WEBVTT

1 00:00:00.010 --> 00:00:01.930 <v Wei>Okay, hello everyone.</v>

2 00:00:01.930 --> 00:00:06.930 Today, we are very fortunate to have Dr. Codruta Chiuzan

3 00:00:11.330 --> 00:00:13.770 as our speaker.

4 00:00:13.770 --> 00:00:17.390 Dr. Chiuzan is Associated Professor,

5 00:00:17.390 --> 00:00:19.350 Institute of Health System Science

6 00:00:20.260 --> 00:00:22.870 at Northwell Health New York.

7 00:00:22.870 --> 00:00:26.300 So before that, she was an Assistant Professor

8 00:00:26.300 --> 00:00:28.000 in the Department of Biostatistics

9 00:00:28.850 --> 00:00:33.140 at Mailman School of Public Health Columbia University.

10 00:00:33.140 --> 00:00:36.760 In her research area focus on earning phase

11 00:00:36.760 --> 00:00:40.320 clinical trial designs and an average aging real-world

12 00:00:40.320 --> 00:00:44.170 evidence to prove all the cons and increased diversity

13 00:00:44.170 --> 00:00:46.500 of population in clinical trials.

14 00:00:46.500 --> 00:00:50.650 Now, she is in receipt of Junior Faculty Research Award

15 00:00:51.510 --> 00:00:54.560 and the Columbia Public Health Innovation Award

16 00:00:54.560 --> 00:00:57.670 from the Mailman School of Public Health.

17 00:00:57.670 --> 00:01:01.563 So, Dr. Chiuzan, has a very strong record or mentoring,

18 00:01:02.730 --> 00:01:07.560 both master's students, PhD students and clinical fatal.

19 00:01:07.560 --> 00:01:09.890 She is an active committee member

20 00:01:09.890 --> 00:01:13.230 of JSM, Diversity Mentoring Program

21 00:01:13.230 --> 00:01:15.280 and she had held leadership positions

22 00:01:15.280 --> 00:01:19.430 as the President of the American Statistical Association

23 00:01:19.430 --> 00:01:22.290 and New York City Metropolitan Area

24 00:01:22.290 --> 00:01:25.960 and she as the Chair over the Student Scholars Committee

25 00:01:25.960 --> 00:01:28.510 at the Society of Clinical Trials.

26 00:01:28.510 --> 00:01:32.323 So, welcome Dr. Chiuzan and time is yours.

27 00:01:34.510 --> 00:01:39.270 <v ->Thank you so much Wei, for the invitation,</v>

28 00:01:39.270 --> 00:01:43.360 it's a pleasure, I'm going to share my...

29 00:01:46.550 --> 00:01:47.383 Hello.

30 00:01:49.630 --> 00:01:53.373 Hello, I hear some echo in the background.

31 00:01:56.380 --> 00:01:57.963 <v Student>Is anybody (indistinct).</v>

32 00:02:09.600 --> 00:02:13.210 <v ->The host, can you disable the screen sharing</v>

33 00:02:13.210 --> 00:02:14.903 so I can share the slides?

34 00:02:25.240 --> 00:02:26.073 Oh, perfect.

35 00:02:39.580 --> 00:02:44.580 Okay, can everybody see the screen, the full screen?

36 00:02:56.800 --> 00:02:57.633 Okay.

37 00:03:01.200 --> 00:03:06.200 All right, so it's a pleasure to be with you

38 00:03:07.160 --> 00:03:12.063 even virtually and I'm glad to see so many people in person

39 00:03:13.460 --> 00:03:17.483 with academic semester ongoing.

40 00:03:20.078 --> 00:03:24.940 Today I'm going to talk about one area of my research

41 00:03:24.940 --> 00:03:29.940 and that is early phase designs for immunotherapies

42 00:03:32.762 --> 00:03:37.033 or cancer immunotherapies and I will take you

43 00:03:38.660 --> 00:03:42.880 through a journey, through a story by giving some examples

44 00:03:42.880 --> 00:03:47.042 and explanation of what are these cancer immunotherapies,

45 00:03:47.042 --> 00:03:49.610 what are the promises, what are the challenges

46 00:03:49.610 --> 00:03:54.610 and how do they actually reflect in the early phase designs?

47 00:03:56.510 --> 00:04:00.840 Then I will talk about current models

48 00:04:00.840 --> 00:04:03.490 and a model that we developed on has been implemented

49 00:04:06.433 --> 00:04:11.433 and has been implemented in an R package and the Shiny app

50 00:04:12.470 --> 00:04:17.173 and I will conclude with a practical demonstration.

51 00:04:18.170 --> 00:04:23.170 Please, if anybody has any questions at any point,

52 00:04:23.990 --> 00:04:27.450 please feel free to raise a hand or just ask,

53 00:04:27.450 --> 00:04:31.830 I like us to have an interactive session

54 00:04:31.830 --> 00:04:36.830 and to have a continuous dialogue if you're able please.

55 00:04:38.510 --> 00:04:41.133 So what is immunotherapy?

56 00:04:42.140 --> 00:04:45.160 The New York times called it a long awaited reality

57 00:04:45.160 --> 00:04:48.913 because immunotherapy has been developed

58 00:04:50.370 --> 00:04:55.370 since the early 1900s, actually by a New York surgeon

59 00:04:55.670 --> 00:04:59.163 that saw that in cancer patients that develop flu,

60 00:05:02.870 --> 00:05:07.260 had a better anti-cancer response.

61 00:05:07.260 --> 00:05:11.480 So immunotherapy works on a different paradigm

62 00:05:11.480 --> 00:05:14.830 compared to cytotoxic agents and by cytotoxic agents,

63 00:05:14.830 --> 00:05:17.540 I mean, chemotherapy or radiations.

64 00:05:18.620 --> 00:05:22.040 So immunotherapy boosts or leverages the body's own immune

65 00:05:22.040 --> 00:05:26.180 system to fight cancer, to recognize it, to attack it

66 00:05:26.180 --> 00:05:29.430 and ultimately to kill the cancer cells.

67 00:05:29.430 --> 00:05:31.882 The three Rs of cancer immunotherapies

68 00:05:31.882 --> 00:05:36.882 are reverse tolerance, rejuvenate the immune system

69 00:05:38.740 --> 00:05:43.653 and restore the internal environment homeostasis.

70 00:05:46.336 --> 00:05:50.670 So, you'll probably hear more and more updates

71 00:05:50.670 --> 00:05:55.050 and FDA approvals for cancer immunotherapies.

72 00:05:55.050 --> 00:06:00.050 Between 2017 and 2020, over 65% increase has been seen

73 00:06:01.020 --> 00:06:04.800 in the number of immunotherapies and these immunotherapies,

74 00:06:04.800 --> 00:06:06.420 most of them have been approved

75 00:06:06.420 --> 00:06:11.257 for immune checkpoint inhibitors, Ipilimumab, Nivolumab

76 00:06:12.253 --> 00:06:15.667 and Pembrolizumab that works by incubator thing,

77 00:06:16.850 --> 00:06:20.430 the relationship, the association between the PD-1

78 00:06:20.430 --> 00:06:25.430 and the PD-L1 receptors, but the largest growth

79 00:06:26.970 --> 00:06:30.520 has been seen for cell therapies.

