329 --> 00:20:14.859 And I think that's probably the main thing that I would think about for that issue.

245 00:20:14.859 --> 00:20:20.846 The other question that I have is, these autoimmune side effects,

246 00:20:20.846 --> 00:20:26.355 the side effects of people's immune system now attacking their own normal cells,

247 00:20:26.355 --> 00:20:28.532 are those permanent? Are

248 00:20:28.532 --> 00:20:37.578 they forever or are they short lived? I mean when you get chemotherapy and you lose your hair,

249 00:20:37.578 --> 00:20:39.319 your hair will grow back.

250 00:20:39.319 --> 00:20:44.597 Is it the same with immunotherapy that this is a short term thing?

251 00:20:44.597 --> 00:20:47.416 Or when your immune system attacks your lungs,

252 00:20:47.416 --> 00:20:50.776 now you've got pulmonary fibrosis forever?

253 00:20:50.776 --> 00:20:55.694 I think it depends on the type of immune side effect that we're talking about.

254 00:20:55.694 --> 00:20:57.013 I think many of them,

255 00:20:57.013 --> 00:20:59.833 if they're controlled with immunosuppressives,

256 00:20:59.833 --> 00:21:04.332 and if you take the patient off of the immunotherapy, will actually go away.

257 00:21:04.332 --> 00:21:06.371 So we see this in a lot of cases,

258 00:21:06.371 --> 00:21:09.730 inflammation in the colon, or inflammation in the lungs.

259 00:21:09.730 --> 00:21:16.951 I think the case in which this isn't necessarily true is when the immune system attacks the cell type

260 00:21:16.951 --> 00:21:26.278 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

261 00:21:26.278 --> 00:21:30.440 is gone, and after that there's really no bringing it back.

262 00:21:30.440 --> 00:21:37.403 So in most cases we actually have been able to give hormone replacement.

263 00:21:37.403 --> 00:21:40.398 It's extremely bad if it's not detected,

264 00:21:40.398 --> 00:21:45.001 but in a lot of cases it can be solved by giving a pill a day.

265 00:21:45.001 --> 00:21:47.413 When you talk about hormones,

266 00:21:47.413 --> 00:21:54.430 are you talking about thyroid are you talking about ovaries, what hormones are we talking about?

267 00:21:54.430 --> 00:21:57.801 Yeah, so thyroid is one that you certainly see,

268 00:21:57.801 --> 00:22:05.179 but you see actually a number of other hormones that are produced in the brain that can also be altered,

269 00:22:05.179 --> 00:22:07.356 and these can be be more rare,

270 00:22:07.356 --> 00:22:10.449 but can be pretty dramatic if you see them.

271 00:22:10.449 --> 00:22:14.289 So given the side effects of immunotherapy,

272 00:22:14.289 --> 00:22:17.953 is immunotherapy really better than classic chemotherapy?

273 00:22:17.953 --> 00:22:24.209 You had mentioned that immunotherapy has now become standard of care for Melanoma.

274 00:22:24.209 --> 00:22:26.925 Is it better than what we used to do?

276 00:22:28.758 --> 00:22:31.474 We used to give chemotherapy for Melanoma,

277 00:22:31.474 --> 00:22:32.991 right?

278 00:22:32.991 --> 00:22:36.846 And Melanoma is not particularly responsive to chemotherapy,

279 00:22:36.846 --> 00:22:41.268 and I think what excited everyone in the field and it's given us all

280 00:22:41.268 --> 00:22:44.680 a lot of excitement and a lot of hope is not even that

281 00:22:44.680 --> 00:22:48.277 everyone responds to these immunotherapy's because they don't,

282 00:22:48.277 --> 00:22:52.444 not enough patients do, and that's something we don't really understand.

283 00:22:52.444 --> 00:22:54.842 We're trying to understand it in the lab,

284 00:22:54.842 --> 00:22:59.238 but it's that some of the patients who respond seem to just keep responding,

285 00:22:59.238 --> 00:23:07.002 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,

286 00:23:07.002 --> 00:23:10.371 the immunotherapy drugs, and that the cancer won't return.

287 00:23:10.371 --> 00:23:15.210 And this is true even in some cases for very aggressive disease.

