WEBVTT

1 00:00:00.000 --> 00:00:03.000 (people chattering)

2 00:00:10.312 --> 00:00:12.012 <v Man>(indistinct) Biostatistics</v>

3 00:00:12.930 --> 00:00:15.107 at the University of Minnesota.

4 00:00:15.107 --> 00:00:18.940 And he's currently attending or an associate professor

5 00:00:18.940 --> 00:00:23.299 at the University of the Texas Dell Medical School.

6 00:00:23.299 --> 00:00:27.160 Dr. Hobbes is a library recognized as an expert

7 00:00:27.160 --> 00:00:31.160 in clinical oncology and research (indistinct).

8 00:00:31.160 --> 00:00:33.743 Among his many accomplishments,

9 00:00:35.309 --> 00:00:39.392 in 2017, Dr. Hobbes (indistinct)

10 00:00:40.400 --> 00:00:44.039 of The National Cancer Institute, clinical trial

11 00:00:44.039 --> 00:00:49.039 (indistinct) a national consensus recommendations

12 00:00:49.680 --> 00:00:50.513 or (indistinct).

13 00:00:54.840 --> 00:00:59.840 In 2019, Dr. Hobbes (indistinct).

14 00:01:08.424 --> 00:01:13.424 In 2021, Dr. Hobbes (indistinct)

15 00:01:46.510 --> 00:01:47.650 <v Brian Hobbes>Thank you, thank you very much,</v>

16 00:01:47.650 --> 00:01:50.893 and for that long and generous introduction.

17 00:01:53.580 --> 00:01:55.410 I'm excited to give this talk today.

18 00:01:55.410 --> 00:01:57.740 I wish I could visit in-person.

19 00:01:57.740 --> 00:02:00.260 I was fortunate to have that opportunity a few years ago,

20 00:02:00.260 --> 00:02:02.483 so thank you for inviting me back.

21 00:02:04.810 --> 00:02:09.530 Okay, so I got tired of giving talks

22 00:02:09.530 --> 00:02:12.720 that were very technical and very specific

23 00:02:12.720 --> 00:02:14.133 to a specific problem.

24 00:02:15.045 --> 00:02:17.697 Because, if you don't have an understanding of the problem,

25 00:02:17.697 --> 00:02:19.450 you don't have an understand that the biomarkers,

26 00:02:19.450 --> 00:02:22.600 or you don't work in a particular area of methodology,

27 00:02:22.600 --> 00:02:25.783 I think it becomes very, you know, what do you wanna say?

28 00:02:25.783 --> 00:02:28.640 I think people lose interest pretty quickly.

29 00:02:28.640 --> 00:02:31.450 And so I decided to start giving talks

30 00:02:31.450 --> 00:02:34.350 that had to do overview a subject

31 00:02:34.350 --> 00:02:37.000 that I think is very relevant in the field right now.

32 00:02:37.890 --> 00:02:42.770 So recently, I'm an external advisor on a grant

33 00:02:42.770 --> 00:02:45.690 that Genentech has got from the FDA

34 00:02:45.690 --> 00:02:48.903 for developing clinical trials that use real-world data.

35 00:02:49.920 --> 00:02:52.130 I've worked with Flatiron in the last few years,

36 00:02:52.130 --> 00:02:54.380 as well as the CancerLinQ.

37 00:02:54.380 --> 00:02:56.130 And I've been watching this field,

38 00:02:56.130 --> 00:02:58.070 sort of the discussions in this field

39 00:02:58.070 --> 00:02:59.250 about real-world evidence,

40 00:02:59.250 --> 00:03:00.290 and where does it fit-in?

41 00:03:00.290 --> 00:03:03.470 and specifically in the context of cancer drug development.

42 00:03:03.470 --> 00:03:05.600 So I decided to talk about that today.

43 00:03:05.600 --> 00:03:09.590 So yeah, I think this is what I'm gonna do.

44 00:03:09.590 --> 00:03:11.330 So does real-world evidence

45 00:03:11.330 --> 00:03:13.280 have a role in cancer drug development?

46 00:03:14.160 --> 00:03:14.993 So if you'll see,

47 00:03:14.993 --> 00:03:18.010 there's a question mark at the end of the statement.

48 00:03:18.010 --> 00:03:20.450 So I'm gonna talk about this,

49 00:03:20.450 --> 00:03:22.660 and I'm gonna give you the perspective that I have,

50 00:03:22.660 --> 00:03:25.033 which comes from a methodologist

51 00:03:25.033 --> 00:03:26.560 that really wants real-world evidence

52 00:03:26.560 --> 00:03:28.470 to have a role in cancer drug development,

53 00:03:28.470 --> 00:03:31.543 because, databases are growing.

54 00:03:32.740 --> 00:03:34.370 Data science becomes more relevant

55 00:03:34.370 --> 00:03:36.800 if those databases are useful.

56 00:03:36.800 --> 00:03:38.150 We all want to write algorithms

57 00:03:38.150 --> 00:03:41.470 and do, you know, causal inference on database.

58 00:03:41.470 --> 00:03:44.300 We want to unlock those databases with our intelligence,

59 00:03:44.300 --> 00:03:45.400 for drug development.

60 00:03:45.400 --> 00:03:47.450 Drug development is incredibly expensive.

61 00:03:48.360 --> 00:03:51.610 Patients need access to therapies

62 00:03:51.610 --> 00:03:52.730 that are gonna save their lives.

63 00:03:52.730 --> 00:03:55.680 We have refractory patients enrolling in clinical trials.

64 00:03:55.680 --> 00:03:58.050 There's probably not enough clinical trials.

65 00:03:58.050 --> 00:04:00.210 And we do have advances in biology

66 00:04:00.210 --> 00:04:05.190 that have manifest themselves in precision therapeutics.

67 00:04:05.190 --> 00:04:07.830 So we want all of this to work together.

68 00:04:07.830 --> 00:04:09.400 We want this to be true.

69 00:04:09.400 --> 00:04:10.540 On the other hand,

70 00:04:10.540 --> 00:04:13.530 I have designed hundreds of clinical trials

71 00:04:13.530 --> 00:04:14.400 and I continue to,

72 00:04:14.400 --> 00:04:15.840 most of my collaborations continue

73 00:04:15.840 --> 00:04:17.533 with MD Anderson in this space.

74 00:04:18.580 --> 00:04:22.280 I've worked with oncologists for over a decade now.

75 00:04:22.280 --> 00:04:24.840 I've worked with translational researchers in oncology,

76 00:04:24.840 --> 00:04:28.840 and I see the issues that are presented.

77 00:04:28.840 --> 00:04:31.400 I mean, maybe I should say the challenges,

78 00:04:31.400 --> 00:04:32.513 the challenges that we confront

79 00:04:32.513 --> 00:04:34.500 when we think about this space.

80 00:04:34.500 --> 00:04:37.550 So I'm gonna talk about this.

81 00:04:37.550 --> 00:04:41.730 And I think if I was the 30-year-old version of myself,

82 00:04:41.730 --> 00:04:43.960 Brian Hobbs, the 30-year-old,

83 00:04:43.960 --> 00:04:46.030 there would not be a question mark here.

84 00:04:46.030 --> 00:04:48.520 I would be saying we can use real-world evidence,

85 00:04:48.520 --> 00:04:50.190 and this is how.

86 00:04:50.190 --> 00:04:54.280 But now that I'm 40 years old, there's a question mark.

87 00:04:54.280 --> 00:04:56.840 And I think that, you know okay,

88 00:04:56.840 --> 00:04:58.650 so when you've seen other talks about this,

89 00:04:58.650 --> 00:05:00.870 I don't know if you're experiencing the same thing I have,

90 00:05:00.870 --> 00:05:05.060 but, I've seen several talks at seminars, conferences,

91 00:05:05.060 --> 00:05:09.400 where people are presenting very specific cases.

92 00:05:09.400 --> 00:05:12.000 Specific cases where they could use real-world evidence

93 00:05:12.000 --> 00:05:12.833 and it made sense,

94 00:05:12.833 --> 00:05:16.120 or it was the only thing that could be done in that context.

95 00:05:16.120 --> 00:05:17.950 So I've seen a lot of talks like that.

96 00:05:17.950 --> 00:05:20.210 I'm gonna take this from the other perspective,

97 00:05:20.210 --> 00:05:22.410 I'm gonna talk about what's going on in oncology right now.

98 00:05:22.410 --> 00:05:24.090 What are the most important developments happening

99 00:05:24.090 --> 00:05:24.923 in oncology?

100 00:05:24.923 --> 00:05:26.660 And then I'm gonna ask the question,

101 00:05:26.660 --> 00:05:30.500 can we use real-world evidence to help augment

102 00:05:30.500 --> 00:05:33.000 our trial designs and drug development in general?

103 00:05:34.600 --> 00:05:37.290 So to begin with what is real-world evidence?

104 00:05:37.290 --> 00:05:40.360 So there's different definitions of this.

105 00:05:40.360 --> 00:05:43.193 It tends to be a very broad definition.

106 00:05:44.950 --> 00:05:49.070 That's, you know, that different people use this.

107 00:05:49.070 --> 00:05:50.980 I've taken this diagram from the CancerLinQ,

108 00:05:50.980 --> 00:05:53.580 which is a nonprofit organization that works

109 00:05:53.580 --> 00:05:57.370 with the American Society of Clinical Oncology.

110 00:05:57.370 --> 00:06:00.300 They are massing and organizing a large database,

111 00:06:00.300 --> 00:06:02.540 I collaborate with Elizabeth Garrett-Mayer at CancerLinQ

112 00:06:02.540 --> 00:06:05.390 who's at ASCO, who's great.

113 00:06:05.390 --> 00:06:08.350 Who's have a PhD statistician working on this.

114 00:06:08.350 --> 00:06:09.946 So this diagram, you know,

115 00:06:09.946 --> 00:06:12.640 what we often think about as real-world evidence,

116 00:06:12.640 --> 00:06:15.190 we think about as the electronic medical health records

117 00:06:15.190 --> 00:06:19.340 that are in sort of community hospital systems, right?

118 00:06:19.340 --> 00:06:22.450 We think about data that's acquired from routine care

119 00:06:22.450 --> 00:06:26.860 or from claims that's not on patients

120 00:06:26.860 --> 00:06:28.800 that are in a clinical study.

121 00:06:28.800 --> 00:06:30.750 We tend to think about that as real-world evidence.

122 00:06:30.750 --> 00:06:34.800 And so CancerLinQ says Real-World Evidence has a capability,

123 00:06:34.800 --> 00:06:37.840 data tools, processes, organization, underpinning functions

124 00:06:37.840 --> 00:06:39.010 to drive business intelligence.

125 00:06:39.010 --> 00:06:41.960 So that's kind of, you know, very broad.

126 00:06:41.960 --> 00:06:44.850 They also tell us that there's other things

127 00:06:44.850 --> 00:06:46.340 that should count as real-world evidence

128 00:06:46.340 --> 00:06:48.040 beyond the EMR data.

129 00:06:48.040 --> 00:06:49.940 Okay, observational data

130 00:06:49.940 --> 00:06:52.300 as well as historical randomized controlled data.

131 00:06:52.300 --> 00:06:53.820 Okay, that makes sense.

132 00:06:53.820 --> 00:06:57.490 Pharmacy data, mortality registries, hospital visits,

133 00:06:57.490 --> 00:07:02.320 lab values, claim databases, social media,

134 00:07:02.320 --> 00:07:04.620 they put on this diagram as well.

135 00:07:04.620 --> 00:07:07.730 So you know maybe, right?

136 00:07:07.730 --> 00:07:10.790 But I think that we're at a place right now

137 00:07:10.790 --> 00:07:12.420 where people are excited about using

138 00:07:12.420 --> 00:07:14.620 these sources of information in research,

139 00:07:14.620 --> 00:07:17.060 but somebody really needs to develop a framework

140 00:07:17.060 --> 00:07:18.030 for each of these.

141 00:07:18.030 --> 00:07:19.730 There's not a single framework that says,

142 00:07:19.730 --> 00:07:22.100 this is how you use all of these

143 00:07:22.100 --> 00:07:24.150 in a clinical research program.

144 00:07:24.150 --> 00:07:26.860 If you're gonna use social media in clinical study

145 00:07:26.860 --> 00:07:28.420 for research purposes, you know,

146 00:07:28.420 --> 00:07:30.100 there needs to be a framework for how to do it,

147 00:07:30.100 --> 00:07:33.110 especially in the context of precision oncology.

148 00:07:33.110 --> 00:07:33.943 But so we have this,

149 00:07:33.943 --> 00:07:37.552 and we have groups that are working on these databases,

150 00:07:37.552 --> 00:07:40.350 they want to make this a realization.

151 00:07:40.350 --> 00:07:42.200 What are the regulators saying?

152 00:07:42.200 --> 00:07:44.410 Well, so real-world data and real-world evidence

153 00:07:44.410 --> 00:07:46.820 really got a boost from the 21st Century Cures Act

154 00:07:46.820 --> 00:07:48.740 signed into law in 2016.

155 00:07:48.740 --> 00:07:50.960 They advocated for the use of real-world evidence

156 00:07:50.960 --> 00:07:53.650 to support new indications for approved drugs.

157 00:07:53.650 --> 00:07:57.457 Of course, the US Government wants the innovations

158 00:07:57.457 --> 00:08:00.550 that we have in biology to translate into therapeutics

159 00:08:00.550 --> 00:08:01.383 for patients.

160 00:08:01.383 --> 00:08:03.840 And we have a very, you know,

161 00:08:03.840 --> 00:08:06.350 I think forward looking approach when it comes to that,

162 00:08:06.350 --> 00:08:08.340 if the drug is relatively safe

163 00:08:08.340 --> 00:08:09.910 and can demonstrate some efficacy

164 00:08:09.910 --> 00:08:12.393 it gets to the market, it gets to patients.

165 00:08:13.320 --> 00:08:14.990 So that there's a guidance document

166 00:08:14.990 --> 00:08:16.300 about the use of real-world evidence

167 00:08:16.300 --> 00:08:18.010 to support regulatory decision-making,

168 00:08:18.010 --> 00:08:20.320 which was initially for devices.