80 00:06:30.520 --> 00:06:33.750 And what are these cell therapies?

81 00:06:33.750 --> 00:06:38.750 The most frequent and the most study one is called T-cells,

82 00:06:39.800 --> 00:06:42.460 so far, which will be approvals.

83 00:06:42.460 --> 00:06:47.460 So that these old therapies use the T-cells in the body

84 00:06:48.320 --> 00:06:51.913 to fight cancer and then you do that by first,

85 00:06:54.061 --> 00:06:57.590 taking blood from the patient, isolating the T-cells

86 00:06:57.590 --> 00:07:01.670 in the lab in the Petri dish and genetically modify

87 00:07:01.670 --> 00:07:06.670 these T-cells to display a specific receptor

88 00:07:06.820 --> 00:07:11.820 that then is introduced and after that when the cells

89 00:07:14.060 --> 00:07:16.810 are being introduced into the body, this T-cell receptor

90 00:07:16.810 --> 00:07:21.530 will bind to specific antigen present on the cancer cells

91 00:07:21.530 --> 00:07:25.063 and trigger an anti-tumor reaction.

92 00:07:26.140 --> 00:07:31.020 So these are the T-cells, these are the cell therapies

93 00:07:32.600 --> 00:07:36.210 that are being studied and they're very promising

94 00:07:36.210 --> 00:07:38.780 in terms of prolonging overall survival

95 00:07:38.780 --> 00:07:42.610 and also in lowering the toxicity,

96 00:07:42.610 --> 00:07:44.760 killing cancer without killing the patient.

97 00:07:47.730 --> 00:07:51.550 Last year update from the Cancer Research Institute

98 00:07:51.550 --> 00:07:56.550 has shown that, as I said, that the most promising field

99 00:07:56.760 --> 00:07:59.330 in cancer therapies are,

100 00:07:59.330 --> 00:08:02.076 has been seen in this T-cell therapies,

101 00:08:02.076 --> 00:08:06.630 most of them for a solid cancer, nonsmall,

102 00:08:06.630 --> 00:08:10.250 renal cancer, colorectal cancer,

103 00:08:10.250 --> 00:08:15.250 but it's moving into the non-solid cancer as well.

104 00:08:17.290 --> 00:08:22.290 So, Hype versus Hope, I entitled this slide,

105 00:08:22.440 --> 00:08:26.810 immunotherapy, is it the holy grail

106 00:08:26.810 --> 00:08:31.780 is the answer to all cancer therapies, yes or no,

107 00:08:31.780 --> 00:08:35.103 because of course it comes with some challenges.

108 00:08:36.350 --> 00:08:40.410 Some of the challenges are immunotherapy sometimes

109 00:08:41.420 --> 00:08:44.040 can trigger delayed responses,

110 00:08:44.040 --> 00:08:46.020 meaning that the treatment has to continue

111 00:08:46.020 --> 00:08:49.680 even if initial response has not been seen,

112 00:08:49.680 --> 00:08:52.660 there's been cases of hyper-progression

113 00:08:52.660 --> 00:08:57.210 where the cancer tumor seen this rapid growth

114 00:08:57.210 --> 00:09:02.210 in the early stages and that can be the problematic

115 00:09:04.470 --> 00:09:06.830 on diminished overall survival.

116 00:09:06.830 --> 00:09:11.340 And most importantly, we're not really sure exactly

117 00:09:11.340 --> 00:09:16.340 what to measure and how to incorporate end points

118 00:09:17.080 --> 00:09:21.680 into all phases of drug development from early phase,

119 00:09:21.680 --> 00:09:24.460 phase one and two, where we're looking at identifying

120 00:09:24.460 --> 00:09:28.770 the optimal dose to later phases.

121 00:09:28.770 --> 00:09:33.230 So, because it's still under development,

122 00:09:33.230 --> 00:09:37.130 there is a lack of biomarkers to predict the responders

123 00:09:37.130 --> 00:09:41.020 versus not the responders and the difficult to correlate

124 00:09:41.020 --> 00:09:43.740 these immunological biomarkers with outcomes,

125 00:09:43.740 --> 00:09:47.640 clinical outcomes, overall survival response progression,

126 00:09:47.640 --> 00:09:51.970 free survival compared to cytotoxic agents, chemotherapy,

127 00:09:51.970 --> 00:09:56.290 immunotherapies have different toxicity profiles,

128 00:09:56.290 --> 00:09:59.020 meaning they can have lower toxicity

129 00:09:59.020 --> 00:10:04.020 and also different grades and different profiles,

130 00:10:05.790 --> 00:10:10.790 is called by, also called as immune-related adverse event.

131 00:10:12.940 --> 00:10:16.460 So if you're familiar with drug development phases,

132 00:10:16.460 --> 00:10:19.800 as you know that usually it will start with early phase.

133 00:10:19.800 --> 00:10:23.790 Phase one, identifying the maximum tolerated dose

134 00:10:23.790 --> 00:10:27.500 to be carried forward then for establishing efficacy

135 00:10:27.500 --> 00:10:30.603 and in later phases.

136 00:10:31.800 --> 00:10:36.710 In the old paradigm, so the objective was to find the MTD

137 00:10:36.710 --> 00:10:41.710 and the MTD was mainly based on toxicity as binary,

138 00:10:41.790 --> 00:10:46.790 yes or no DLT, the patient has after receiving treatment,

139 00:10:47.890 --> 00:10:51.390 we quantify the number of those limiting toxicities,

140 00:10:51.390 --> 00:10:55.000 unacceptable toxicity within a certain interval.

141 00:10:55.000 --> 00:10:59.030 However, the new immunotherapies have,

142 00:10:59.030 --> 00:11:00.330 as I mentioned before,

143 00:11:00.330 --> 00:11:02.410 they have different toxicity profiles,

144 00:11:02.410 --> 00:11:07.190 so this old paradigm of finding the MTD,

145 00:11:07.190 --> 00:11:10.190 does longer stint, there are a lot of trials

146 00:11:10.190 --> 00:11:13.640 where the dose escalation moved quickly

147 00:11:13.640 --> 00:11:17.070 to the maximum dose level and MTD.

148 00:11:17.070 --> 00:11:21.010 There were no DLTs, the MTD was not identified

149 00:11:21.010 --> 00:11:25.660 and most importantly, toxicity and efficacy

150 00:11:25.660 --> 00:11:28.200 might not necessarily be those dependents.

151 00:11:28.200 --> 00:11:31.150 So you might be able to find a safe dose,

152 00:11:31.150 --> 00:11:35.720 but that might not necessarily be the most promising one

153 00:11:35.720 --> 00:11:37.150 in terms of efficacy.