288 00:23:15.210 --> 00:23:19.686 And so seeing those effects are the ones that have really made everybody excited.

289 00:23:19.686 --> 00:23:26.730 And you see that in clinical trials when we study how patients survive on different drugs and

290 00:23:26.730 --> 00:23:30.730 it was no contest between the immunotherapy's and chemotherapy.

291 00:23:30.730 --> 00:23:44.059 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

292 00:23:44.059 --> 00:23:48.154 eat, what receptors cancer has,

293 00:23:48.154 --> 00:23:51.446 what genes are turned on and turned off,

294 00:23:51.446 --> 00:23:54.900 and then we target our therapy accordingly.

295 00:23:54.900 --> 00:24:04.340 Talk about immunotherapy. It seems to me like we're talking about a blanket turning on supercharging the immune system,

296 00:24:04.340 --> 00:24:09.962 is that right, or are there ways where we're actually tailoring this therapy?

297 00:24:09.962 --> 00:24:20.484 Are we looking at who those people are that are super responsive to immunotherapy versus the people who are not super responsive to immunotherapy?

298 00:24:20.484 --> 00:24:25.170 And which immunotherapy might work better in particular patients?

299 00:24:25.170 --> 00:24:28.638 Yeah, so this question is near and dear to my heart.

300 00:24:28.638 --> 00:24:39.308 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

301 00:24:39.308 --> 00:24:43.237 we talked about PDL1 and PD1 is one of these key pathways,

302 00:24:43.237 --> 00:24:51.484 so if you have PDL1 expressed in the tumor microenvironment either by immune cells in the micro environment or by the tumor,

303 00:24:51.484 --> 00:24:57.809 we know that you are more likely to have a response to targeting the PD1 PDL1 axis.

304 00:24:57.809 --> 00:25:07.530 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

305 00:25:07.530 --> 00:25:10.712 in their tumor who won't respond well to these drugs.

306 00:25:10.712 --> 00:25:18.018 And conversely, there are a lot of patients who won't have PDL1 expression in the tumor who will still respond to these drugs.

307 00:25:18.018 --> 00:25:20.257 So what's the point of the biomarker then?

308 00:25:20.257 --> 00:25:28.799 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

309 00:25:28.799 --> 00:25:32.184 a signal of the drug working in a patient population and unless,

310 00:25:32.184 --> 00:25:37.234 you used a biomarker, and also it's a stand in because we haven't done a good enough job yet of

311 00:25:37.234 --> 00:25:40.563 finding better ones.

312 00:25:40.563 --> 00:25:44.446 So we have this biomarker that if you have it,

313 00:25:44.446 --> 00:25:49.421 you won't necessarily respond to the immunotherapy, if you don't have it,

314 00:25:49.421 --> 00:25:52.009 you may still respond to the therapy,

315 00:25:52.009 --> 00:25:57.257 so either way you're likely going to get immunotherapy if you have Melanoma,

316 00:25:57.257 --> 00:26:01.430 regardless of whether you have the biomarker or not.

317 00:26:01.430 --> 00:26:06.644 That's true, and that's where I think we have the potential to do much better,

318 00:26:06.644 --> 00:26:10.737 particularly as we talked about these two pathways,

319 00:26:10.737 --> 00:26:19.978 there are a lot of other immuno regulatory pathways that can activate immune cells or can activate the tumor to recruit immune cells.

320 00:26:19.978 --> 00:26:23.740 And we're still at the beginning of understanding these.

321 00:26:23.740 --> 00:26:31.859 But as these drugs come out and as they are available we have the potential to start thinking about OK for a given patient.

322 00:26:31.859 --> 00:26:37.201 How can we assess that patients immune system and how can we understand the tumor,

323 00:26:37.201 --> 00:26:45.880 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.

324 00:26:45.880 --> 00:26:48.942 That sounds really interesting,

325 00:26:48.942 --> 00:26:59.007 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

326 00:26:59.007 --> 00:27:02.883 better. What targeted pathways are turned on versus turned off.

327 00:27:02.883 --> 00:27:09.695 Should you be using, you know an anti HER-2 agent in somebody who's got a HER-2-positive breast cancer?

328 00:27:09.695 --> 00:27:12.759 Or should you be targeting KRAS in lung cancer?