169 00:08:20.320 --> 00:08:22.980 There's another one for biologics in 2019,

170 00:08:22.980 --> 00:08:24.930 there's actually a website you can go to,

171 00:08:24.930 --> 00:08:29.145 which is the framework they discussed in 2018.

172 00:08:29.145 --> 00:08:33.257 If you go to that website, and this was done,

173 00:08:33.257 --> 00:08:36.210 they have quotes from Scott Gottlieb here.

174 00:08:36.210 --> 00:08:38.600 You can see that a little more of a definition,

175 00:08:38.600 --> 00:08:40.930 real-world data can be used to improve efficiency

176 00:08:40.930 --> 00:08:42.980 of clinical trials, even if it's not used

177 00:08:42.980 --> 00:08:44.820 for product effectiveness.

178 00:08:44.820 --> 00:08:46.550 So the FDA is still saying,

179 00:08:46.550 --> 00:08:49.430 we don't want to use real-world data as a control arm

180 00:08:49.430 --> 00:08:52.630 to replace a randomized control, for example,

181 00:08:52.630 --> 00:08:55.660 but we could use it to generate hypothesis, right?

182 00:08:55.660 --> 00:08:57.030 What is the expected event rate

183 00:08:57.030 --> 00:08:59.080 for this population that we're enrolling?

184 00:09:00.000 --> 00:09:00.910 How many events do we expected

185 00:09:00.910 --> 00:09:03.200 to have in a certain timeframe?

186 00:09:03.200 --> 00:09:06.320 How likely is it that we can roll that population.

187 00:09:06.320 --> 00:09:09.090 Trial feasibility and forming prior distributions

188 00:09:09.090 --> 00:09:09.923 in Bayesian models.

189 00:09:09.923 --> 00:09:11.170 So I liked that observation,

190 00:09:11.170 --> 00:09:14.610 but, you know, what is our expectation?

191 00:09:14.610 --> 00:09:16.490 Maybe we're not starting from nothing.

192 00:09:16.490 --> 00:09:18.660 And then prognostic indicators.

193 00:09:18.660 --> 00:09:20.420 Are there things we should stratify for

194 00:09:20.420 --> 00:09:22.850 or account for an analysis that could be imbalanced,

195 00:09:22.850 --> 00:09:25.410 especially when we don't randomize?

196 00:09:25.410 --> 00:09:27.310 So this is what regulators are saying,

197 00:09:28.250 --> 00:09:29.640 but they also say the standard

198 00:09:29.640 --> 00:09:32.300 for drug approval remains the same.

199 00:09:32.300 --> 00:09:33.960 And this is an important statement.

200 00:09:33.960 --> 00:09:35.510 The basis of approval remains the same.

201 00:09:35.510 --> 00:09:37.730 Substantial evidence that the drug will have the effect,

202 00:09:37.730 --> 00:09:40.700 and adequate well-controlled clinical investigations.

203 00:09:40.700 --> 00:09:43.970 So. and I was just at a meeting at UNC

204 00:09:43.970 --> 00:09:47.830 with Genentech and FDA and people from the EMA,

205 00:09:47.830 --> 00:09:50.533 and they're standing firm on this.

206 00:09:52.000 --> 00:09:53.270 While we're discussing

207 00:09:53.270 --> 00:09:55.910 how you could potentially augment a randomized-control

208 00:09:55.910 --> 00:09:57.203 with real-world controls,

209 00:09:58.070 --> 00:10:01.270 there's no sort of interest in replacing

210 00:10:02.438 --> 00:10:04.760 of randomized-control right now.

211 00:10:04.760 --> 00:10:07.960 Not unless there's absolutely no ethical way

212 00:10:07.960 --> 00:10:08.960 you could randomize.

213 00:10:10.595 --> 00:10:12.400 So they say that, you know,

214 00:10:12.400 --> 00:10:14.410 there's more flexibility when the disease is rare,

215 00:10:14.410 --> 00:10:17.163 and the patient population lacks a suitable control.

216 00:10:18.715 --> 00:10:19.947 So what about the CancerLinQ?

217 00:10:19.947 --> 00:10:22.140 So these slides are a little dated

218 00:10:22.140 --> 00:10:23.810 as of the last year, March of 2020,

219 00:10:23.810 --> 00:10:25.960 but they had at that time

220 00:10:25.960 --> 00:10:30.050 over two and a half million patients in their database.

221 00:10:30.050 --> 00:10:31.870 So they have worked on data codes

222 00:10:31.870 --> 00:10:36.870 and structuring outcomes, structuring CONMED data.

223 00:10:37.010 --> 00:10:38.860 They've done a lot with this database,

224 00:10:38.860 --> 00:10:41.103 and I used it at Cleveland Clinic.

225 00:10:42.760 --> 00:10:45.463 So this is growing as a resource.

226 00:10:46.430 --> 00:10:50.529 Also what happened is that Flatiron,

227 00:10:50.529 --> 00:10:53.660 which has over 2 million active patients in their database.

228 00:10:53.660 --> 00:10:56.530 Of course, this is an industry group

229 00:10:56.530 --> 00:10:59.660 that's partially owned by Roche.

230 00:10:59.660 --> 00:11:02.210 They have partnered with Foundation Medicine,

231 00:11:02.210 --> 00:11:05.010 and now there's an intersection of Flatiron patients

232 00:11:05.010 --> 00:11:08.670 that also have genetic testing from Foundation Medicine.

233 00:11:08.670 --> 00:11:12.390 And they're calling this the Clinical Genomic Database.

234 00:11:12.390 --> 00:11:14.300 And at the time that I took this slide,

235 00:11:14.300 --> 00:11:15.443 they had over 40,000 patients

236 00:11:15.443 --> 00:11:20.443 that had the real-world data matched to the molecular data.

237 00:11:20.582 --> 00:11:22.370 I think that's very interesting,

238 00:11:22.370 --> 00:11:24.070 and I think that's very important.

239 00:11:25.000 --> 00:11:27.950 One of the main issues with real-world evidence

240 00:11:27.950 --> 00:11:29.610 in the oncology setting

241 00:11:30.450 --> 00:11:33.680 is that we don't have a real-world tumor response.

242 00:11:33.680 --> 00:11:35.500 So for those of you that work in oncology,

243 00:11:35.500 --> 00:11:39.620 of course, you know that phase one, phase two trials

244 00:11:39.620 --> 00:11:42.800 are designed on the basis of endpoints

245 00:11:42.800 --> 00:11:45.223 that measure reductions in tumor burden.

246 00:11:46.250 --> 00:11:48.610 So for solid tumors, this is done through scans.

247 00:11:48.610 --> 00:11:50.370 So patients are scanned at baseline.

248 00:11:50.370 --> 00:11:52.930 They're scanned regularly at follow-up intervals

249 00:11:52.930 --> 00:11:56.740 after every visit or every cycle of therapy.

250 00:11:56.740 --> 00:11:59.860 Those scans go for an adjudication process,

251 00:11:59.860 --> 00:12:01.930 which is done by more than one person

252 00:12:01.930 --> 00:12:03.780 where they actually measure how much reduction

253 00:12:03.780 --> 00:12:06.100 in tumor burden happens after treatment.

254 00:12:06.100 --> 00:12:08.240 And then we look at that longitudinally,

255 00:12:08.240 --> 00:12:10.490 we take the best reduction

256 00:12:10.490 --> 00:12:12.600 or the most reduction that we saw,

257 00:12:12.600 --> 00:12:15.610 we consider did they have distant migration of disease?

258 00:12:15.610 --> 00:12:17.770 So for example, if they had a brain tumor,

259 00:12:17.770 --> 00:12:21.775 did they also come in with tumors in their liver?

260 00:12:21.775 --> 00:12:25.370 And then we come up, we have a four point ordinal scale,

261 00:12:25.370 --> 00:12:28.720 and it tells us whether the patient has a complete response,

262 00:12:28.720 --> 00:12:31.120 which means the tumor burden's gone, right?

263 00:12:31.120 --> 00:12:32.110 The lesions are gone,

264 00:12:32.110 --> 00:12:34.520 or the blast counts in their blood are gone,

265 00:12:34.520 --> 00:12:36.290 if they have leukemia.

266 00:12:36.290 --> 00:12:37.650 They had a partial response.

267 00:12:37.650 --> 00:12:39.920 That means there was a reduction in their tumor size,

268 00:12:39.920 --> 00:12:43.210 and it was a clinically meaningful reduction.

269 00:12:43.210 --> 00:12:44.290 They had stable disease,

270 00:12:44.290 --> 00:12:46.420 which means that there could have been a reduction,

271 00:12:46.420 --> 00:12:48.210 but it wasn't clinically meaningful,

272 00:12:48.210 --> 00:12:50.140 and it didn't really increase.

273 00:12:50.140 --> 00:12:52.920 And progressive disease, the tumor burden is much higher

274 00:12:52.920 --> 00:12:54.770 than it was at baseline.

275 00:12:54.770 --> 00:12:59.080 So this process is critical for understanding

276 00:12:59.080 --> 00:13:01.900 and making decisions in phase two trials,

277 00:13:01.900 --> 00:13:03.427 as well as now the phase one trials

278 00:13:03.427 --> 00:13:06.870 that we have in oncology, which are very large.

279 00:13:06.870 --> 00:13:09.120 This forms the basis for many go-decisions

280 00:13:09.120 --> 00:13:10.700 of whether you continue to develop a drug.

281 00:13:10.700 --> 00:13:14.020 Did it have a local effect on the tumor burden?

282 00:13:14.020 --> 00:13:15.330 It's very expensive to do this.

283 00:13:15.330 --> 00:13:17.680 It's very difficult to do this.

284 00:13:17.680 --> 00:13:18.630 So now we have to think

285 00:13:18.630 --> 00:13:21.913 about how can we get this information from an EMR?

286 00:13:22.870 --> 00:13:25.930 Certainly patients may have scans in an EMR

287 00:13:25.930 --> 00:13:27.510 that we could use,

288 00:13:27.510 --> 00:13:29.820 but there's several issues with that.

289 00:13:29.820 --> 00:13:32.810 So if we're going to use scans in a database

290 00:13:32.810 --> 00:13:35.500 to assess a patient's tumor burden,

291 00:13:35.500 --> 00:13:39.473 number one, those scans don't go for a central review.

292 00:13:40.440 --> 00:13:42.280 The process by which the community

293 00:13:42.280 --> 00:13:45.290 or the non-trial evaluation of those scans

294 00:13:45.290 --> 00:13:47.843 is very different than the clinical trial process.

295 00:13:48.710 --> 00:13:51.290 They don't really have an ordinal scale

296 00:13:51.290 --> 00:13:52.973 like this that they use.

297 00:13:53.960 --> 00:13:57.520 Certainly, I think you could distinguish progressive disease

298 00:13:57.520 --> 00:13:58.570 from complete response.

299 00:13:58.570 --> 00:13:59.890 I think it'd be very difficult

300 00:13:59.890 --> 00:14:02.870 to distinguish partial response from stable disease.

301 00:14:02.870 --> 00:14:05.210 So we have groups that are saying they can do this, right?

302 00:14:05.210 --> 00:14:07.440 They're going back to the clinical annotations

303 00:14:07.440 --> 00:14:09.080 and the writing algorithms that look

304 00:14:09.080 --> 00:14:11.190 at the clinical annotations that says,

305 00:14:11.190 --> 00:14:13.840 well, if the notes say the lesions are all gone,

306 00:14:13.840 --> 00:14:16.030 then they had a complete response, right?

307 00:14:16.030 --> 00:14:19.980 If there was an increase, overall increase,

308 00:14:19.980 --> 00:14:22.930 or there was new lesions, they had progressive disease.

309 00:14:22.930 --> 00:14:24.930 So if the annotations are good enough,

310 00:14:24.930 --> 00:14:27.420 I guess, you could get to progressive disease

311 00:14:27.420 --> 00:14:28.773 versus complete response.

312 00:14:29.870 --> 00:14:32.890 However, there are several issues with this.

313 00:14:32.890 --> 00:14:35.820 Everything in oncology is based on the line of therapy.

314 00:14:35.820 --> 00:14:39.130 Patients come in, they get a sequence of treatments.

315 00:14:39.130 --> 00:14:42.850 Usually, they progress and go to a second line of therapy.

316 00:14:42.850 --> 00:14:43.820 Or they progress again

317 00:14:43.820 --> 00:14:45.780 and they go to a third line of therapy.

318 00:14:45.780 --> 00:14:48.700 The expectations for tumor response as both survival

319 00:14:48.700 --> 00:14:51.060 are very different by line of therapy.

320 00:14:51.060 --> 00:14:52.290 So if you're gonna go into the EMR,

321 00:14:52.290 --> 00:14:54.550 you have to now make sure

322 00:14:54.550 --> 00:14:58.180 that the scans you're getting align with the line of therapy

323 00:14:58.180 --> 00:15:00.500 that you're enrolling in your clinical study.

324 00:15:00.500 --> 00:15:03.890 So most clinical studies in oncology require

325 00:15:03.890 --> 00:15:05.120 a specific line of therapy.

326 00:15:05.120 --> 00:15:07.070 So first-line therapy means patients

327 00:15:07.070 --> 00:15:08.910 that haven't been treated previously.

328 00:15:08.910 --> 00:15:10.450 Second-line therapy means patients

329 00:15:10.450 --> 00:15:12.460 that have progressed on a prior treatment,

330 00:15:12.460 --> 00:15:14.700 and now they're trying a subsequent treatment.

331 00:15:14.700 --> 00:15:17.650 So the expectations are very different for response by that.

332 00:15:17.650 --> 00:15:20.170 So you would have to know that this is the first,

333 00:15:20.170 --> 00:15:22.027 if you're using a first-line therapy study,

334 00:15:22.027 --> 00:15:23.270 you would have to know

335 00:15:23.270 --> 00:15:25.100 that this is this patient's first line of therapy

336 00:15:25.100 --> 00:15:27.070 and these scans correspond to that.

337 00:15:27.070 --> 00:15:28.540 Not only that, you'd have to make sure

338 00:15:28.540 --> 00:15:31.400 the scans reasonably aligned with the time-frame

339 00:15:31.400 --> 00:15:32.410 by which the clinical trial

340 00:15:32.410 --> 00:15:34.513 is actually going to acquire their energy.