154 00:11:37.150 --> 00:11:41.010 In many cases, we actually see this plateau trend

155 00:11:41.010 --> 00:11:43.380 where after a certain level,

156 00:11:43.380 --> 00:11:46.770 the efficacy levels out plateaus

157 00:11:46.770 --> 00:11:50.523 and we don't see any effect.

158 00:11:51.540 --> 00:11:55.803 Another challenge, so in this context of different toxicity,

159 00:11:57.661 --> 00:12:00.480 is different levels of toxicity incorporation of efficacy

160 00:12:00.480 --> 00:12:05.480 into the dose finding process, we need to reconsider

161 00:12:05.800 --> 00:12:10.800 the definition and think of more in terms of identifying

162 00:12:11.080 --> 00:12:14.730 the optimal biological dose versus the MTD,

163 00:12:14.730 --> 00:12:17.910 a dose that is acceptable in terms of toxicity,

164 00:12:17.910 --> 00:12:22.910 but also this place, a good efficacy profile.

165 00:12:25.250 --> 00:12:30.250 So in terms of methodology, again in early-phase,

166 00:12:33.130 --> 00:12:38.130 research has been dominated in the past decades

167 00:12:38.390 --> 00:12:40.820 by algorithmic designs by algorithmic,

168 00:12:40.820 --> 00:12:42.480 I mean the three plus three,

169 00:12:42.480 --> 00:12:47.480 which is definitely not preferred by,

170 00:12:49.458 --> 00:12:54.458 and actually strongly disapproved by statisticians

171 00:12:54.760 --> 00:12:59.760 and even until 2014, when we did the last review

172 00:13:01.540 --> 00:13:05.414 of early-phase methodology, we saw that over 90%

173 00:13:05.414 --> 00:13:10.180 of this trials have implemented a rule-based design.

174 00:13:10.180 --> 00:13:13.670 Rule-based working only on toxicity with absolutely

175 00:13:13.670 --> 00:13:18.343 no statistical background.

176 00:13:20.070 --> 00:13:24.720 From 2012, we saw more than 60% of the trials

177 00:13:24.720 --> 00:13:27.400 that the tested targeted or immunotherapies

178 00:13:28.520 --> 00:13:32.683 and only 7.6 actually used a model-based design.

179 00:13:33.650 --> 00:13:36.270 So what do I mean by model-based design?

180 00:13:36.270 --> 00:13:38.960 Well, we criticize in three plus three,

181 00:13:38.960 --> 00:13:41.973 but are there alternatives actually several.

182 00:13:44.700 --> 00:13:49.700 One alternative that addresses the matter

183 00:13:50.190 --> 00:13:53.660 of late onset toxicities that is usually seen

184 00:13:53.660 --> 00:13:58.030 in immunotherapies, meaning you see DLTs on toxicity

185 00:13:58.030 --> 00:14:03.030 outside of DLT window, that is usually 28 days

186 00:14:03.860 --> 00:14:08.230 so longer toxicities, for that we have the time to event

187 00:14:09.414 --> 00:14:11.870 continual reassessment method that was proposed

188 00:14:11.870 --> 00:14:14.423 by Jenga Chapelle in 2000.

189 00:14:16.380 --> 00:14:19.130 The problem with multiple toxicities

190 00:14:19.130 --> 00:14:22.230 across different varying grades and moving away

191 00:14:22.230 --> 00:14:26.760 from the binary DLT has been tackled by Ezzalfani and others

192 00:14:26.760 --> 00:14:30.390 by using, by incorporating these types,

193 00:14:30.390 --> 00:14:33.100 different toxicity types and different grades

194 00:14:33.100 --> 00:14:35.120 into the total toxicity score,

195 00:14:35.120 --> 00:14:39.023 which is a quasi continuous measure.

196 00:14:40.300 --> 00:14:42.610 As I mentioned for immunotherapies,

197 00:14:42.610 --> 00:14:46.240 it makes more sense to incorporate both toxicity

198 00:14:46.240 --> 00:14:51.240 and efficacy and for that we have models that look at,

199 00:14:52.790 --> 00:14:56.220 that incorporate both toxicity and efficacy

200 00:14:56.220 --> 00:14:59.210 and these are the F-stocks designs method

201 00:15:00.090 --> 00:15:04.123 or the bivariate continual reassessment method.

202 00:15:05.060 --> 00:15:10.060 And more recently, other measures have been looked

203 00:15:10.480 --> 00:15:14.330 at in immunotherapies and these are the PK,

204 00:15:14.330 --> 00:15:17.117 the pharmacokinetics or the pharmacodynamics

205 00:15:17.117 --> 00:15:19.900 and these have been incorporated by, for example,

206 00:15:19.900 --> 00:15:23.523 Ursino, in a patient design proposed in 2017.

207 00:15:24.740 --> 00:15:28.890 So this is to present the status quo

208 00:15:28.890 --> 00:15:33.470 of what's being proposed out there, what we are suggesting

209 00:15:33.470 --> 00:15:37.640 is also a design that is specific

210 00:15:37.640 --> 00:15:42.640 or for immunotherapy trials and this was published in 2018

211 00:15:43.510 --> 00:15:46.840 and since then we have added a different measure

212 00:15:46.840 --> 00:15:51.280 of toxicity, we have implemented it into an R package

213 00:15:51.280 --> 00:15:54.710 that is on a available on cram, iAdapt

214 00:15:54.710 --> 00:15:58.760 and also can be tried using charmia.

215 00:15:58.760 --> 00:16:03.710 So this design for immunotherapies uses both toxicity

216 00:16:03.710 --> 00:16:08.550 and efficacy to identify the optimal dose.

217 00:16:08.550 --> 00:16:11.310 Optimal dose meaning unacceptable dose

218 00:16:11.310 --> 00:16:14.203 with promising efficacy profile.

219 00:16:16.030 --> 00:16:18.880 The design is unique in the sense it can incorporate

220 00:16:18.880 --> 00:16:23.220 both binary or quasi continuous toxicity scores,

221 00:16:23.220 --> 00:16:26.100 and it's looking at the continuous efficacy outcomes.

222 00:16:26.100 --> 00:16:29.150 Most of the designs that I mentioned before are using

223 00:16:29.150 --> 00:16:31.890 either binary or ordinal efficacy.

224 00:16:31.890 --> 00:16:34.830 In this one we're looking at continuous outcomes,

225 00:16:34.830 --> 00:16:39.440 such as T-cell persistence at followup compared to baseline

226 00:16:39.440 --> 00:16:42.103 why the cell persistence, as I mentioned before,

227 00:16:43.030 --> 00:16:46.080 well, about this engineered T-cells

228 00:16:46.080 --> 00:16:48.170 when they are being put into the body,

229 00:16:48.170 --> 00:16:50.860 they maintain the steer soul store,

230 00:16:50.860 --> 00:16:54.910 then the genetic information and the trigger

231 00:16:57.842 --> 00:16:59.792 and tumor response and it's been shown,

232 00:17:02.350 --> 00:17:06.180 there's some studies shown that the number of T-cells

233 00:17:06.180 --> 00:17:10.060 that are still present, still survive in the blood

234 00:17:10.060 --> 00:17:15.060 at one or two months after being reinfused tends to predict

235 00:17:16.740 --> 00:17:21.650 response on the overall survival on the long-term.