329 00:27:12.759 --> 00:27:16.509 Sounds like you're moving in the same direction in Melanoma.

330 00:27:16.509 --> 00:27:19.384 But looking at it from an immune perspective,

331 00:27:19.384 --> 00:27:23.884 and I should say this is mostly on the research side,

332 00:27:23.884 --> 00:27:29.884 right now we're trying to understand the flavors of inflammation in the tumor microenvironment.

333 00:27:29.884 --> 00:27:35.009 The composition of the immune cells that are there and why they're there,

334 00:27:35.009 --> 00:27:44.134 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,

335 00:27:44.134 --> 00:27:46.759 if we study them in a dish and treat them

336 00:27:46.759 --> 00:27:52.940 with different immunotherapy drugs, can we see patterns of response from some patients but not from others?

337 00:27:52.940 --> 00:27:55.515 Those are things that we're working on here,

338 00:27:55.515 --> 00:28:01.237 and others are working on as well that we think could lead to the development of better biomarkers.

339 00:28:01.237 --> 00:28:03.239 That's one kind of major approach.

340 00:28:03.239 --> 00:28:09.248 Another one is focusing on the technologies that have emerged to sequence patient genomes.

341 00:28:09.248 --> 00:28:11.479 The immune cells from patient genomes.

342 00:28:11.479 --> 00:28:15.141 We do technologies now to look at individual cells in sequence.

343 00:28:15.141 --> 00:28:17.460 Everything that that cell is expressing.

344 00:28:17.460 --> 00:28:24.708 Basically everything it's doing and we can do that for a bunch of cells in the micro environment all at once,

345 00:28:24.708 --> 00:28:33.669 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.

346 00:28:33.669 --> 00:28:40.851 We may find particular features of the immune system that interact with the tumor as well that predict that,

347 00:28:40.851 --> 00:28:47.045 and so I think that in the next 5 or 10 years we're likely to see progress in this direction.

348 00:28:47.045 --> 00:28:50.009 Whether that will translate affectively into

349 00:28:50.009 --> 00:28:53.933 guiding precise therapy choice for a patients

350 00:28:53.933 --> 00:28:59.750 Melanoma, I'm not sure.

351 00:28:59.750 --> 00:29:01.787 When you talk about,

352 00:29:01.787 --> 00:29:09.392 essentially taking tumors and looking at the micro environment and seeing the composition of these cancer cells,

353 00:29:09.392 --> 00:29:13.125 and what kinds of immune therapy they may benefit from,

354 00:29:13.125 --> 00:29:16.656 you can also look at the immune system and see,

355 00:29:16.656 --> 00:29:23.922 maybe my immune system is different from your immune system in terms of attacking a particular cell.

356 00:29:23.922 --> 00:29:26.366 Is that on the right track?

357 00:29:26.366 --> 00:29:28.606 It's exactly on the right track,

358 00:29:28.606 --> 00:29:36.617 and you know, even taking a step back when we first started to see that these therapies could work for patients,

359 00:29:36.617 --> 00:29:38.384 people started to ask,

360 00:29:38.384 --> 00:29:41.982 why do they work for some patients but not for others?

361 00:29:41.982 --> 00:29:51.471 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

362 00:29:51.471 --> 00:29:54.480 even prior to immunotherapy and others don't.

363 00:29:54.480 --> 00:29:56.509 And just unpacking that basic

364 00:29:56.509 --> 00:30:00.107 observation is something we're still doing,

365 00:30:00.107 --> 00:30:09.059 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.

366 00:30:09.059 --> 00:30:15.050 It's giving us a lot of inputs to try to determine which drugs could be affective in each case,

367 00:30:15.050 --> 00:30:18.796 and what the basic flavors of immune micro environment are.

368 00:30:18.796 --> 00:30:25.098 Doctor Jeffrey Ishizuka is an Assistant Professor of Medical Oncology at the Yale School of Medicine.

369 00:30:25.098 --> 00:30:35.021 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.

370 00:30:35.021 --> 00:30:39.890 We hope you'll join us next week to learn more about the fight against cancer

371 00:30:39.890 --> 00:30:43.248 here on Connecticut Public Radio.