341 00:15:36.900 --> 00:15:40.062 Beyond that, you'd have to, you know,

342 00:15:40.062 --> 00:15:43.290 there are several other issues with that, right?

343 00:15:43.290 --> 00:15:47.210 Patients may not be scanned in the community setting.

344 00:15:47.210 --> 00:15:49.210 And working with oncologists for a long time,

345 00:15:49.210 --> 00:15:51.530 I know that there's a certain point

346 00:15:51.530 --> 00:15:54.063 where if a patient fails a few lines of therapy,

347 00:15:55.000 --> 00:15:58.230 they may not wanna risk the patient getting nephrotoxicity

348 00:15:58.230 --> 00:16:00.940 from the contrast that are used in the scans.

349 00:16:00.940 --> 00:16:04.440 So if a patient doesn't have a lot of good treatment options

350 00:16:04.440 --> 00:16:06.193 or they're reasonably unhealthy,

351 00:16:06.193 --> 00:16:09.180 where there's concern about kidney or liver issues,

352 00:16:09.180 --> 00:16:11.660 they don't scan the patients in the community.

353 00:16:11.660 --> 00:16:15.900 So up till now, I think that the consensus has been,

354 00:16:15.900 --> 00:16:18.560 there is no real-world tumor response right now.

355 00:16:18.560 --> 00:16:19.510 We don't have that.

356 00:16:19.510 --> 00:16:21.790 And I think that's difficult because

357 00:16:22.910 --> 00:16:26.130 we want to use real-world data to sort of augment

358 00:16:26.130 --> 00:16:27.410 or supplement the areas

359 00:16:27.410 --> 00:16:29.650 where we don't have a lot of information, right?

360 00:16:29.650 --> 00:16:32.750 And that is the early phase studies, right?

361 00:16:32.750 --> 00:16:33.830 Once you go to phase three,

362 00:16:33.830 --> 00:16:36.960 you've kind of established that the drug may be promising

363 00:16:36.960 --> 00:16:39.240 and you're gonna run a seven-year trial.

364 00:16:39.240 --> 00:16:40.350 And over that seven years,

365 00:16:40.350 --> 00:16:42.570 you're gonna acquire lots of information,

366 00:16:42.570 --> 00:16:45.030 and you're gonna follow them for survival.

367 00:16:45.030 --> 00:16:46.710 This could, with really the narrative

368 00:16:46.710 --> 00:16:47.927 about real-world evidence in oncology,

369 00:16:47.927 --> 00:16:49.500 has really been we can supplement

370 00:16:49.500 --> 00:16:51.830 those early phase decisions.

371 00:16:51.830 --> 00:16:52.663 But to do that,

372 00:16:52.663 --> 00:16:54.710 we really have to have a real-world tumor response.

373 00:16:54.710 --> 00:16:57.010 And right now we don't have it.

374 00:16:57.010 --> 00:16:59.020 This is a paper from Advanced Therapeutics

375 00:16:59.020 --> 00:17:00.900 that was published this year.

376 00:17:00.900 --> 00:17:03.560 We have the Flatiron group going back

377 00:17:03.560 --> 00:17:05.670 to the major immunotherapy trials

378 00:17:05.670 --> 00:17:08.160 that have been implemented in recent years.

379 00:17:08.160 --> 00:17:09.760 They're comparing their algorithm

380 00:17:09.760 --> 00:17:11.980 for real-world response rates

381 00:17:11.980 --> 00:17:16.030 with the trial confirmed response.

382 00:17:16.030 --> 00:17:16.863 So they're saying,

383 00:17:16.863 --> 00:17:19.300 for each patient, what did we say the response was

384 00:17:19.300 --> 00:17:21.430 based on our EMR data?

385 00:17:21.430 --> 00:17:23.060 What did the trial said the response was?

386 00:17:23.060 --> 00:17:24.880 And they're looking at sort of coordinates

387 00:17:24.880 --> 00:17:26.480 between those measures.

388 00:17:26.480 --> 00:17:28.290 And they're doing this by line of therapy.

389 00:17:28.290 --> 00:17:29.940 So maybe we'll get there,

390 00:17:29.940 --> 00:17:32.290 but right now the consensus is we're not there.

391 00:17:33.563 --> 00:17:38.210 So we presented this paper at ASCO,

392 00:17:38.210 --> 00:17:41.270 which is a big cancer meeting in the US last year,

393 00:17:41.270 --> 00:17:42.103 talking about,

394 00:17:42.103 --> 00:17:44.210 can we actually replace randomized controls

395 00:17:44.210 --> 00:17:46.310 with external real-world controls?

396 00:17:46.310 --> 00:17:50.710 And we actually built some tools that Genentech is using

397 00:17:50.710 --> 00:17:51.820 that actually calculate,

398 00:17:51.820 --> 00:17:56.200 that takes your assumptions about bias, heterogeneity,

399 00:17:56.200 --> 00:17:57.730 or other things that you might see in a trial

400 00:17:57.730 --> 00:18:00.580 and actually tells you how wrong you can go

401 00:18:00.580 --> 00:18:04.350 with a go-decision when you use an external control.

402 00:18:04.350 --> 00:18:06.503 And of course, I think maybe everybody knows this,

403 00:18:06.503 --> 00:18:10.796 that the reality is that if there's no bias, it's useful.

404 00:18:10.796 --> 00:18:14.010 If there is bias, things can go really wrong very quickly,

405 00:18:14.010 --> 00:18:15.940 depending on the direction of the bias.

406 00:18:15.940 --> 00:18:18.220 And that is really unknown.

407 00:18:18.220 --> 00:18:23.220 So we tried to think about this in a very systematic way,

408 00:18:23.330 --> 00:18:25.330 and I think it's challenging.

409 00:18:25.330 --> 00:18:26.980 I don't know that we can do this.

410 00:18:27.920 --> 00:18:31.040 So that leads to, you know, what this discussion was

411 00:18:31.040 --> 00:18:33.950 at UNC with the FDA, the EMA, and Genentech

412 00:18:33.950 --> 00:18:35.110 where we're talking

413 00:18:35.110 --> 00:18:39.130 about now, can we augment randomized control arms

414 00:18:39.130 --> 00:18:42.330 with data from real-world sources?

415 00:18:42.330 --> 00:18:46.283 So we don't get rid of the randomized control,.

416 00:18:46.283 --> 00:18:47.670 We keep the randomized control,

417 00:18:47.670 --> 00:18:50.740 but we supplement it with some external controls.

418 00:18:50.740 --> 00:18:51.597 How could we do that?

419 00:18:51.597 --> 00:18:53.040 And could we even acquire those

420 00:18:53.040 --> 00:18:55.950 before the trial gets initiated?

421 00:18:55.950 --> 00:18:57.940 Of course, it takes a long time for protocols

422 00:18:57.940 --> 00:19:00.140 to be reviewed and other things to happen.

423 00:19:00.140 --> 00:19:03.180 Well, this gets interesting to me

424 00:19:03.180 --> 00:19:07.570 because while I developed tools to do this a long time ago,

425 00:19:07.570 --> 00:19:10.610 which I called Multi-source Adaptive Designs.

426 00:19:10.610 --> 00:19:14.840 And this was done many years ago

427 00:19:14.840 --> 00:19:17.090 before we talked about real-world evidence.

428 00:19:17.090 --> 00:19:20.140 We were talking about historical controls at that time,

429 00:19:20.140 --> 00:19:21.660 but of course we can do interesting things

430 00:19:21.660 --> 00:19:22.623 with modeling here.

431 00:19:23.640 --> 00:19:25.550 We could take real-world controls,

432 00:19:25.550 --> 00:19:28.860 we could think about an interim analysis

433 00:19:28.860 --> 00:19:29.950 of a randomized trial,

434 00:19:29.950 --> 00:19:33.100 where we have randomized treated and randomized controls.

435 00:19:33.100 --> 00:19:36.570 We could do any sort of fancy model that you wanna fit,

436 00:19:36.570 --> 00:19:39.990 and we could assess how biased are these historical controls

437 00:19:39.990 --> 00:19:43.020 or real-world controls in relation to the control data

438 00:19:43.020 --> 00:19:45.710 that we're seeing in the actual randomized trial.

439 00:19:45.710 --> 00:19:47.070 On the basis of this model,

440 00:19:47.070 --> 00:19:50.130 we could actually adapt the allocation, right?

441 00:19:50.130 --> 00:19:51.440 If we don't see a lot of bias,

442 00:19:51.440 --> 00:19:55.370 so those patients, based on the eligibility of the trial,

443 00:19:55.370 --> 00:19:56.710 those patients from the community,

444 00:19:56.710 --> 00:19:59.500 they look a lot like the patients in the trial,

445 00:19:59.500 --> 00:20:01.720 then you have more information on the control side.

446 00:20:01.720 --> 00:20:04.090 You need to rebalance the rest of your allocation

447 00:20:04.090 --> 00:20:05.890 so that you can increase power.

448 00:20:05.890 --> 00:20:07.040 So this is the only designs

449 00:20:07.040 --> 00:20:09.807 where you can actually increase statistical power

450 00:20:09.807 --> 00:20:12.010 with a smaller trial.

451 00:20:12.010 --> 00:20:13.100 Because what we're trying to do,

452 00:20:13.100 --> 00:20:15.090 is we're trying to balance the overall information

453 00:20:15.090 --> 00:20:17.130 between the treatments, right?

454 00:20:17.130 --> 00:20:19.628 If you look at the outcome, adaptive randomized studies,

455 00:20:19.628 --> 00:20:21.320 they required larger trials

456 00:20:21.320 --> 00:20:22.810 because they're imbalancing.

457 00:20:22.810 --> 00:20:24.770 They're imbalancing based on outcomes.

458 00:20:24.770 --> 00:20:27.010 We're trying to balance based on bias.

459 00:20:27.010 --> 00:20:28.990 So we worked out this methodology

460 00:20:28.990 --> 00:20:31.550 and you know, ASCO and Flatiron

461 00:20:31.550 --> 00:20:33.083 are interested in using this.

462 00:20:34.240 --> 00:20:35.510 We have a paper that describes

463 00:20:35.510 --> 00:20:37.000 an open-source tool that we have.

464 00:20:37.000 --> 00:20:38.700 It's still on MD Anderson's website

465 00:20:38.700 --> 00:20:41.763 that I built when I was at MD Anderson with Nan Chen.

466 00:20:42.660 --> 00:20:43.970 Who is pictured is here.

467 00:20:43.970 --> 00:20:45.503 So Nan is now at Gilead.

468 00:20:46.640 --> 00:20:49.000 But if you interested in this, it's here.

469 00:20:49.000 --> 00:20:54.000 So I think based on in oncology setting,

470 00:20:54.290 --> 00:20:56.260 we need to focus on this area.

471 00:20:56.260 --> 00:20:57.930 We need to focus on hybrid controls,

472 00:20:57.930 --> 00:21:00.050 not replacing control arms, right?

473 00:21:00.050 --> 00:21:01.680 At least for most studies.

474 00:21:01.680 --> 00:21:05.700 Of course, in rare diseases or areas of pediatric cancer,

475 00:21:05.700 --> 00:21:08.300 or both, you need to do something else, right?

476 00:21:08.300 --> 00:21:09.990 And that's what the FDA is talking about

477 00:21:09.990 --> 00:21:11.300 when they talk about flexibility.

478 00:21:11.300 --> 00:21:12.133 But I'm talking about

479 00:21:12.133 --> 00:21:16.020 from kind of the standard drug development program

480 00:21:16.020 --> 00:21:17.203 in oncology right now.

481 00:21:18.354 --> 00:21:20.840 So I've talked about the issues,

482 00:21:20.840 --> 00:21:23.650 I've talked about the databases

483 00:21:23.650 --> 00:21:24.750 and sort of what's going on

484 00:21:24.750 --> 00:21:26.550 with real-world data in oncology.

485 00:21:26.550 --> 00:21:29.940 There's another group of sort of players in the space.

486 00:21:29.940 --> 00:21:30.773 And I would call them

487 00:21:30.773 --> 00:21:33.233 kind of the real-world evidence zealots.

488 00:21:34.642 --> 00:21:39.642 This guy, Dr. Butte from Stanford has,

489 00:21:39.670 --> 00:21:41.620 I think represents one of these people.

490 00:21:42.520 --> 00:21:46.540 So he is a strong advocate for using databases

491 00:21:46.540 --> 00:21:49.623 to replace clinical research.

492 00:21:51.910 --> 00:21:54.300 He has at least three TED Talks,

493 00:21:54.300 --> 00:21:57.293 and I was going through them yesterday.

494 00:21:58.610 --> 00:22:01.220 He has a very strong feeling that we just need

495 00:22:01.220 --> 00:22:02.640 to organize these databases,

496 00:22:02.640 --> 00:22:05.770 and we can answer any medical or scientific question

497 00:22:05.770 --> 00:22:07.290 that we want to answer.

498 00:22:07.290 --> 00:22:08.461 And in fact, he even says,

499 00:22:08.461 --> 00:22:12.310 the problem is there's not enough people asking questions.

500 00:22:12.310 --> 00:22:13.910 That's the real issue right now.

501 00:22:15.240 --> 00:22:17.470 So there's this other group of people

502 00:22:17.470 --> 00:22:19.610 that are you know really hyping up

503 00:22:20.640 --> 00:22:22.620 the fact that it's just a computing problem.

504 00:22:22.620 --> 00:22:23.453 we have the data,

505 00:22:23.453 --> 00:22:26.630 we can use algorithms to answer any question we want.

506 00:22:26.630 --> 00:22:31.233 This group of people seems to lack any recognition

507 00:22:31.233 --> 00:22:34.840 of the principles of experimental design.

508 00:22:34.840 --> 00:22:37.840 They don't seem to acknowledge them anywhere in the process.

509 00:22:39.619 --> 00:22:43.950 And Dr. Butte and his TED talks actually says

510 00:22:43.950 --> 00:22:46.270 that we don't need randomized controls after all,

511 00:22:46.270 --> 00:22:49.420 we just need to build databases.

512 00:22:49.420 --> 00:22:50.489 So we had these groups,

513 00:22:50.489 --> 00:22:53.220 so these are the kind of the players pushing this forward.

514 00:22:53.220 --> 00:22:54.460 So now I'm gonna transition here.