236 00:17:21.650 --> 00:17:25.750 The design has, does not impose any monotonicity assumption

237 00:17:25.750 --> 00:17:30.050 in terms of those efficacy relationship and does not account

238 00:17:30.050 --> 00:17:32.633 for dependence between toxicity and efficacy.

239 00:17:33.970 --> 00:17:35.823 So now let's take a look at the two,

240 00:17:36.700 --> 00:17:40.047 the difference between incorporating toxicity only

241 00:17:40.047 --> 00:17:43.010 and looking at efficacy also.

242 00:17:43.010 --> 00:17:47.310 So the cartoon on the left shows the dose toxicity

243 00:17:47.310 --> 00:17:49.740 relationship or five dose level.

244 00:17:49.740 --> 00:17:52.743 So in this graph, let's say we have five dose levels

245 00:17:52.743 --> 00:17:57.743 and we have a threshold of unacceptable toxicity set at 40%.

246 00:17:58.130 --> 00:18:03.130 So based on this graph, we have about four dose levels

247 00:18:04.140 --> 00:18:08.843 that are below the threshold, one dose level that is above.

248 00:18:11.140 --> 00:18:16.050 So if we have 40% toxicity threshold, dose number four

249 00:18:17.810 --> 00:18:22.370 would be identified as the MTD, the maximum tolerated dose.

250 00:18:22.370 --> 00:18:26.700 However, if we are to look also at efficacy

251 00:18:26.700 --> 00:18:30.130 and in this case, the dose efficacy has this umbrella,

252 00:18:30.130 --> 00:18:31.820 this non-monitoring trend.

253 00:18:31.820 --> 00:18:35.130 We will see that by looking at the MTD,

254 00:18:35.130 --> 00:18:39.450 we would totally miss the optimal dose

255 00:18:39.450 --> 00:18:44.450 because dose number four has actually a lower efficacy

256 00:18:46.040 --> 00:18:49.140 as compared to dose number three.

257 00:18:49.140 --> 00:18:53.230 So this is to pretty much justify the need to incorporate

258 00:18:53.230 --> 00:18:57.373 both toxicity and efficacy into the dose finding process.

259 00:18:59.250 --> 00:19:01.150 So the design has two stages.

260 00:19:01.150 --> 00:19:04.850 In stage one, we're establishing the safety profile

261 00:19:04.850 --> 00:19:08.830 at each dose, after we establish the safety profile,

262 00:19:08.830 --> 00:19:12.550 the acceptable doses are carried to stage number two,

263 00:19:12.550 --> 00:19:15.480 where we using efficacy driven randomization

264 00:19:15.480 --> 00:19:18.980 to allocate patients to acceptable doses

265 00:19:18.980 --> 00:19:23.083 that emphasis towards more promising efficacious ones.

266 00:19:24.500 --> 00:19:26.920 So, now let's take a look at stage one,

267 00:19:26.920 --> 00:19:29.340 establishing the safety profile.

268 00:19:29.340 --> 00:19:33.050 We have a number of pre-specified dose levels

269 00:19:33.050 --> 00:19:37.490 and we start by defining the set of hypothesis,

270 00:19:37.490 --> 00:19:42.240 where hypothesis one represents the unacceptable DLT rate

271 00:19:42.240 --> 00:19:45.880 and hypothesis two, represent unacceptable DLT rate.

272 00:19:45.880 --> 00:19:50.880 DLT, meaning the Dose Limiting Toxicity.

273 00:19:53.130 --> 00:19:58.130 So the quantification of this evidence

274 00:19:58.950 --> 00:20:03.363 in favor of hypothesis one or hypothesis two,

275 00:20:04.445 --> 00:20:09.370 is done by the likelihood ratio V, the evidential paradigm.

276 00:20:10.490 --> 00:20:15.350 So to give you a little bit of a background,

277 00:20:15.350 --> 00:20:17.880 in statistics there pretty much three school of thoughts,

278 00:20:17.880 --> 00:20:22.070 we have the frequencies approach based on Pearson,

279 00:20:22.070 --> 00:20:24.000 you'll have the patient school of thought,

280 00:20:24.000 --> 00:20:26.100 and then you have the evidential paradigm.

281 00:20:27.229 --> 00:20:29.750 The evidential paradigm and the frequent tests

282 00:20:29.750 --> 00:20:34.750 are somehow similar, but the difference between the two

283 00:20:34.960 --> 00:20:38.640 is the evidential paradigm based on the law of likelihood

284 00:20:38.640 --> 00:20:42.403 the couples, the strength of evidence from uncertainty.

285 00:20:43.270 --> 00:20:45.450 So the strength of the evidence is quantified

286 00:20:45.450 --> 00:20:48.370 by the likelihood ratio and our certainty

287 00:20:48.370 --> 00:20:53.370 is quantified by the probability of misleading evidence

288 00:20:53.500 --> 00:20:58.500 and the probability of observing weak or strong evidence

289 00:20:58.620 --> 00:21:00.217 in favor of the other two.

290 00:21:02.550 --> 00:21:05.420 Yeah, in comparison the frequent is the approach,

291 00:21:05.420 --> 00:21:07.770 that's not the couple, the strength of evidence

292 00:21:09.188 --> 00:21:10.021 and from uncertainty.

293 00:21:12.220 --> 00:21:17.220 So evidential paradigm used to establish acceptability

294 00:21:19.890 --> 00:21:21.150 in stage number one.

295 00:21:21.150 --> 00:21:22.440 And how do we do that?

296 00:21:22.440 --> 00:21:27.040 Let's say we have a certain number of levels, each show,

297 00:21:27.040 --> 00:21:32.040 and we treat cohorts of size M patients

298 00:21:32.170 --> 00:21:37.170 to each of these dose levels based on toxicity information,

299 00:21:38.230 --> 00:21:43.230 we calculate the likelihood ratio and evaluate evidence

300 00:21:43.670 --> 00:21:47.890 as one of the three, either we have strong evidence

301 00:21:47.890 --> 00:21:50.970 in favor of hypothesis two,

302 00:21:50.970 --> 00:21:53.600 declaring that the dose is acceptable.

303 00:21:53.600 --> 00:21:56.413 Either we have strong evidence in favor of H1,

304 00:21:57.420 --> 00:22:02.070 it's unacceptable or we conclude the weak evidence

305 00:22:02.070 --> 00:22:05.410 that doesn't support either of the hypothesis,

306 00:22:05.410 --> 00:22:09.253 the likelihood ratio is compared to a threshold, okay?

307 00:22:10.310 --> 00:22:12.920 So how do we, let's take a look at an example

308 00:22:12.920 --> 00:22:14.970 to see how we set the hypothesis

309 00:22:14.970 --> 00:22:17.133 and how we started this threshold, okay?

310 00:22:18.350 --> 00:22:22.590 So let's say that we have hypothesis one 40%,

311 00:22:22.590 --> 00:22:27.290 this is unacceptable, the DLT rate toxic

312 00:22:27.290 --> 00:22:32.290 and hypothesis two 15%, that is an acceptable DLT rate

313 00:22:33.540 --> 00:22:36.050 and we want, we evaluate each dose

314 00:22:37.070 --> 00:22:39.520 based on these two hypothesis.

315 00:22:39.520 --> 00:22:44.520 And for that one, in this case, we use a k threshold

316 00:22:45.933 --> 00:22:50.016 equal to two, so there's been a lot of literature

317 00:22:51.024 --> 00:22:55.939 written on this evidential paradigm and the k thresholds

318 00:22:55.939 --> 00:23:00.106 can vary, we can take values from two, four, eight

319 00:23:01.900 --> 00:23:05.330 all the way to 32, depending on the sample size,

320 00:23:05.330 --> 00:23:10.330 the bigger the sample size, the bigger the k thresholds.

321 00:23:11.420 --> 00:23:15.480 Because in phase one, we tend to deal with limited

322 00:23:15.480 --> 00:23:20.480 sample sizes, 30 maybe all the way to 50 number of patients,

323 00:23:21.890 --> 00:23:26.890 of k threshold or two or four seems to be sufficient

324 00:23:27.530 --> 00:23:30.780 to be able to quantify the strength of evidence.

325 00:23:30.780 --> 00:23:34.603 So I teach dose levels based on cohorts of three patients,

326 00:23:35.590 --> 00:23:40.070 we compare the likelihood ratio and if the likelihood ratio

327 00:23:40.070 --> 00:23:43.670 is greater than one over k in this case two,

328 00:23:43.670 --> 00:23:46.340 we decide that the dose is acceptable and safe

329 00:23:46.340 --> 00:23:49.680 and it will be carried forward to station number two.

330 00:23:49.680 --> 00:23:54.540 Otherwise, the dose is considered unacceptably toxic

331 00:23:54.540 --> 00:23:57.730 and it's being discarded and will not be considered

332 00:23:59.360 --> 00:24:00.510 for further evaluation.

333 00:24:01.350 --> 00:24:06.250 So in this case, let's say that we have two or more

334 00:24:06.250 --> 00:24:11.250 the maximum doses in stage one, we continue to stage two

335 00:24:11.290 --> 00:24:15.548 to employ an adaptive randomization.

336 00:24:15.548 --> 00:24:17.780 So in stage two, we use a linear model

337 00:24:18.780 --> 00:24:21.180 to calculate the randomization probabilities

338 00:24:21.180 --> 00:24:26.000 based on efficacy and in this case we use indicator variable

339 00:24:26.000 --> 00:24:31.000 for each dose level and Y represents the continuous

340 00:24:31.650 --> 00:24:35.580 immunological response and as I mentioned before

341 00:24:35.580 --> 00:24:40.580 in our application, that response is a T-cell persistence

342 00:24:40.600 --> 00:24:42.343 at one month after infusion.

343 00:24:43.740 --> 00:24:48.410 So based on the estimated Ys,

344 00:24:48.410 --> 00:24:52.720 we calculate the randomization probability for each dose

345 00:24:52.720 --> 00:24:57.720 and allocate patients sequentially based on this path.

346 00:24:57.880 --> 00:25:00.870 So how does this look, let's say again,

347 00:25:00.870 --> 00:25:05.440 that we have for dose levels and three patients treated

348 00:25:05.440 --> 00:25:09.500 at each dose level, we measure the T-cell persistence

349 00:25:09.500 --> 00:25:11.710 for all patients within the cohort

350 00:25:11.710 --> 00:25:15.671 and we feed the linear model

351 00:25:15.671 --> 00:25:19.623 to generate the estimated efficiencies.

352 00:25:21.220 --> 00:25:23.287 Based on the estimated efficiencies,

353 00:25:23.287 --> 00:25:25.537 we calculate the randomization probabilities.

354 00:25:26.854 --> 00:25:30.166 So for each dose, in this case,

355 00:25:30.166 --> 00:25:33.740 the randomization probability for dose one is 5%,

356 00:25:33.740 --> 00:25:37.270 the highest is for dose number 49.

357 00:25:37.270 --> 00:25:40.467 So the next patient that will be allocated,

358 00:25:43.200 --> 00:25:47.790 that will be randomized, will probably be randomized

359 00:25:47.790 --> 00:25:49.260 to dose number four,

360 00:25:49.260 --> 00:25:52.733 because this one has the highest randomization probability,

361 00:25:53.763 --> 00:25:56.200 and the process continues in stage two

362 00:25:56.200 --> 00:26:00.410 and feel you have reached the maximum sample size

363 00:26:00.410 --> 00:26:02.210 that you've specified for the trial.

364 00:26:05.000 --> 00:26:09.300 So how did we evaluate the model behavior?

365 00:26:09.300 --> 00:26:11.550 Well, we looked at two different sample sizes,

366 00:26:11.550 --> 00:26:16.253 25 and 50 patients in total for the trial.

367 00:26:17.310 --> 00:26:20.350 The number of levels varied from three to five,

368 00:26:20.350 --> 00:26:24.520 we don't recommend using this design

369 00:26:24.520 --> 00:26:27.880 for less than three of dose levels is just not enough

370 00:26:27.880 --> 00:26:32.720 and the design that you don't gain anything by using it

371 00:26:32.720 --> 00:26:34.323 if you have less than three.

372 00:26:36.260 --> 00:26:41.260 We use the 5,000 simulations for each scenario

373 00:26:41.261 --> 00:26:46.261 and in terms of establishing the operating characteristics,

374 00:26:46.430 --> 00:26:48.430 we quantified two things.

375 00:26:48.430 --> 00:26:51.750 One, we looked at present those allocation

376 00:26:51.750 --> 00:26:55.300 and we looked at estimation of efficacy outcomes,

377 00:26:55.300 --> 00:26:59.200 because that is the main goal actually, after implementing.

378 00:26:59.200 --> 00:27:02.890 you're looking at both toxicity and efficacy

379 00:27:02.890 --> 00:27:04.810 in determining the optimal dose

380 00:27:04.810 --> 00:27:08.380 with the goal of allocating more patients,

381 00:27:08.380 --> 00:27:12.890 skewing the allocation to a dose that is acceptably safe

382 00:27:12.890 --> 00:27:16.990 and has promising efficacy,

383 00:27:16.990 --> 00:27:21.523 in this case has a higher percentage of these helper system.

384 00:27:24.160 --> 00:27:29.160 So this is our combination of efficacy and toxicity scenario

385 00:27:29.240 --> 00:27:34.240 in panel A you see that we have five dose level

386 00:27:35.310 --> 00:27:39.160 on the x-axis and on the y we have the T-cell persistence

387 00:27:39.160 --> 00:27:40.940 as a functional skills

388 00:27:40.940 --> 00:27:45.940 and the scenarios vary from completely flat to monotonic

389 00:27:46.710 --> 00:27:51.710 increasing to non-monotonic and also to plateau,

390 00:27:53.020 --> 00:27:55.180 which is scenario number three.