515 00:22:54.460 --> 00:22:56.110 I'm gonna talk about what's going on

516 00:22:56.110 --> 00:22:57.453 in precision oncology.

517 00:22:58.980 --> 00:23:00.550 Okay, so this is how you learned

518 00:23:00.550 --> 00:23:02.610 about drug development programs.

519 00:23:02.610 --> 00:23:06.109 You learned that we chose dose in phase one,

520 00:23:06.109 --> 00:23:11.010 if the dose was promising and we were able to discover

521 00:23:12.020 --> 00:23:15.050 what the MTD was, and we felt like it wasn't toxic

522 00:23:15.050 --> 00:23:15.900 and we had a good dose,

523 00:23:15.900 --> 00:23:17.640 we would go to a phase two trial.

524 00:23:17.640 --> 00:23:19.850 In oncology, we would look at tumor response.

525 00:23:19.850 --> 00:23:21.960 So again, reduction in tumor burden.

526 00:23:21.960 --> 00:23:23.940 Usually these would be uncontrolled.

527 00:23:23.940 --> 00:23:26.360 They would be about 50-100 patients.

528 00:23:26.360 --> 00:23:29.660 If we saw the drug had local activity on tumor burden,

529 00:23:29.660 --> 00:23:31.540 we would go to a phase three trial.

530 00:23:31.540 --> 00:23:33.190 The phase three trial would randomize

531 00:23:33.190 --> 00:23:35.090 to the existing standard of care.

532 00:23:35.090 --> 00:23:38.073 And would see if the treatment prolonged survival.

533 00:23:38.910 --> 00:23:40.830 This is what you learned about,

534 00:23:40.830 --> 00:23:44.090 but oncology has changed very rapidly.

535 00:23:44.090 --> 00:23:47.000 Regulatory policy has changed as well.

536 00:23:47.000 --> 00:23:50.770 So molecular biologists have some victories recently.

537 00:23:50.770 --> 00:23:53.430 They have really, you know, a lot of the biological models

538 00:23:53.430 --> 00:23:56.620 that were discovered a decade ago

539 00:23:56.620 --> 00:23:59.890 have been translated into therapeutics.

540 00:23:59.890 --> 00:24:02.570 So it used to be that we needed one

541 00:24:02.570 --> 00:24:04.640 or two well-controlled phase three trials

542 00:24:04.640 --> 00:24:08.150 before we got regulatory approval.

543 00:24:08.150 --> 00:24:11.380 It turns out that cancer biologists

544 00:24:11.380 --> 00:24:14.520 have identified very specific cancer subsets

545 00:24:14.520 --> 00:24:16.893 based on genetics and based on immunology.

546 00:24:17.930 --> 00:24:21.040 With those cancer subsets, we have seen very promising,

547 00:24:21.040 --> 00:24:26.040 very exciting results in phase two trials without controls.

548 00:24:26.360 --> 00:24:29.050 The FDA started to allow conditional approvals

549 00:24:29.050 --> 00:24:30.720 after phase two on the basis

550 00:24:30.720 --> 00:24:33.210 of those biomarker targeted treatments.

551 00:24:33.210 --> 00:24:35.730 Now we're in kind of stage three here.

552 00:24:35.730 --> 00:24:38.220 Now we have the awareness that many of the targets,

553 00:24:38.220 --> 00:24:39.390 many of the genetic targets,

554 00:24:39.390 --> 00:24:44.330 as well as the immune phenotypes that we're interested in,

555 00:24:44.330 --> 00:24:46.710 they actually exist across several different

556 00:24:46.710 --> 00:24:50.380 sort of traditionally distinct cancer patients.

557 00:24:50.380 --> 00:24:54.260 So patients with pancreatic cancer and lung cancer

558 00:24:54.260 --> 00:24:56.960 may be very different from a clinical perspective,

559 00:24:56.960 --> 00:24:58.710 but they might share a molecular feature

560 00:24:58.710 --> 00:25:01.380 that can be targeted by the same drug.

561 00:25:01.380 --> 00:25:02.940 And we're now in the space

562 00:25:02.940 --> 00:25:06.210 of histology-agnostic drug development,

563 00:25:06.210 --> 00:25:09.048 where we might be replacing

564 00:25:09.048 --> 00:25:11.220 traditional classification criteria

565 00:25:11.220 --> 00:25:13.310 based on molecular features.

566 00:25:13.310 --> 00:25:17.603 So we're basically finding new subtypes of cancers as we go.

567 00:25:18.820 --> 00:25:20.800 These subtypes are very small,

568 00:25:20.800 --> 00:25:21.940 and they're becoming smaller

569 00:25:21.940 --> 00:25:23.943 as we learn more about cancer biology.

570 00:25:24.830 --> 00:25:28.270 But a few of them had had very exceptional results.

571 00:25:28.270 --> 00:25:29.650 A few drugs targeting these event,

572 00:25:29.650 --> 00:25:31.080 have had very exceptional results,

573 00:25:31.080 --> 00:25:32.950 crossing many tumor types.

574 00:25:32.950 --> 00:25:36.940 And they have gotten accelerated approval for agnostic drugs

575 00:25:36.940 --> 00:25:38.330 and drugs that can be administered

576 00:25:38.330 --> 00:25:40.850 without regard to the tissue of origin.

577 00:25:40.850 --> 00:25:42.653 And this has happened in phase one.

578 00:25:43.790 --> 00:25:45.410 So the regulatory landscape has changed,

579 00:25:45.410 --> 00:25:50.330 the development landscape has changed.

580 00:25:50.330 --> 00:25:52.840 So I got to be a part of this review

581 00:25:52.840 --> 00:25:55.093 for Nature of Clinical Oncology,

582 00:25:57.200 --> 00:26:00.340 where we talked about these tissue-agnostic drugs.

583 00:26:00.340 --> 00:26:02.480 There's actually four drugs so far

584 00:26:02.480 --> 00:26:04.110 that have been approved by the FDA

585 00:26:04.110 --> 00:26:07.580 that could be administered based on a marker feature,

586 00:26:07.580 --> 00:26:09.873 not on the actual cancer tissue.

587 00:26:11.050 --> 00:26:13.883 So now look at the issues with this.

588 00:26:13.883 --> 00:26:17.260 There's four drugs, and there's three different biomarkers

589 00:26:17.260 --> 00:26:19.960 that have been approved for tissue-agnostic treatment.

590 00:26:20.870 --> 00:26:23.190 One of the biomarkers is the NTRK fusion,

591 00:26:23.190 --> 00:26:25.200 which we'll talk about little later.

592 00:26:25.200 --> 00:26:27.040 It's exceedingly rare.

593 00:26:27.040 --> 00:26:28.360 You can see that breast cancer,

594 00:26:28.360 --> 00:26:30.602 we're talking about less than 0.1%

595 00:26:30.602 --> 00:26:33.607 of the patients have an NTRK fusion, right?

596 00:26:33.607 --> 00:26:37.320 And CRC it's about 1% of patients.

597 00:26:37.320 --> 00:26:40.470 There's a few tumors where it's more common,

598 00:26:40.470 --> 00:26:42.180 but this becomes very challenging.

599 00:26:42.180 --> 00:26:45.410 It becomes very challenging to design a study

600 00:26:45.410 --> 00:26:48.350 where we can actually study patients with NTRK fusions.

601 00:26:48.350 --> 00:26:49.890 And then who are you gonna get in your study?

602 00:26:49.890 --> 00:26:52.960 You're going to get a mixture of many different tissues

603 00:26:52.960 --> 00:26:54.100 that were traditionally thought

604 00:26:54.100 --> 00:26:55.503 to be separate cancers.

605 00:26:56.670 --> 00:27:01.670 So with this transition to tissue-agnostic drug development,

606 00:27:03.210 --> 00:27:05.210 there's a statistical question that we have to answer,

607 00:27:05.210 --> 00:27:07.331 and that is who can be averaged?

608 00:27:07.331 --> 00:27:12.331 Which tissue types could be averaged statistically,

609 00:27:12.770 --> 00:27:16.510 when we assess the effectiveness of a biomarker targets

610 00:27:16.510 --> 00:27:18.451 and a therapeutic?

611 00:27:18.451 --> 00:27:22.250 And that's the question of statistical exchangeability.

612 00:27:22.250 --> 00:27:24.460 So we have developed patient models

613 00:27:24.460 --> 00:27:28.470 that actually characterize

614 00:27:28.470 --> 00:27:32.770 what subsets of tumors actually respond in a similar way

615 00:27:32.770 --> 00:27:33.950 to a targeted therapy.

616 00:27:33.950 --> 00:27:37.240 And this gives us statistical criteria

617 00:27:37.240 --> 00:27:40.320 for understanding what is agnostic and what is not.

618 00:27:40.320 --> 00:27:42.580 And I got the, you know, this is the first time,

619 00:27:42.580 --> 00:27:44.040 I got to collaborate with Dr. Kane

620 00:27:44.040 --> 00:27:46.170 on actually building out tools for this.

621 00:27:46.170 --> 00:27:49.920 So I can do the methods, but the tools or something else.

622 00:27:49.920 --> 00:27:51.730 So Michael got these incredible tools.

623 00:27:51.730 --> 00:27:55.520 And we have an open source package for fitting these models.

624 00:27:55.520 --> 00:27:57.690 Just to give you sort of motivation here.

625 00:27:57.690 --> 00:27:58.990 This is an actual trial

626 00:27:58.990 --> 00:28:03.760 that was evaluating a drug called Bendroflumeth

627 00:28:03.760 --> 00:28:07.670 in BRAF tumors, patients that have BRAF mutations.

628 00:28:07.670 --> 00:28:09.500 So there is BRAF mutations can occur

629 00:28:09.500 --> 00:28:10.770 in many different tumors.

630 00:28:10.770 --> 00:28:12.980 They initially developed this drug in Melanoma,

631 00:28:12.980 --> 00:28:15.020 but then they saw BRAF tumors,

632 00:28:15.020 --> 00:28:17.230 BRAF mutations exist in these other cancers.

633 00:28:17.230 --> 00:28:19.810 Histiocytosis, thyroid cancer,

634 00:28:19.810 --> 00:28:21.940 cholangiocarcinoma, for example.

635 00:28:21.940 --> 00:28:23.880 So they ran up, what's known as a Basket Trial,

636 00:28:23.880 --> 00:28:26.220 where they allowed these different tumor types

637 00:28:26.220 --> 00:28:27.363 in the same trial.

638 00:28:28.386 --> 00:28:31.170 So we show in this nature of these clinical oncology paper,

639 00:28:31.170 --> 00:28:33.530 how these exchangeability models work.

640 00:28:33.530 --> 00:28:36.110 We call them multi-source exchangeability models.

641 00:28:36.110 --> 00:28:39.400 Where we start with an assumption that these tumors

642 00:28:39.400 --> 00:28:41.210 are gonna act in the same way, right?

643 00:28:41.210 --> 00:28:42.680 So the drug target combination

644 00:28:42.680 --> 00:28:47.090 is going to be kind of equally efficacious

645 00:28:47.090 --> 00:28:47.960 among all the tumors.

646 00:28:47.960 --> 00:28:49.590 So they're exchangeable statistically.

647 00:28:49.590 --> 00:28:51.300 We can average them.

648 00:28:51.300 --> 00:28:54.610 As we start to get data from the trial,

649 00:28:54.610 --> 00:28:57.670 we can now start to assess the heterogeneity

650 00:28:57.670 --> 00:28:58.917 that we see across these tumors.

651 00:28:58.917 --> 00:29:00.690 And we can ask the question,

652 00:29:00.690 --> 00:29:03.810 is it really agnostic to the tumor type?

653 00:29:03.810 --> 00:29:05.220 Now, when it comes to vendor afatinib,

654 00:29:05.220 --> 00:29:08.700 we had three tumor types that did really well in this trial,

655 00:29:08.700 --> 00:29:11.800 histiocytosis, thyroid, and non-small cell lung cancer.

656 00:29:11.800 --> 00:29:13.910 Colorectal did not do well.

657 00:29:13.910 --> 00:29:15.640 So even though colorectal cancer patients

658 00:29:15.640 --> 00:29:17.350 had BRAF mutations,

659 00:29:17.350 --> 00:29:19.740 they did not respond to vendor afatinib.

660 00:29:19.740 --> 00:29:22.160 These tumors did respond.

661 00:29:22.160 --> 00:29:23.770 We don't know about cholangiocarcinoma.

662 00:29:23.770 --> 00:29:25.750 There wasn't enough information in that trial

663 00:29:25.750 --> 00:29:26.583 to really tell us.

664 00:29:26.583 --> 00:29:28.520 So they're kind of in the center here.

665 00:29:28.520 --> 00:29:31.010 So, you know, this is just to give you a flavor

666 00:29:31.010 --> 00:29:33.182 of what's going on in oncology right now,

667 00:29:33.182 --> 00:29:35.750 As we start to go towards precision medicine,

668 00:29:35.750 --> 00:29:38.730 that means that we have features across traditionally

669 00:29:38.730 --> 00:29:39.790 very different cancers.

670 00:29:39.790 --> 00:29:40.790 And we have to understand

671 00:29:40.790 --> 00:29:43.570 whether it's actually the feature that's driving,

672 00:29:43.570 --> 00:29:45.582 what we see in the response.

673 00:29:45.582 --> 00:29:47.930 Okay, so this is an issue

674 00:29:47.930 --> 00:29:52.430 that I don't think is that well understood outside

675 00:29:52.430 --> 00:29:55.200 of our sort of biostatistical and statistical communities.

676 00:29:55.200 --> 00:29:57.260 And that is how, just the extent

677 00:29:57.260 --> 00:29:59.518 to which prognostic heterogeneity plays a role

678 00:29:59.518 --> 00:30:02.730 in the precision oncology space, or any space

679 00:30:02.730 --> 00:30:06.470 where you're doing biomarker driven therapeutics.

680 00:30:06.470 --> 00:30:09.240 So what I'm showing you here is the cancer immunity cycle

681 00:30:09.240 --> 00:30:11.020 by Chen and Mellman.

682 00:30:11.020 --> 00:30:13.090 So this diagram sort of revolutionized

683 00:30:13.090 --> 00:30:16.025 how we think about how the immune system identifies

684 00:30:16.025 --> 00:30:19.043 and counteracts malignant cells.