391 00:27:55.180 --> 00:27:58.570 As I mentioned, this is a pretty frequent scenario

392 00:27:59.460 --> 00:28:04.460 at a certain dose level, the efficacy, that's not,

393 00:28:04.690 --> 00:28:08.450 we don't see any big increases in the efficacy.

394 00:28:08.450 --> 00:28:13.450 In terms of toxicity, again, different flat trends

395 00:28:15.420 --> 00:28:19.033 on the steeper dose toxicities scenario.

396 00:28:21.580 --> 00:28:26.380 In terms of beta stimulation, toxicity was stimulated

397 00:28:26.380 --> 00:28:30.860 from a Bernoulli distribution, persistence was simulated

398 00:28:30.860 --> 00:28:34.650 from a beta-binomial and for variance,

399 00:28:34.650 --> 00:28:38.053 the variance was assumed to be a constant,

400 00:28:39.580 --> 00:28:43.740 but we then read the values of small and large,

401 00:28:43.740 --> 00:28:45.460 and to give you an idea of what means

402 00:28:45.460 --> 00:28:50.440 a large variance at 1%, that is equivalent to about 20%

403 00:28:50.440 --> 00:28:55.420 deviation from the mean T-cell persistence

404 00:28:55.420 --> 00:28:58.793 toxicity and efficacy are modeled independently.

405 00:29:01.150 --> 00:29:06.150 So some results, the paper on had the has several scenarios,

406 00:29:07.860 --> 00:29:12.860 but just to illustrate, this is for a total sample size

407 00:29:13.680 --> 00:29:18.160 of 25 patients both in stage one and in stage two

408 00:29:18.160 --> 00:29:21.020 and the design was compared to MTPI,

409 00:29:21.020 --> 00:29:25.330 which is the Modified Toxicity Probability Interval.

410 00:29:25.330 --> 00:29:29.460 And we wanted to compare and this is one of the operating

411 00:29:29.460 --> 00:29:33.600 correctors, 6% patient allocation.

412 00:29:33.600 --> 00:29:37.760 How does the design allocate patients based on toxicity

413 00:29:37.760 --> 00:29:39.410 and efficacy?

414 00:29:39.410 --> 00:29:44.410 So in this case, that toxicity we see is toxicity three,

415 00:29:45.560 --> 00:29:50.060 we have five, dose levels, the three dose levels

416 00:29:51.250 --> 00:29:56.250 have toxicities lower than 15%.

417 00:29:56.370 --> 00:30:01.370 Dose number four has a toxicity between 15 and 40%,

418 00:30:02.200 --> 00:30:04.730 and dose number five pretty much

419 00:30:04.730 --> 00:30:07.910 is at the maximum DLT threshold,

420 00:30:07.910 --> 00:30:10.620 'cause remember that we had two hypothesis,

421 00:30:10.620 --> 00:30:15.370 15% acceptable toxicity and 40%, so dose one, two, three

422 00:30:15.370 --> 00:30:16.670 are considered acceptable.

423 00:30:16.670 --> 00:30:19.497 Dose four is within the interval,

424 00:30:19.497 --> 00:30:24.497 15, 40 and 40% as shown in red is considered a toxic dose.

425 00:30:28.350 --> 00:30:31.290 So this is the same toxicity

426 00:30:31.290 --> 00:30:35.210 for different efficacy scenarios increasing,

427 00:30:35.210 --> 00:30:39.870 this is non-monotonic this umbrella plateau,

428 00:30:41.240 --> 00:30:42.430 this umbrella trend,

429 00:30:42.430 --> 00:30:45.650 this efficacy three is the plateau trend

430 00:30:45.650 --> 00:30:50.650 and the efficacy four is constant efficacy across all doses.

431 00:30:54.170 --> 00:30:58.830 So what we noticed that the design does a good job

432 00:30:58.830 --> 00:31:01.150 allocating most of the patients

433 00:31:01.150 --> 00:31:04.380 to a dose that is considered safe

434 00:31:04.380 --> 00:31:09.380 and also has the optimal efficacy.

435 00:31:09.630 --> 00:31:14.630 So this would be dose number three in panel A,

436 00:31:14.900 --> 00:31:19.107 again, dose number three in panel B and similar for C

437 00:31:22.160 --> 00:31:27.160 and so ultimately we allocate most of the patients

438 00:31:29.040 --> 00:31:32.073 to this optimal level.

439 00:31:34.690 --> 00:31:39.690 Now let me, I would like to show you an illustration

440 00:31:39.690 --> 00:31:43.423 of how can we use this design,

441 00:31:44.360 --> 00:31:48.903 its implementation in the R package and in the Shiny app,

442 00:31:49.750 --> 00:31:53.190 because the package has two purposes.

443 00:31:53.190 --> 00:31:57.210 One, is to run simulation, to observe to quantify

444 00:31:57.210 --> 00:32:00.253 the operating correctly sticks for different dose,

445 00:32:01.100 --> 00:32:06.100 toxicity dose efficacy scenarios and another benefit

446 00:32:07.303 --> 00:32:11.300 is that you can implement it to actually allocate,

447 00:32:11.300 --> 00:32:14.200 to run the trial, to allocate the next patient

448 00:32:16.978 --> 00:32:18.380 to the optimal dose.

449 00:32:18.380 --> 00:32:23.030 So simulation and implementation and the scenario

450 00:32:23.030 --> 00:32:28.030 that I will discuss next is inspired from a real study

451 00:32:28.800 --> 00:32:33.800 that we worked on when I was at the Cancer Center

452 00:32:34.620 --> 00:32:37.550 at Columbia and this was a phase-one trial

453 00:32:37.550 --> 00:32:41.400 evaluating modified autologous T-cells

454 00:32:41.400 --> 00:32:45.570 this genetically modified T-cells in patients

455 00:32:45.570 --> 00:32:47.810 where the recurrent solid tumors.

456 00:32:47.810 --> 00:32:50.520 So if you think that all these designs

457 00:32:50.520 --> 00:32:55.170 are usually theoretical or just great statistical proposals,

458 00:32:55.170 --> 00:32:59.210 actually this one had an implementation

459 00:33:03.247 --> 00:33:05.430 and had a real setting.

460 00:33:05.430 --> 00:33:10.430 So the initial design that was proposed

461 00:33:11.970 --> 00:33:15.840 was of course, an role-based design derivation,

462 00:33:15.840 --> 00:33:19.490 this was a two-by-two with up to five dose levels,

463 00:33:19.490 --> 00:33:22.530 and I wanna bring your attention to the dose levels.

464 00:33:22.530 --> 00:33:27.530 So in immunotherapy, especially in this T-cell therapies,

465 00:33:28.370 --> 00:33:31.180 the dose levels are not quantities of dose age

466 00:33:33.799 --> 00:33:36.470 of the medication are not milligrams,

467 00:33:36.470 --> 00:33:41.020 but they are actually the number of T-cells

468 00:33:41.020 --> 00:33:44.370 that are being infused back into the body.

469 00:33:44.370 --> 00:33:49.370 So in this case the dose levels vary from 50 to 10

470 00:33:52.670 --> 00:33:57.670 to the six to 500 and 10 the six viable T-cells,

471 00:33:58.180 --> 00:34:02.773 so millions of cells.

472 00:34:05.030 --> 00:34:10.030 And we wanted to explore what is the optimal dose

473 00:34:12.611 --> 00:34:14.253 for this regimen.

474 00:34:15.900 --> 00:34:20.900 So, this is a snapshot of the Shiny app,

475 00:34:25.950 --> 00:34:29.150 we redesigned the trial to incorporate both toxicity

476 00:34:29.150 --> 00:34:32.880 and continuous efficacy and in this case continue,

477 00:34:32.880 --> 00:34:37.850 this T-cell persistence was a reasonable biomarker,

478 00:34:37.850 --> 00:34:42.760 we looked at five dose levels, we had in simulations,

479 00:34:42.760 --> 00:34:47.360 you have to specify what are the toxicity to toxicity rates

480 00:34:47.360 --> 00:34:51.910 and what are the T-cell persistence levels.

481 00:34:51.910 --> 00:34:55.330 The true toxicity rates varied from five to 40%,

482 00:34:55.330 --> 00:35:00.130 the T-cell persistence varied from 15 to 40%.

483 00:35:00.130 --> 00:35:02.950 We didn't see that we're going to see more than 40%

484 00:35:02.950 --> 00:35:07.950 persistence followup and we looked at the total sample size

485 00:35:08.450 --> 00:35:12.230 of 30 patients for the trial, this was feasible

486 00:35:13.540 --> 00:35:14.373 and practical.

487 00:35:15.700 --> 00:35:19.210 So the setup it's very simple,

488 00:35:19.210 --> 00:35:20.880 you just put the number of dose levels,

489 00:35:20.880 --> 00:35:24.780 you specify the toxicities, you specify the mean efficacy,

490 00:35:24.780 --> 00:35:28.393 the variance for the efficacy, we chose 1%,

491 00:35:29.460 --> 00:35:34.460 but this can take different values,

492 00:35:35.040 --> 00:35:36.700 then of course, this is a dialogue

493 00:35:36.700 --> 00:35:41.540 that you have with your clinical investigator,

494 00:35:41.540 --> 00:35:45.030 hopefully with data supported from previous studies

495 00:35:45.030 --> 00:35:50.030 and what is considered to be to very these parameters.

496 00:35:50.040 --> 00:35:54.380 Then for stage one, you have to specify the two hypothesis,

497 00:35:54.380 --> 00:35:56.603 acceptable and unacceptable DLT.

498 00:35:57.855 --> 00:36:02.260 For this one, we set it at 15 and 40%,

499 00:36:02.260 --> 00:36:05.060 the likelihood ratio was set at two

500 00:36:05.060 --> 00:36:10.060 because of the sample size of 30 with k equals to two

501 00:36:11.500 --> 00:36:16.500 is reasonable and three cohorts, three patients per cohort,

502 00:36:16.780 --> 00:36:21.780 meaning each of the five dose levels we have three patients

503 00:36:21.910 --> 00:36:23.273 allocated each.

504 00:36:24.360 --> 00:36:27.700 Total sample size of 30 on the stopping rule,

505 00:36:27.700 --> 00:36:32.490 stopping rule meaning if none of the doses

506 00:36:32.490 --> 00:36:35.430 are considered acceptable in stage one,

507 00:36:35.430 --> 00:36:38.220 we're going to allocate up to nine patients

508 00:36:39.676 --> 00:36:43.430 at the first dose to further establish toxicity,

509 00:36:43.430 --> 00:36:48.430 and this can be changed to six or other number.

510 00:36:52.260 --> 00:36:55.263 So these are, how did the scenario looks?

511 00:36:56.440 --> 00:36:59.910 This is the graphs actually generated by the app

512 00:37:01.330 --> 00:37:04.980 toxicity and efficacy as a function of dose level,

513 00:37:04.980 --> 00:37:09.980 and now I'd like to ask you, ask for your participation,

514 00:37:12.040 --> 00:37:13.800 looking at these two scenarios,

515 00:37:13.800 --> 00:37:17.843 what do you think would be an optimal dose level,

516 00:37:19.280 --> 00:37:22.843 the recommended to be studied in phase-two or later?

517 00:37:35.010 --> 00:37:38.560 Okay, maybe we need some hint,

518 00:37:38.560 --> 00:37:41.763 so we want an acceptable dose.

519 00:37:43.750 --> 00:37:44.583 <v ->[] Three.</v>

520 00:37:46.170 --> 00:37:48.700 <v ->Dose number three, dose number three,</v>

521 00:37:48.700 --> 00:37:52.080 because dose number three is way outside

522 00:37:55.080 --> 00:38:00.080 of the acceptability range and also dose number three

523 00:38:00.250 --> 00:38:05.250 tends to have a good efficacy after dose number three

524 00:38:06.020 --> 00:38:10.903 we don't see any improvement in terms of efficacy.

525 00:38:10.903 --> 00:38:14.360 Dose number four is between the 15 and 40%

526 00:38:14.360 --> 00:38:17.700 then dose number five was probably toxic.

527 00:38:17.700 --> 00:38:21.470 So, dose number three is the optimal dose

528 00:38:21.470 --> 00:38:23.103 and what we would like to see,

529 00:38:25.660 --> 00:38:28.920 is most patients being allocated at this level.

530 00:38:28.920 --> 00:38:33.920 So in simulations, this is simulations for stage one,

531 00:38:36.660 --> 00:38:40.260 where based on observed the DLTs,

532 00:38:40.260 --> 00:38:45.260 we calculate the likelihood ratio and mark the doses

533 00:38:49.080 --> 00:38:52.750 as being acceptable or unacceptable.

534 00:38:52.750 --> 00:38:57.240 So in this case, based on the simulations, we see dose one,

535 00:38:57.240 --> 00:39:02.240 two, three and four are considered acceptably safe

536 00:39:03.330 --> 00:39:06.920 and they will be carried forward to stage number two,

537 00:39:06.920 --> 00:39:10.190 to be considered for that different organization,

538 00:39:10.190 --> 00:39:13.130 dose number five will be discarded

539 00:39:13.130 --> 00:39:15.193 and will not be used in stage two.

540 00:39:16.210 --> 00:39:17.320 And why is that?

541 00:39:17.320 --> 00:39:22.320 Because the likelihood ratio is less than 0.05.