685 00:30:20.880 --> 00:30:23.956 So cancer cells release antigens.

686 00:30:23.956 --> 00:30:27.883 They have to be detected by the immune system.

687 00:30:29.115 --> 00:30:31.680 If the immune system detects antigens,

688 00:30:31.680 --> 00:30:33.370 means your immune system is actually aware

689 00:30:33.370 --> 00:30:35.000 that you have cancer.

690 00:30:35.000 --> 00:30:38.550 They have to produce natural killer cells.

691 00:30:38.550 --> 00:30:40.620 So the T cells have to be produced in the lymph nodes.

692 00:30:40.620 --> 00:30:43.250 They have to infiltrate the tumor.

693 00:30:43.250 --> 00:30:45.900 They have to recognize which cells are malignant cells,

694 00:30:45.900 --> 00:30:48.350 and then they have to kill the malignant cells.

695 00:30:48.350 --> 00:30:50.650 This process is very complicated

696 00:30:50.650 --> 00:30:52.340 and there are biomarkers

697 00:30:52.340 --> 00:30:56.030 that can tell us about what's happening with the patient.

698 00:30:56.030 --> 00:30:59.070 What's happening with the patient's innate immune response

699 00:30:59.070 --> 00:31:00.700 to cancer.

700 00:31:00.700 --> 00:31:04.360 So the biomarkers that have been most developed recently

701 00:31:04.360 --> 00:31:08.240 are the PD-L1 biomarkers, which is this last step.

702 00:31:08.240 --> 00:31:09.870 So if a patient is expressing

703 00:31:09.870 --> 00:31:12.150 a lot of program death like in one,

704 00:31:12.150 --> 00:31:13.920 it means that the malignant cells

705 00:31:13.920 --> 00:31:16.390 are actually hiding from the T cells.

706 00:31:16.390 --> 00:31:18.750 So the patients might be producing lymphocytes.

707 00:31:18.750 --> 00:31:22.100 They might be getting to the tumor, but they can't attach.

708 00:31:22.100 --> 00:31:24.620 They can't identify which cells are malignant cells,

709 00:31:24.620 --> 00:31:26.490 malignant cells are hiding.

710 00:31:26.490 --> 00:31:28.140 So there're very interesting things that happen

711 00:31:28.140 --> 00:31:30.333 when you get to a biological perspective.

712 00:31:31.520 --> 00:31:34.490 The immune phenotypes based on these biomarkers.

713 00:31:34.490 --> 00:31:38.320 If we look at T-cell infiltration versus PD-L1 expression.

714 00:31:38.320 --> 00:31:40.280 Patients that are producing T cells

715 00:31:41.530 --> 00:31:43.720 and that have low PD-L1 expression.

716 00:31:43.720 --> 00:31:45.540 So that means T-cells are being produced,

717 00:31:45.540 --> 00:31:47.250 they're coming to the tumor

718 00:31:47.250 --> 00:31:49.580 and then they're effective when they get to the tumor.

719 00:31:49.580 --> 00:31:52.950 These patients have a different immune profile,

720 00:31:52.950 --> 00:31:54.640 than the opposite case

721 00:31:54.640 --> 00:31:57.190 where patients are not producing T cells.

722 00:31:57.190 --> 00:31:59.100 So it's like their immune system isn't aware

723 00:31:59.100 --> 00:32:00.260 that they have cancer.

724 00:32:00.260 --> 00:32:02.540 And then even if they did produce T cells,

725 00:32:02.540 --> 00:32:05.320 they're not effective once they get to the tumor.

726 00:32:05.320 --> 00:32:09.760 So there's various things happening in this phase.

727 00:32:09.760 --> 00:32:12.450 And so now I go back to Professor Butte

728 00:32:13.360 --> 00:32:15.653 and sort of what he's saying,

729 00:32:16.630 --> 00:32:18.560 So there's several articles that he's written

730 00:32:18.560 --> 00:32:19.690 that say things like this,

731 00:32:19.690 --> 00:32:22.810 precision medicine makes doctors nervous.

732 00:32:22.810 --> 00:32:25.830 And he says, the reason that makes doctors nervous

733 00:32:25.830 --> 00:32:29.350 is because they have to admit that what they were doing

734 00:32:29.350 --> 00:32:31.043 before was not precise.

735 00:32:31.900 --> 00:32:35.245 So we see these things

736 00:32:35.245 --> 00:32:37.395 and we see these kinds of narratives coming

737 00:32:38.490 --> 00:32:40.260 from the group that's really pushing that

738 00:32:40.260 --> 00:32:42.473 we just need to analyze these databases.

739 00:32:43.860 --> 00:32:46.900 So he's talking about retroactive crowdsourcing, right?

740 00:32:46.900 --> 00:32:49.050 A high school kid can do it.

741 00:32:49.050 --> 00:32:50.270 So if you've listened to his talks,

742 00:32:50.270 --> 00:32:52.320 he's always saying, a high school kid can do that.

743 00:32:52.320 --> 00:32:53.900 A high school kid could do this.

744 00:32:53.900 --> 00:32:57.550 I think a high school kid could apply a T test to a dataset.

745 00:32:57.550 --> 00:32:59.433 I don't disagree with that.

746 00:33:00.500 --> 00:33:02.700 But I have a 14 year old at home

747 00:33:02.700 --> 00:33:04.540 and he has trouble making his bed.

748 00:33:04.540 --> 00:33:09.510 So I think that there's a narrative out there

749 00:33:09.510 --> 00:33:13.350 that doesn't recognize things like this.

750 00:33:13.350 --> 00:33:15.730 So when I was at MD Anderson,

751 00:33:15.730 --> 00:33:17.040 we spent a lot of time thinking

752 00:33:17.040 --> 00:33:19.040 about these immune phenotypes.

753 00:33:19.040 --> 00:33:21.490 And I actually developed radiomics models,

754 00:33:21.490 --> 00:33:23.550 that characterized patterns

755 00:33:23.550 --> 00:33:25.770 that we saw in images in the tumor

756 00:33:25.770 --> 00:33:28.790 that reflected these immune phenotypes.

757 00:33:28.790 --> 00:33:30.460 And the reason we were doing that,

758 00:33:30.460 --> 00:33:33.210 is because these biomarkers were incredibly unreliable.

759 00:33:34.600 --> 00:33:36.270 What I'm showing you here is a scatter plot,

760 00:33:36.270 --> 00:33:39.100 that this came from the Garcia student's lab at MD Anderson,

761 00:33:39.100 --> 00:33:43.330 probably the best immune pathologists

762 00:33:43.330 --> 00:33:45.203 in the field right now.

763 00:33:46.280 --> 00:33:48.570 These are patients with non-small cell lung cancer.

764 00:33:48.570 --> 00:33:50.540 They all got treated with definitive surgery.

765 00:33:50.540 --> 00:33:52.500 So there was no chemotherapy.

766 00:33:52.500 --> 00:33:55.850 They came in, they could be treated with surgery.

767 00:33:55.850 --> 00:33:58.830 So we don't have sort of a confounding factor

768 00:33:58.830 --> 00:34:01.320 of chemotherapy here with these patients.

769 00:34:01.320 --> 00:34:04.970 We got their tissue microarray staining,

770 00:34:04.970 --> 00:34:07.640 and this was both malignant cells and immune cells,

771 00:34:07.640 --> 00:34:10.200 are PD-L1 positivity at biopsy.

772 00:34:10.200 --> 00:34:12.180 So the patients are coming in, they're getting a biopsy.

773 00:34:12.180 --> 00:34:13.820 The biopsy is taking a needle,

774 00:34:13.820 --> 00:34:16.130 sticking it in a few different locations.

775 00:34:16.130 --> 00:34:17.780 We use that tissue and we try to assess

776 00:34:17.780 --> 00:34:19.050 how much PD-L1 expression

777 00:34:19.050 --> 00:34:21.470 do they have and their lung cancer?

778 00:34:21.470 --> 00:34:23.780 Then they go in, they had surgery.

779 00:34:23.780 --> 00:34:26.760 We took their whole excise tumor.

780 00:34:26.760 --> 00:34:28.880 And we went back and we did whole section staining,

781 00:34:28.880 --> 00:34:32.210 of the excise tumor for PD-L1 expression.

782 00:34:32.210 --> 00:34:33.850 This is a scatterplot we got.

783 00:34:33.850 --> 00:34:35.550 So each point is the same patient.

784 00:34:36.600 --> 00:34:38.740 So this patient at biopsy,

785 00:34:38.740 --> 00:34:40.090 just this isn't the worst one,

786 00:34:40.090 --> 00:34:43.460 but this patient at biopsy was over 50%.

787 00:34:43.460 --> 00:34:45.693 After surgery, they're only at 15%.

788 00:34:46.970 --> 00:34:49.020 This patient is much worse.

789 00:34:49.020 --> 00:34:51.433 So what's going on here?

790 00:34:52.370 --> 00:34:54.330 Either the immune system is constantly changing

791 00:34:54.330 --> 00:34:56.533 and these biomarkers are not reproducible,

792 00:34:56.533 --> 00:34:59.500 in the sense that your state is changing,

793 00:34:59.500 --> 00:35:01.610 or when we stick that needle in

794 00:35:01.610 --> 00:35:04.920 and we take just a few points,

795 00:35:04.920 --> 00:35:07.720 we get a very different answer than when we do surgery.

796 00:35:07.720 --> 00:35:09.080 Of course, we have to use biopsy

797 00:35:09.080 --> 00:35:11.225 if we're gonna make a treatment selection.

798 00:35:11.225 --> 00:35:13.760 So this is problematic.

799 00:35:13.760 --> 00:35:16.610 So when I think about, you know, we just need databases,

800 00:35:16.610 --> 00:35:18.120 we don't have to understand the science

801 00:35:18.120 --> 00:35:20.595 and we can answer all these fundamental questions,

802 00:35:20.595 --> 00:35:22.093 I don't think it's true.

803 00:35:23.810 --> 00:35:25.900 You know, you have,

804 00:35:25.900 --> 00:35:28.520 There's issues like this with every biomarker.

805 00:35:28.520 --> 00:35:30.210 The biomarkers have to be reproducible.

806 00:35:30.210 --> 00:35:32.683 We have to understand them in a rigorous manner,

807 00:35:33.580 --> 00:35:35.463 if you're going to use scanning data.

808 00:35:37.080 --> 00:35:38.020 So, you know,

809 00:35:38.020 --> 00:35:40.190 so we've published this paper in scientific reports.

810 00:35:40.190 --> 00:35:42.150 It has been cited I think almost a hundred times

811 00:35:42.150 --> 00:35:43.260 in a few years.

812 00:35:43.260 --> 00:35:45.310 Where we actually developed a radiomics model

813 00:35:45.310 --> 00:35:49.010 for understanding the immune pathology.

814 00:35:49.010 --> 00:35:50.620 Now, why did we do that?

815 00:35:50.620 --> 00:35:51.810 We did that because we didn't think

816 00:35:51.810 --> 00:35:53.760 these biopsy assessments were reliable.

817 00:35:54.700 --> 00:35:57.230 So we thought that maybe the scans were more reliable.

818 00:35:57.230 --> 00:35:58.320 Maybe we could take the scans

819 00:35:58.320 --> 00:36:00.550 and we can understand the patterns in the scans.

820 00:36:00.550 --> 00:36:02.570 And you can see that patients

821 00:36:02.570 --> 00:36:03.980 with different immune phenotypes,

822 00:36:03.980 --> 00:36:06.550 but in terms of T-cell infiltration and PD-L1,

823 00:36:06.550 --> 00:36:09.490 they had very different expectations for survival.

824 00:36:09.490 --> 00:36:11.930 So this is not a treatment effect.

825 00:36:11.930 --> 00:36:14.800 This is just simply the impact

826 00:36:14.800 --> 00:36:17.470 of the fact that the patients have different immune systems.

827 00:36:17.470 --> 00:36:22.210 And those immune systems have differential effectiveness

828 00:36:22.210 --> 00:36:24.463 in fighting the tumor.

829 00:36:25.340 --> 00:36:28.440 So patients that have T-cells and low PD-L1 positivity,

830 00:36:28.440 --> 00:36:30.060 they're doing well.

831 00:36:30.060 --> 00:36:31.620 The opposite is true for patients

832 00:36:31.620 --> 00:36:33.723 that have high PD-L1 and low T cells.

833 00:36:34.840 --> 00:36:37.640 So we developed a radiomics model,

834 00:36:37.640 --> 00:36:41.040 which take the scans and actually assess these patterns.

835 00:36:41.040 --> 00:36:44.513 Of course, there's complications with that.

836 00:36:45.590 --> 00:36:48.080 If you're to scan any data in oncology,

837 00:36:48.080 --> 00:36:49.600 you're probably having contrast.

838 00:36:49.600 --> 00:36:51.330 You need to understand what the protocol

839 00:36:51.330 --> 00:36:54.050 for contrast was for that scan.

840 00:36:54.050 --> 00:36:56.610 Because you need to take the image

841 00:36:56.610 --> 00:36:59.020 when the contrast is in the tumor.

842 00:36:59.020 --> 00:37:00.710 So of course you can't just go blindly

843 00:37:00.710 --> 00:37:03.121 and grab a bunch of images from a database.

844 00:37:03.121 --> 00:37:05.690 So, I've talked a little bit about

845 00:37:05.690 --> 00:37:07.320 what's happening on precision oncology.

846 00:37:07.320 --> 00:37:08.780 Where we're developing biomarkers,

847 00:37:08.780 --> 00:37:10.410 we want to use to guide treatment,

848 00:37:10.410 --> 00:37:12.000 but it's very complicated.

849 00:37:12.000 --> 00:37:13.390 And I don't think doctors are scared

850 00:37:13.390 --> 00:37:14.480 because they're not precise,

851 00:37:14.480 --> 00:37:16.183 they're scared because we need to understand

852 00:37:16.183 --> 00:37:17.440 that these biomarkers

853 00:37:17.440 --> 00:37:20.420 and make sure they're reliable and reproducible.

854 00:37:20.420 --> 00:37:22.203 And that knowledge is important.

855 00:37:23.760 --> 00:37:26.480 Not only that, but because of all this complexity,

856 00:37:26.480 --> 00:37:29.060 drug development on oncology has changed a lot.

857 00:37:29.060 --> 00:37:33.117 And we no longer have this, phase one to phase two.

858 00:37:33.117 --> 00:37:37.677 This is what early phase drug trials look like now,

859 00:37:37.677 --> 00:37:39.420 especially for the big companies

860 00:37:39.420 --> 00:37:41.170 that have a lot of money to invest.

861 00:37:42.340 --> 00:37:45.370 They're taking multiple dose levels from dose expansion,

862 00:37:45.370 --> 00:37:48.400 they're running massive dose expansion cohorts.

863 00:37:48.400 --> 00:37:49.520 Those dose expansion cohorts,

864 00:37:49.520 --> 00:37:53.780 usually span multiple tumor types.

865 00:37:53.780 --> 00:37:55.770 And they might randomize across dose level,

866 00:37:55.770 --> 00:37:57.050 because we don't have

867 00:37:57.050 --> 00:37:59.550 these very clear monotonic relationships

868 00:37:59.550 --> 00:38:01.660 between dose and toxicity anymore.

869 00:38:01.660 --> 00:38:04.540 And selecting a dose isn't as simple as it used to be

870 00:38:04.540 --> 00:38:06.720 when we did cytotoxic drug development.

871 00:38:06.720 --> 00:38:08.900 So these non cytotoxic targeted therapies,

872 00:38:08.900 --> 00:38:10.850 it's hard to select a dose.

873 00:38:10.850 --> 00:38:13.823 These dose expansion cohorts can be hundreds of patients.

874 00:38:14.900 --> 00:38:17.260 They may not even stop for a phase two trial.

875 00:38:17.260 --> 00:38:19.360 They may go straight to phase two

876 00:38:19.360 --> 00:38:21.570 and expand on the expansion.

877 00:38:21.570 --> 00:38:23.430 Or they may skip phase two altogether

878 00:38:23.430 --> 00:38:25.380 because they've already acquired so much information

879 00:38:25.380 --> 00:38:27.130 in their phase one trial.

880 00:38:27.130 --> 00:38:28.710 So this is what we see happening now.

881 00:38:28.710 --> 00:38:32.100 Of course, the keynote trial evaluated in Pembrolizumab

882 00:38:32.100 --> 00:38:33.680 had eight expansion cohorts.

883 00:38:33.680 --> 00:38:35.140 There was over a thousand patients

884 00:38:35.140 --> 00:38:37.860 in this first in human phase one trial.

885 00:38:37.860 --> 00:38:39.240 This trial is what motivated

886 00:38:39.240 --> 00:38:42.380 that NCI Clinical Trial Design Task Force,

887 00:38:42.380 --> 00:38:43.213 that I got to be a part of,

888 00:38:43.213 --> 00:38:45.870 because this was a massive departure

889 00:38:45.870 --> 00:38:48.180 from what we saw typically in oncology

890 00:38:48.180 --> 00:38:52.190 and how IRBs would review these studies.

891 00:38:52.190 --> 00:38:55.950 More recently, Genentech drug (indistinct)

892 00:38:55.950 --> 00:38:59.160 had a phase one trial with nine expansion cohort.

893 00:38:59.160 --> 00:39:00.630 Looking at the dose, expansions alone,

894 00:39:00.630 --> 00:39:03.290 the bladder cancer cohort had 97 patients,

895 00:39:03.290 --> 00:39:05.610 and they randomized the three dose levels.

896 00:39:05.610 --> 00:39:06.863 So this is a new world.

897 00:39:08.510 --> 00:39:11.990 97 patients already in their dose expansion.

898 00:39:11.990 --> 00:39:14.430 So this is where Master Protocols come in.

899 00:39:14.430 --> 00:39:16.630 So we have innovations in design

900 00:39:16.630 --> 00:39:18.000 that are sort of targeting this

901 00:39:18.000 --> 00:39:22.787 and there's many, many methodology recommendations.

902 00:39:23.730 --> 00:39:24.890 The other thing that's happened in oncology

903 00:39:24.890 --> 00:39:28.060 is that phase three continues to be poor.

904 00:39:28.060 --> 00:39:29.590 So phase three trials continue

905 00:39:29.590 --> 00:39:31.490 to have a poor track record relative

906 00:39:31.490 --> 00:39:34.040 to other areas of medicine.

907 00:39:34.040 --> 00:39:36.490 You can see lots of articles that described this.

908 00:39:37.860 --> 00:39:40.040 Of course, Gan et al did a review

909 00:39:40.040 --> 00:39:43.010 of 235 published randomized controlled trials.

910 00:39:43.010 --> 00:39:46.410 Regulatory approval was, you know, less than 38%.

911 00:39:46.410 --> 00:39:47.940 And what's happening?

912 00:39:47.940 --> 00:39:49.730 While the investigators are not very good

913 00:39:49.730 --> 00:39:52.886 about making the assumptions for that phase three trial,

914 00:39:52.886 --> 00:39:55.310 we see a lot of phase three trials in oncology

915 00:39:55.310 --> 00:39:57.463 that have unrealistic expectations.

916 00:39:58.990 --> 00:40:02.180 Okay, so now I talked about precision oncology.

917 00:40:02.180 --> 00:40:03.690 I'm gonna go into some case studies

918 00:40:03.690 --> 00:40:05.540 that I think are interesting.

919 00:40:05.540 --> 00:40:08.600 And I want you ask the question,

920 00:40:08.600 --> 00:40:11.060 how could you have used real-world evidence

921 00:40:11.060 --> 00:40:12.563 to change what happens here?

922 00:40:13.610 --> 00:40:14.670 So this is coming at it

923 00:40:14.670 --> 00:40:15.937 from, these are the high profile trials

924 00:40:15.937 --> 00:40:20.210 that we have been running in the last few years in oncology.

925 00:40:20.210 --> 00:40:21.370 We want to know,

926 00:40:21.370 --> 00:40:22.900 how could we have used real-world evidence

927 00:40:22.900 --> 00:40:24.453 in these settings?

928 00:40:25.660 --> 00:40:28.090 So I'm gonna talk about Atezolizumab

929 00:40:28.090 --> 00:40:30.300 and bladder cancer.

930 00:40:30.300 --> 00:40:33.290 So Atezolizumab is another PD-1 inhibitor.

931 00:40:33.290 --> 00:40:36.283 So immunotherapy, similar to Pembrolizumab.

932 00:40:37.670 --> 00:40:39.820 So it was developed for many different areas.

933 00:40:39.820 --> 00:40:41.750 Again, we're talking about tissue-agnostic here.

934 00:40:41.750 --> 00:40:45.440 So it's targeting a feature of the immune system,

935 00:40:45.440 --> 00:40:47.140 that feature of the immune system can exist

936 00:40:47.140 --> 00:40:49.130 across many different tumor types.

937 00:40:49.130 --> 00:40:51.880 They evaluated nine in their phase one trial.

938 00:40:51.880 --> 00:40:53.177 So after the phase one trial,

939 00:40:53.177 --> 00:40:57.030 they ran a bunch of trials and different types of cancers

940 00:40:57.030 --> 00:40:58.620 and different lines of therapy.

941 00:40:58.620 --> 00:41:01.540 One of them was second-line bladder cancer.

942 00:41:01.540 --> 00:41:03.340 So these are patients with bladder cancer

943 00:41:03.340 --> 00:41:06.020 that have progressed on a prior therapy.

944 00:41:06.020 --> 00:41:09.030 So they already progressed on chemotherapy,

945 00:41:09.030 --> 00:41:11.130 now they're getting this immunotherapy.

946 00:41:11.130 --> 00:41:15.010 So they ran this study and the biomarker they're targeting

947 00:41:15.010 --> 00:41:18.080 is they're calling IC2/3.

948 00:41:18.080 --> 00:41:21.130 That is immune cell staining of PD-L1.

949 00:41:21.130 --> 00:41:24.864 And those immune cells have 5% or more expression.

950 00:41:24.864 --> 00:41:29.864 So 5% of the immune cells that they stained had,

951 00:41:29.973 --> 00:41:34.083 at least 5% had Programmed Death Ligand 1.

952 00:41:34.083 --> 00:41:36.260 That's their target.

953 00:41:36.260 --> 00:41:38.160 So, but they enrolled in this phase two trial,

954 00:41:38.160 --> 00:41:39.450 they enrolled all comers.

955 00:41:39.450 --> 00:41:41.200 It wasn't restricted to the target.

956 00:41:42.180 --> 00:41:43.070 They enrolled all comers.

957 00:41:43.070 --> 00:41:45.190 So the IC2/3 population is their target.

958 00:41:45.190 --> 00:41:47.950 That's where the mechanism is supposed to work.

959 00:41:47.950 --> 00:41:49.420 So among a hundred patients

960 00:41:49.420 --> 00:41:52.930 with that target they got a 26% response rate.

961 00:41:52.930 --> 00:41:54.840 You can see patients that don't have the target,

962 00:41:54.840 --> 00:41:57.020 there was 11 and there was eight.

963 00:41:57.020 --> 00:41:58.790 And if you look back at their paper,

964 00:41:58.790 --> 00:42:01.580 they told us that they expected 10%.

965 00:42:01.580 --> 00:42:04.220 So they said the null hypothesis was 10%

966 00:42:04.220 --> 00:42:05.220 for this population.

967 00:42:05.220 --> 00:42:06.550 We got 26%.

968 00:42:06.550 --> 00:42:08.753 This is very exciting, right?

969 00:42:09.940 --> 00:42:11.760 This is the survival curves that they present

970 00:42:11.760 --> 00:42:13.110 from their phase two trial.

971 00:42:13.110 --> 00:42:15.020 Again, this is uncontrolled.

972 00:42:15.020 --> 00:42:17.100 There's no chemotherapy arm here.

973 00:42:17.100 --> 00:42:20.570 This is just the treated arm, Atezolizumub

974 00:42:20.570 --> 00:42:22.690 by biomarker status.

975 00:42:22.690 --> 00:42:23.580 And when you look at this,

976 00:42:23.580 --> 00:42:25.210 you see this blue Kaplan-Meier curve,

977 00:42:25.210 --> 00:42:26.950 that's above everybody else.

978 00:42:26.950 --> 00:42:29.010 That Kaplan-Meier curve is the target feature.

979 00:42:29.010 --> 00:42:31.020 That's the IC2/3 population.

980 00:42:31.020 --> 00:42:32.150 So they're responding,

981 00:42:32.150 --> 00:42:34.780 their tumors are shrinking and they're living longer.

982 00:42:34.780 --> 00:42:37.600 It looks like this is very promising, right?

983 00:42:37.600 --> 00:42:39.890 On the basis of that, they got accelerated approval.

984 00:42:39.890 --> 00:42:42.240 And that was given in 2016.

985 00:42:42.240 --> 00:42:45.400 And the reason was increased levels of PD-L1 expression

986 00:42:45.400 --> 00:42:48.150 on immune cells are associated with increased response.

987 00:42:49.190 --> 00:42:51.370 Let's go to the phase three trial.

988 00:42:51.370 --> 00:42:53.500 So as a part of the conditional approval

989 00:42:53.500 --> 00:42:54.520 with accelerated approval,

990 00:42:54.520 --> 00:42:56.287 they have to run a randomized phase three trial

991 00:42:56.287 --> 00:42:58.890 and sort of replicate this result.

992 00:42:58.890 --> 00:43:01.570 So they designed this trial, IMvigor211,

993 00:43:01.570 --> 00:43:04.030 multi-center open-label phase three trial.

994 00:43:04.030 --> 00:43:05.900 They compared to three chemotherapies,

995 00:43:05.900 --> 00:43:07.950 which were standard chemotherapies used at the time.

996 00:43:07.950 --> 00:43:10.550 So there was a physician's choice.

997 00:43:10.550 --> 00:43:12.230 If the patient was randomized to chemotherapy,

998 00:43:12.230 --> 00:43:13.860 the physician would choose

999 00:43:13.860 --> 00:43:16.300 which among these three chemotherapies.

1000 00:43:16.300 --> 00:43:18.000 So what happened?

1001 00:43:18.000 --> 00:43:20.860 We had this blockbuster results in phase two,

1002 00:43:20.860 --> 00:43:22.040 but there was no difference

1003 00:43:22.040 --> 00:43:24.230 in overall survival in phase three.

1004 00:43:24.230 --> 00:43:26.340 Not only was there not a difference in overall survival,

1005 00:43:26.340 --> 00:43:28.100 the objective response rates were similar.

1006 00:43:28.100 --> 00:43:30.240 So the tumor responses were similar.

1007 00:43:30.240 --> 00:43:33.280 Moreover they enrolled 931 patients

1008 00:43:33.280 --> 00:43:35.723 and only 234 actually had the target.

1009 00:43:36.863 --> 00:43:41.863 So 24% of the trial was used for the primary analysis.

1010 00:43:43.110 --> 00:43:45.750 When we look at the data, what happened?

1011 00:43:45.750 --> 00:43:49.180 23% of the IC2/3 population responded.

1012 00:43:49.180 --> 00:43:50.740 So that's close to 26%.

1013 00:43:50.740 --> 00:43:52.740 It looks like that was replicated.

1014 00:43:52.740 --> 00:43:54.800 When you look at the intention to treat populations,

1015 00:43:54.800 --> 00:43:57.370 that's everybody here, regardless of biomarker,

1016 00:43:57.370 --> 00:43:59.820 it's 13 and 13.

1017 00:43:59.820 --> 00:44:02.180 So it was also lower without the target.

1018 00:44:02.180 --> 00:44:05.160 But what's happening with chemotherapy with the target?

1019 00:44:05.160 --> 00:44:07.420 It's 22%, right?

1020 00:44:07.420 --> 00:44:11.160 So chemotherapy is doing great with this biomarker.

1021 00:44:11.160 --> 00:44:13.450 So this biomarker profile

1022 00:44:13.450 --> 00:44:17.180 is doing just as well as the targeted therapy,

1023 00:44:17.180 --> 00:44:19.330 when the patients get the standard of care.

1024 00:44:20.660 --> 00:44:23.240 Here's the survival curve.

1025 00:44:23.240 --> 00:44:26.020 Okay, proportional hazards is probably violated.

1026 00:44:26.020 --> 00:44:28.210 There is a heavy tail here for the Atezo group.

1027 00:44:28.210 --> 00:44:29.450 Maybe there's, it looks like

1028 00:44:29.450 --> 00:44:31.610 there's some long-term stable disease,

1029 00:44:31.610 --> 00:44:33.531 people that are benefiting.

1030 00:44:33.531 --> 00:44:36.190 But overall, this is not significant.

1031 00:44:36.190 --> 00:44:39.220 And on the basis of this, actually this year,

1032 00:44:39.220 --> 00:44:43.810 this drug was withdrawn from accelerated approval.

1033 00:44:43.810 --> 00:44:45.930 So it got the accelerated approval,

1034 00:44:45.930 --> 00:44:47.740 which was for very exciting drugs

1035 00:44:47.740 --> 00:44:52.150 that need an accelerated pathway for regulatory.

1036 00:44:52.150 --> 00:44:53.670 And then this phase three,

1037 00:44:53.670 --> 00:44:55.020 on the basis of this phase three trial,

1038 00:44:55.020 --> 00:44:56.523 they had to withdraw from that.

1039 00:44:57.380 --> 00:44:58.803 So the question is,

1040 00:44:59.740 --> 00:45:02.890 how do we use real-world evidence to change this?

1041 00:45:02.890 --> 00:45:05.423 At the end, there were flaws in this design.

1042 00:45:07.940 --> 00:45:11.103 They didn't understand the biomarker.

1043 00:45:12.550 --> 00:45:14.280 They didn't understand the biomarker profile

1044 00:45:14.280 --> 00:45:16.650 on the basis of the standard of care.

1045 00:45:16.650 --> 00:45:19.880 So when I first got involved in sort of,

1046 00:45:19.880 --> 00:45:22.610 well, over this past year, I've been thinking about

1047 00:45:22.610 --> 00:45:23.887 how could we have used real-world evidence?

1048 00:45:23.887 --> 00:45:26.720 Here's the case where, you know, there's,

1049 00:45:26.720 --> 00:45:29.830 it's kind of a failure of the system here

1050 00:45:29.830 --> 00:45:32.320 that we had this drug withdrawn from accelerated approval.

1051 00:45:32.320 --> 00:45:34.550 And it's not the only one, by the way.

1052 00:45:34.550 --> 00:45:38.210 Is there something in the historical data

1053 00:45:38.210 --> 00:45:40.700 or the real-world data that we could have used

1054 00:45:40.700 --> 00:45:44.910 that could have informed us to design a better trial,

1055 00:45:44.910 --> 00:45:46.700 or could have told us something

1056 00:45:46.700 --> 00:45:50.033 about the fact that this biomarker may be prognostic?

1057 00:45:51.290 --> 00:45:52.960 Now it gets complicated

1058 00:45:52.960 --> 00:45:56.040 because actually it's not prognostic for surgery.

1059 00:45:56.040 --> 00:45:59.340 Patients that have surgery that have IC2/3 status,

1060 00:45:59.340 --> 00:46:01.730 they're going to die sooner

1061 00:46:01.730 --> 00:46:05.030 than patients that have IC1, IC0,

1062 00:46:05.030 --> 00:46:07.840 So this marker seems to be a predictive marker

1063 00:46:07.840 --> 00:46:10.930 for both chemotherapy and for Atezo.

1064 00:46:10.930 --> 00:46:12.330 So, but we didn't know.

1065 00:46:12.330 --> 00:46:13.550 I didn't know if that was true.

1066 00:46:13.550 --> 00:46:16.850 So my postdoc and I went back and we did a meta-analysis.

1067 00:46:16.850 --> 00:46:20.090 We went and we extracted all of the trials

1068 00:46:20.090 --> 00:46:23.480 that had enrolled second-line bladder cancer patients

1069 00:46:23.480 --> 00:46:25.150 in a prospective study

1070 00:46:25.150 --> 00:46:26.880 that evaluated the three chemotherapies

1071 00:46:26.880 --> 00:46:29.160 that were used in the control arm.

1072 00:46:29.160 --> 00:46:30.980 So those are given here.

1073 00:46:30.980 --> 00:46:34.590 So I think back to Dr. Butte saying, you know,

1074 00:46:34.590 --> 00:46:35.810 the real problem in research

1075 00:46:35.810 --> 00:46:38.685 is you don't have enough people asking questions.

1076 00:46:38.685 --> 00:46:42.894 When we did this literature search,

1077 00:46:42.894 --> 00:46:46.623 there were like 200 papers on second-line bladder cancer,

1078 00:46:48.020 --> 00:46:50.770 Most of them were retrospective reviews and case studies,

1079 00:46:50.770 --> 00:46:52.430 the overwhelming majority.

1080 00:46:52.430 --> 00:46:57.400 There were only 11 that were actual perspective studies

1081 00:46:57.400 --> 00:46:59.060 that we could use in this population.

1082 00:46:59.060 --> 00:47:01.080 So there's a lot of people writing papers

1083 00:47:01.080 --> 00:47:03.610 on retrospective databases, there's lots,

1084 00:47:03.610 --> 00:47:06.916 but what we actually need are prospective studies.

1085 00:47:06.916 --> 00:47:10.000 So we see here, we have these 11 trials.

1086 00:47:10.000 --> 00:47:11.730 We're looking at the overall response rate

1087 00:47:11.730 --> 00:47:12.680 from these 11 trials,

1088 00:47:12.680 --> 00:47:14.813 we're doing a standard meta-analysis.

1089 00:47:15.690 --> 00:47:20.150 You can see that Genentech said 10% was their null, right?

1090 00:47:20.150 --> 00:47:22.050 And really the case for real-world evidence

1091 00:47:22.050 --> 00:47:25.050 is you can do a better job specifying your null hypothesis.

1092 00:47:25.050 --> 00:47:26.770 Your null hypothesis can be specified better

1093 00:47:26.770 --> 00:47:29.800 because you know what to expect for control.

1094 00:47:29.800 --> 00:47:33.340 So based on our meta-analysis of the objective response,

1095 00:47:33.340 --> 00:47:35.390 10% is really good estimate.

1096 00:47:35.390 --> 00:47:38.950 And 10% is like the hierarchal mean of this meta-analysis.

1097 00:47:38.950 --> 00:47:40.710 So now we go to the chemotherapy arms

1098 00:47:40.710 --> 00:47:43.167 that we saw in the Atezo trial.

1099 00:47:43.167 --> 00:47:46.490 We see the IC0/1 population is right at 10%.

1100 00:47:46.490 --> 00:47:47.910 But look at this,

1101 00:47:47.910 --> 00:47:49.660 this IC2/3 population.

1102 00:47:49.660 --> 00:47:52.090 Again, this is with chemotherapy.

1103 00:47:52.090 --> 00:47:54.770 They're statistically significantly better

1104 00:47:54.770 --> 00:47:58.160 than the hierarchal mean that we estimated

1105 00:47:58.160 --> 00:48:00.180 from meta-analysis.

1106 00:48:00.180 --> 00:48:01.330 So what does this mean?

1107 00:48:02.460 --> 00:48:05.453 This means that this profile has not been studied before.

1108 00:48:06.700 --> 00:48:11.300 These trials are mixtures of different immune phenotypes.

1109 00:48:11.300 --> 00:48:14.412 So we don't know which mean phenotype they're studying.

1110 00:48:14.412 --> 00:48:16.820 They have a different distribution.

1111 00:48:16.820 --> 00:48:19.500 Maybe this one has more IC2/3 population

1112 00:48:19.500 --> 00:48:20.750 because it's pulled over.

1113 00:48:22.260 --> 00:48:24.640 But the reality is the information

1114 00:48:24.640 --> 00:48:26.510 in these historical studies

1115 00:48:26.510 --> 00:48:28.843 doesn't tell us about immune staining.

1116 00:48:29.980 --> 00:48:33.083 So this is a biomarker that wasn't studied before.

1117 00:48:34.060 --> 00:48:35.540 And certainly that's goNNA be the case

1118 00:48:35.540 --> 00:48:37.450 in the community databases.

1119 00:48:37.450 --> 00:48:39.230 Because there's only a few institutions

1120 00:48:39.230 --> 00:48:41.590 that really can have the infrastructure

1121 00:48:41.590 --> 00:48:45.420 to quickly stain these patients

1122 00:48:45.420 --> 00:48:47.363 as these biomarkers are developing.

1123 00:48:48.410 --> 00:48:51.720 So we extracted the Kaplan-Meier curves

1124 00:48:51.720 --> 00:48:53.220 from these historical studies.

1125 00:48:54.210 --> 00:48:57.370 And we did a meta-analysis of these Kaplan-Meier curves.

1126 00:48:57.370 --> 00:48:58.340 And that's given here,

1127 00:48:58.340 --> 00:49:01.980 we have a piece-wise exponential model and a Weibull model.

1128 00:49:01.980 --> 00:49:04.010 When we put the Kaplan-Meier curves together

1129 00:49:04.010 --> 00:49:05.053 with the survival.

1130 00:49:05.890 --> 00:49:07.420 Oh, sorry, when you put the overall response

1131 00:49:07.420 --> 00:49:08.290 with the survival data,

1132 00:49:08.290 --> 00:49:11.970 we see this purple line is the chemotherapy arm

1133 00:49:11.970 --> 00:49:16.630 with this targeted biomarker from the phase three study,

1134 00:49:16.630 --> 00:49:18.400 that was implemented by Genentech.

1135 00:49:18.400 --> 00:49:22.730 So responses is better, survival is significantly better

1136 00:49:22.730 --> 00:49:26.317 than what our expectation was based on historical evidence.

1137 00:49:26.317 --> 00:49:29.270 And we actually went back and did simulation studies

1138 00:49:29.270 --> 00:49:32.260 where we fit piece-wise exponential and Weibull curves,

1139 00:49:32.260 --> 00:49:33.463 till all of these Kaplan-Meier curves

1140 00:49:33.463 --> 00:49:36.568 that we extracted from the web digitize the tool.

1141 00:49:36.568 --> 00:49:37.920 When we actually simulated,

1142 00:49:37.920 --> 00:49:39.850 was it the probability of success

1143 00:49:39.850 --> 00:49:41.343 for the design implements?

1144 00:49:42.287 --> 00:49:44.680 And we looked at that for the PDL-1 population,

1145 00:49:44.680 --> 00:49:46.060 as well as the ITT population.

1146 00:49:46.060 --> 00:49:48.960 We only give this trial 20% chance of success

1147 00:49:48.960 --> 00:49:52.260 based on the extent to which chemo is interacting

1148 00:49:52.260 --> 00:49:53.630 with PD-L1.

1149 00:49:53.630 --> 00:49:55.900 If you like, if you wanna account for the heavy tail

1150 00:49:55.900 --> 00:49:58.410 that we see in the model, and do piece of exponential,

1151 00:49:58.410 --> 00:50:00.230 it goes up to 24%.

1152 00:50:00.230 --> 00:50:02.280 So another case of a phase three trial

1153 00:50:02.280 --> 00:50:05.253 there was, had unrealistic expectations, right?

1154 00:50:06.140 --> 00:50:07.730 And it's a case

1155 00:50:07.730 --> 00:50:11.090 where we didn't understand the biomarker profile.

1156 00:50:11.090 --> 00:50:14.010 That biomarker profile had not been characterized

1157 00:50:14.010 --> 00:50:16.220 in the historical evidence.

1158 00:50:16.220 --> 00:50:18.640 It's not only Atezolizumab, this happened to Durvalumab.

1159 00:50:19.584 --> 00:50:22.340 It happened in bladder cancer for Durvalumab again as well.

1160 00:50:22.340 --> 00:50:25.393 Also a PD-1 inhibitor from AstraZeneca.

1161 00:50:30.664 --> 00:50:33.747 So Precision Oncology is hard, right?

1162 00:50:34.610 --> 00:50:35.443 It's hard.

1163 00:50:35.443 --> 00:50:39.210 It's not, what I presented here,

1164 00:50:39.210 --> 00:50:43.750 was not really about the lack of having information,

1165 00:50:43.750 --> 00:50:47.040 it was a lack of having the biomarker target characterized

1166 00:50:47.040 --> 00:50:48.683 in prior research studies.

1167 00:50:49.710 --> 00:50:50.950 And without the understanding

1168 00:50:50.950 --> 00:50:55.950 that profile could be predictive for the standard of care,

1169 00:50:56.340 --> 00:51:00.030 we have these drugs withdrawing from accelerated approval.

1170 00:51:00.030 --> 00:51:01.310 There's other issues when we look

1171 00:51:01.310 --> 00:51:03.210 at tissue-agnostic development.

1172 00:51:03.210 --> 00:51:06.140 So I worked with Bayer and MD Anderson last year

1173 00:51:06.140 --> 00:51:09.360 to investigate and NTRK fusions.

1174 00:51:09.360 --> 00:51:12.260 This is that rare biomarker profile

1175 00:51:12.260 --> 00:51:16.810 that has led to two drugs getting tissue-agnostic approval,

1176 00:51:16.810 --> 00:51:18.850 larotrectinib and entrectnib

1177 00:51:20.410 --> 00:51:24.330 So Bayer bought larotrectinib from LAKSO

1178 00:51:25.520 --> 00:51:28.173 and Roche bought entrectnib from Igniter.

1179 00:51:29.120 --> 00:51:31.330 So they wanted to understand,

1180 00:51:31.330 --> 00:51:35.690 and this was used actually in the Canadian approval process.

1181 00:51:35.690 --> 00:51:37.540 The Canadian approval process is different.

1182 00:51:37.540 --> 00:51:39.160 You have a higher level of threshold

1183 00:51:39.160 --> 00:51:41.660 that you have to characterize

1184 00:51:41.660 --> 00:51:44.750 for biomarker targeted therapies.

1185 00:51:44.750 --> 00:51:46.600 And they wanted to know specifically,

1186 00:51:47.570 --> 00:51:50.565 what is the evidence that NTRK is a prognostic marker?

1187 00:51:50.565 --> 00:51:52.168 How do we know the drugs working

1188 00:51:52.168 --> 00:51:55.283 and when it may just be the profile is favorable?

1189 00:51:56.151 --> 00:51:59.303 And that's kind of exactly what happened with Ateza.

1190 00:51:59.303 --> 00:52:04.303 So we thought that maybe we could interrogate this

1191 00:52:04.840 --> 00:52:06.650 by matching.

1192 00:52:06.650 --> 00:52:08.870 So we had 77 patients from MD Anderson

1193 00:52:08.870 --> 00:52:10.812 that had NTRK fusions.

1194 00:52:10.812 --> 00:52:12.750 Where MD Anderson did the staining,

1195 00:52:12.750 --> 00:52:15.350 we knew they had NTRK fusions and we followed them.

1196 00:52:15.350 --> 00:52:17.900 And some of these patients were on clinical trials.

1197 00:52:18.800 --> 00:52:21.420 So we thought, okay, real-world evidence, right?

1198 00:52:21.420 --> 00:52:24.233 We could match these patients to TCGA data.

1199 00:52:25.260 --> 00:52:28.580 And we could use TCGA data kind of as a control.

1200 00:52:28.580 --> 00:52:29.670 And we could compare them.

1201 00:52:29.670 --> 00:52:32.440 We can kind of get a sense of what the expectation was

1202 00:52:32.440 --> 00:52:34.160 based on TCGA data.

1203 00:52:34.160 --> 00:52:38.200 TCGA doesn't have NTRK fusion as one of the mutations.

1204 00:52:38.200 --> 00:52:41.340 But they have these indications that were enrolled.

1205 00:52:41.340 --> 00:52:43.100 So among these 77 patients,

1206 00:52:43.100 --> 00:52:46.190 we have like 14 different tumor types.

1207 00:52:46.190 --> 00:52:47.820 So we did this study,

1208 00:52:47.820 --> 00:52:50.070 we went to TCGA,

1209 00:52:50.070 --> 00:52:51.279 here are the different tumor types

1210 00:52:51.279 --> 00:52:53.033 that we had in this trial.

1211 00:52:54.630 --> 00:52:56.560 So we're talking about breast cancer

1212 00:52:56.560 --> 00:53:01.560 adenocarcinoma, cholangiocarcinoma, GBM.

1213 00:53:01.770 --> 00:53:06.400 What I'm showing you here is we extracted the TCGA data

1214 00:53:06.400 --> 00:53:08.680 from these different tumor types.

1215 00:53:08.680 --> 00:53:10.290 We matched on stage.

1216 00:53:10.290 --> 00:53:12.180 We matched on sort of performance status.

1217 00:53:12.180 --> 00:53:15.330 We matched on gender or sex, I should say,

1218 00:53:15.330 --> 00:53:18.570 we matched on all these factors that are relevant

1219 00:53:18.570 --> 00:53:20.510 for understanding whether patient's expectation

1220 00:53:20.510 --> 00:53:22.230 is for survival.

1221 00:53:22.230 --> 00:53:27.110 And look at the tumor driven heterogeneity.

1222 00:53:27.110 --> 00:53:28.700 Thyroid cancers is way up here.

1223 00:53:28.700 --> 00:53:30.530 The patients with thyroid cancer that are matched

1224 00:53:30.530 --> 00:53:32.130 to these patients at MD Anderson,

1225 00:53:32.130 --> 00:53:33.830 they're living a really long time.

1226 00:53:34.870 --> 00:53:39.240 Down here we have patients with GBM, Glioblastoma.

1227 00:53:39.240 --> 00:53:41.050 This is pancreas.

1228 00:53:41.050 --> 00:53:43.430 So even though these patients share

1229 00:53:43.430 --> 00:53:45.720 a common biomarker profile,

1230 00:53:45.720 --> 00:53:47.730 they have tissue types that are very different,

1231 00:53:47.730 --> 00:53:50.750 and have very different expectations for survival.

1232 00:53:50.750 --> 00:53:54.330 Putting this all together to try to understand

1233 00:53:54.330 --> 00:53:56.900 whether NTRK was prognostic or not,

1234 00:53:56.900 --> 00:53:58.533 was almost impossible to do.

1235 00:54:01.060 --> 00:54:04.720 So, you know, conceptually, we have the idea,

1236 00:54:04.720 --> 00:54:06.140 we have The Cancer Genome Atlas,

1237 00:54:06.140 --> 00:54:06.973 we should be using it.

1238 00:54:06.973 --> 00:54:08.530 We can use it to do these things.

1239 00:54:08.530 --> 00:54:10.920 But when it comes down to actually doing it,

1240 00:54:10.920 --> 00:54:12.240 it's a real challenge,

1241 00:54:12.240 --> 00:54:14.843 and it may not provide the information that we need.

1242 00:54:15.870 --> 00:54:19.640 Okay, so I have two conclusions, very simple ones.

1243 00:54:19.640 --> 00:54:23.500 Okay, so real-world evidence in precision oncology,

1244 00:54:23.500 --> 00:54:24.740 how do we use it?

1245 00:54:24.740 --> 00:54:25.860 Can we use it?

1246 00:54:25.860 --> 00:54:27.350 The reason we wanna use it,

1247 00:54:27.350 --> 00:54:30.253 again is because it's very expensive to do,

1248 00:54:31.510 --> 00:54:33.850 to run trials in oncology.

1249 00:54:33.850 --> 00:54:35.490 We have these biomarker profiles.

1250 00:54:35.490 --> 00:54:37.360 Patients have to be stained repeatedly.

1251 00:54:37.360 --> 00:54:39.350 They have to get imaging,

1252 00:54:39.350 --> 00:54:42.520 it's it's burdensome for the patient, and it's expensive.

1253 00:54:42.520 --> 00:54:46.620 So we wanna make better decisions in early phase

1254 00:54:46.620 --> 00:54:48.980 because we have all these failures in phase three.

1255 00:54:48.980 --> 00:54:50.020 We want to do a better job

1256 00:54:50.020 --> 00:54:52.490 of designing our phase three trials as well.

1257 00:54:52.490 --> 00:54:53.660 So what we really wanna know

1258 00:54:53.660 --> 00:54:56.030 is can we use real-world evidence to do a better job

1259 00:54:56.030 --> 00:54:57.850 of setting our null.

1260 00:54:57.850 --> 00:54:59.203 Where our expectation is.

1261 00:55:00.038 --> 00:55:01.980 In that case, in that way we can run

1262 00:55:01.980 --> 00:55:04.320 these uncontrolled trials in early phase

1263 00:55:04.320 --> 00:55:06.680 and, you know, save all the patients

1264 00:55:06.680 --> 00:55:10.300 to be treated on the potentially promising therapies.

1265 00:55:10.300 --> 00:55:12.770 Because we'll have a better idea of what our expectation is

1266 00:55:12.770 --> 00:55:14.880 and whether this is really promising or not.

1267 00:55:14.880 --> 00:55:17.010 That is the promise that you hear

1268 00:55:17.010 --> 00:55:19.580 about real-word evidence in this setting.

1269 00:55:19.580 --> 00:55:21.893 So it's really about, can we define the null?

1270 00:55:23.270 --> 00:55:25.470 So I think I showed you two examples here

1271 00:55:25.470 --> 00:55:27.860 where we really couldn't.

1272 00:55:27.860 --> 00:55:29.473 We tried to.

1273 00:55:29.473 --> 00:55:31.890 Like the case is second-line bladder cancer,

1274 00:55:31.890 --> 00:55:35.060 we went back to the randomized control trial evidence

1275 00:55:35.060 --> 00:55:38.070 and the null hypothesis was exactly null hypothesis

1276 00:55:38.070 --> 00:55:39.710 that Genentech used.

1277 00:55:39.710 --> 00:55:42.333 It's just that, that profile was not steady before.

1278 00:55:43.260 --> 00:55:44.800 So we couldn't do it there.

1279 00:55:44.800 --> 00:55:46.620 When we went to the NTRK studies,

1280 00:55:46.620 --> 00:55:50.370 the TCGA data didn't characterize NTRK,

1281 00:55:50.370 --> 00:55:53.100 but NTRK is so rare that didn't bother us.

1282 00:55:53.100 --> 00:55:54.410 So those patients are a mixture

1283 00:55:54.410 --> 00:55:57.020 of different other mutations.

1284 00:55:57.020 --> 00:55:58.080 We matched them based

1285 00:55:58.080 --> 00:56:00.270 on the clinical prognostic characteristics,

1286 00:56:00.270 --> 00:56:02.670 but the tumors are so different.

1287 00:56:02.670 --> 00:56:05.790 The expectations are so different across the tumors.

1288 00:56:05.790 --> 00:56:08.723 It's really hard to understand it from the TCGA data.

1289 00:56:10.180 --> 00:56:13.950 In fact, this draws in the question,

1290 00:56:13.950 --> 00:56:17.470 can you really say, if a patient has GBM

1291 00:56:17.470 --> 00:56:19.200 and they also have thyroid cancer,

1292 00:56:19.200 --> 00:56:21.070 but they share a mutation,

1293 00:56:21.070 --> 00:56:24.463 can we really say something that mutation is the target?

1294 00:56:26.180 --> 00:56:29.730 Can you really treat those cancers as one cancer type?

1295 00:56:29.730 --> 00:56:33.190 Which is what the tissue-agnostic model says you can.

1296 00:56:33.190 --> 00:56:35.740 Right, so the biology is that important.

1297 00:56:35.740 --> 00:56:37.287 In some cases it has been,

1298 00:56:37.287 --> 00:56:39.210 in the Pembrolizumab it is,

1299 00:56:39.210 --> 00:56:42.270 like immunotherapy, the immune phenotypes really seem

1300 00:56:42.270 --> 00:56:45.540 to transcend these cancer tissues,

1301 00:56:45.540 --> 00:56:47.330 but for other genetic markers,

1302 00:56:47.330 --> 00:56:48.920 it doesn't seem to be the case.

1303 00:56:48.920 --> 00:56:51.920 So I guess my conclusion is retrospectively,

1304 00:56:51.920 --> 00:56:53.370 we really can't.

1305 00:56:53.370 --> 00:56:55.093 We can't use it right now.

1306 00:56:56.060 --> 00:56:57.780 It doesn't seem like we can

1307 00:56:57.780 --> 00:57:01.080 because we are now in the precision oncology setting.

1308 00:57:01.080 --> 00:57:02.300 And yes, of course,

1309 00:57:02.300 --> 00:57:03.930 if you're in rare disease setting

1310 00:57:03.930 --> 00:57:07.830 or you're in a non something else, that's unique.

1311 00:57:07.830 --> 00:57:09.880 You may have to, and do the best you can.

1312 00:57:10.880 --> 00:57:12.590 But for the trials I showed you here,

1313 00:57:12.590 --> 00:57:14.050 I don't see a solution here

1314 00:57:14.050 --> 00:57:16.570 based on retrospective real-world evidence.

1315 00:57:16.570 --> 00:57:18.470 I think you could do it prospectively.

1316 00:57:19.900 --> 00:57:22.770 But I think if you're gonna do it prospectively,

1317 00:57:22.770 --> 00:57:25.380 there has to be a commitment

1318 00:57:25.380 --> 00:57:27.950 that right when you start the phase one trial,

1319 00:57:27.950 --> 00:57:29.520 you need to start staining patients

1320 00:57:29.520 --> 00:57:31.660 and following them for survival.

1321 00:57:31.660 --> 00:57:33.390 We don't have a real-world tumor response right now,

1322 00:57:33.390 --> 00:57:35.320 we can't use that.

1323 00:57:35.320 --> 00:57:40.320 But you need to have a sort of prospective cohort study

1324 00:57:40.520 --> 00:57:42.400 that enrolls patients from the community.

1325 00:57:42.400 --> 00:57:45.460 You need to pay for them to get their assays.

1326 00:57:45.460 --> 00:57:49.030 You need to understand that the assays may change

1327 00:57:49.030 --> 00:57:51.490 or develop but to store some information.

1328 00:57:51.490 --> 00:57:53.000 And then I think later on

1329 00:57:53.000 --> 00:57:54.000 when you're coming to a decision

1330 00:57:54.000 --> 00:57:55.390 about phase three or phase two,

1331 00:57:55.390 --> 00:57:57.760 you go back to that prospective cohort.

1332 00:57:57.760 --> 00:58:01.260 And you look for patterns based on the relationships

1333 00:58:01.260 --> 00:58:04.060 between the biomarker and the standard of care.

1334 00:58:04.060 --> 00:58:05.380 So I think you can do it prospectively.

1335 00:58:05.380 --> 00:58:06.800 That's not what people wanna do though,

1336 00:58:06.800 --> 00:58:08.987 they want to use these retrospective databases.

1337 00:58:08.987 --> 00:58:13.987 So yeah, I guess that's the end of my talk.

1338 00:58:14.590 --> 00:58:16.790 I didn't leave very much time for questions,

1339 00:58:17.740 --> 00:58:19.890 but I'm happy to take a few if there's any.

1340 00:58:24.079 --> 00:58:26.496 (indistinct)

1341 00:59:26.340 --> 00:59:28.760 So it's somebody asking a question?

1342 00:59:28.760 --> 00:59:30.760 I can't really hear.

1343 00:59:30.760 --> 00:59:33.423 I'm sorry, I can't hear it at all, actually.

1344 00:59:35.900 --> 00:59:38.900 (people chattering)

1345 00:59:45.810 --> 00:59:48.140 <v Man>Professor Hobbes, can you hear us?</v>

1346 00:59:48.140 --> 00:59:49.780 <v Brian Hobbes>Yeah, I can kind of hear you,</v>

1347 00:59:49.780 --> 00:59:51.543 but there's a lot of noise.

1348 00:59:52.520 --> 00:59:54.826 <v Man>We also have people trying to get in the room</v>

1349 00:59:54.826 --> 00:59:56.646 so (indistinct)

1350 00:59:56.646 --> 00:59:59.813 (students chattering)

1351 01:00:07.500 --> 01:00:09.502 Thank you so much, Professor Hobbes.

1352 01:00:09.502 --> 01:00:10.827 (students clapping)

1353 01:00:10.827 --> 01:00:12.533 <v ->All right, thank you very much.</v>

1354 01:00:19.030 --> 01:00:20.780 <v Man>Have a great time, thank you.</v>

1355 01:00:20.780 --> 01:00:23.780 (people chattering)