542 00:39:28.700 --> 00:39:32.690 Now these are the simulations for a stage number two,

543 00:39:32.690 --> 00:39:36.960 so in the first part, we had five dose levels,

544 00:39:36.960 --> 00:39:40.030 three patients each, so that's a total of 15 patients

545 00:39:40.030 --> 00:39:45.030 starting with patient number 16, we moved to stage two

546 00:39:45.260 --> 00:39:47.250 and we do this adaptive randomization

547 00:39:47.250 --> 00:39:50.810 until we reach the maximum sample size of 30.

548 00:39:50.810 --> 00:39:55.273 So the app actually gives you simulations and allocations

549 00:39:57.850 --> 00:40:02.420 for all the patients from 16 to 30 dose assignments

550 00:40:02.420 --> 00:40:06.930 and efficacy outcome and this gives you a graph

551 00:40:06.930 --> 00:40:10.820 of the estimated efficacy and the medians

552 00:40:12.840 --> 00:40:15.613 and inter quartile ranges.

553 00:40:17.460 --> 00:40:21.193 So we repeated this a hundred times, you can repeat it more

554 00:40:21.193 --> 00:40:26.193 1,000, 5,000 in terms of allocation based on the setting,

555 00:40:29.420 --> 00:40:33.600 based on the parameters, the hypothesis, the k threshold,

556 00:40:33.600 --> 00:40:38.180 the toxicity and efficacy scenarios scenario,

557 00:40:38.180 --> 00:40:42.620 we see that dose three tends to be favored

558 00:40:42.620 --> 00:40:47.620 in terms of allocation, where the highest media allocation,

559 00:40:48.420 --> 00:40:53.420 26.7 and going all the way to 33.3 for the 75th percentile.

560 00:40:57.120 --> 00:41:02.120 In terms of efficacy estimation, dose number three

561 00:41:04.211 --> 00:41:06.960 or if you remember when we specify the true mean

562 00:41:06.960 --> 00:41:11.820 efficacy was 40, the median estimated efficacy

563 00:41:11.820 --> 00:41:13.553 in this case is 39.75,

564 00:41:15.216 --> 00:41:18.800 the 75 percentile goes all the way to 45,

565 00:41:18.800 --> 00:41:21.693 but of course that will be improved with,

566 00:41:23.038 --> 00:41:24.488 as the sample size increases.

567 00:41:27.780 --> 00:41:32.780 So in conclusion, what does iAdapt proposals?

568 00:41:36.820 --> 00:41:39.920 It's an option, it's a viable option

569 00:41:39.920 --> 00:41:44.090 for incorporating toxicity and efficacy outcomes,

570 00:41:44.090 --> 00:41:49.090 especially for immunotherapy trials.

571 00:41:49.110 --> 00:41:52.890 The novelty is in the designing allows

572 00:41:56.300 --> 00:42:00.820 to model toxicity, both of binary

573 00:42:00.820 --> 00:42:04.300 and also as quasi-continuous measures

574 00:42:04.300 --> 00:42:08.220 and this was actually updated this year in the package

575 00:42:08.220 --> 00:42:13.220 to use the several types of toxicities and several grades,

576 00:42:16.700 --> 00:42:19.710 that continuous efficacy outcome

577 00:42:21.560 --> 00:42:26.090 is very relevant for immunotherapies and I really showed

578 00:42:26.090 --> 00:42:28.880 the example from the trial with T-cell persistence,

579 00:42:28.880 --> 00:42:33.880 it is a relevant biomarker, but you can use for example,

580 00:42:35.010 --> 00:42:38.940 absolute counts, you can use a full changes,

581 00:42:38.940 --> 00:42:41.470 so design is flexible in incorporating

582 00:42:41.470 --> 00:42:43.330 other continuous outcomes.

583 00:42:43.330 --> 00:42:46.750 As far as I know, this is the only design at this point

584 00:42:47.670 --> 00:42:51.273 that uses continuous efficacy outcomes.

585 00:42:52.800 --> 00:42:55.463 So in terms of operating characteristics,

586 00:42:57.910 --> 00:43:00.050 the design as well and allocating,

587 00:43:00.050 --> 00:43:03.970 skewing the allocation to optimal doses,

588 00:43:03.970 --> 00:43:08.120 estimation is marginally improved depends of course,

589 00:43:08.120 --> 00:43:10.810 on the level of various and the sample size

590 00:43:10.810 --> 00:43:14.403 and if anybody wants to try, you can use the R package,

591 00:43:14.403 --> 00:43:18.390 you can use the Shiny app to simulate

592 00:43:18.390 --> 00:43:22.070 to look at the behavior of different scenarios

593 00:43:22.070 --> 00:43:26.350 to put that in trial and of course,

594 00:43:26.350 --> 00:43:28.793 to use it to run the trial.

595 00:43:29.670 --> 00:43:34.490 I'd like to thank two former students, Alyssa and Laura,

596 00:43:34.490 --> 00:43:39.490 that helped in uploading the R package

597 00:43:39.600 --> 00:43:43.020 and Laura has created the Shiny app.

598 00:43:43.020 --> 00:43:47.460 And I do have some references in case you're interested,

599 00:43:47.460 --> 00:43:52.460 but I can also share the slides later on.

600 00:43:52.710 --> 00:43:57.380 So I think that is it and I wanted to allow some time

601 00:43:57.380 --> 00:44:02.370 for questions and comments and feedback from you.

602 00:44:02.370 --> 00:44:03.430 Thank you so much.

603 00:44:05.590 --> 00:44:07.035 <v ->Thank you very much professor.</v>

604 00:44:07.035 --> 00:44:09.285 (applauds)

605 00:44:13.177 --> 00:44:16.677 Do you ave any questions in the room here?

606 00:44:27.643 --> 00:44:30.183 Does anyone from Zoom have any questions?

607 00:44:34.680 --> 00:44:36.530 <v ->Cody, thank you for the presentation,</v>

608 00:44:36.530 --> 00:44:40.080 I think it's very useful to talk her way,

609 00:44:40.080 --> 00:44:45.080 as well as my future like your possible designs

610 00:44:45.851 --> 00:44:50.851 of the trials related to immunotherapy, I have one question.

611 00:44:52.730 --> 00:44:57.730 So you mentioned toxicity and...

612 00:45:01.320 --> 00:45:06.143 Does anywhere in the design actually dependent

613 00:45:08.070 --> 00:45:13.070 on the independence of toxicity and efficacy profile?

614 00:45:16.780 --> 00:45:18.400 <v ->It's a great point to talking</v>

615 00:45:18.400 --> 00:45:22.820 if we actually modeled jointly toxicity and efficacy.

616 00:45:22.820 --> 00:45:26.205 <v ->So I'm actually looking at the slide</v>

617 00:45:26.205 --> 00:45:31.205 that you have the toxicity and like also efficacy profile,

618 00:45:32.935 --> 00:45:35.713 I think like say if we have an ordinal categorical,

619 00:45:36.720 --> 00:45:41.720 lets say for example, like say we pick a number three

620 00:45:42.290 --> 00:45:46.040 because it's intolerable toxicity

621 00:45:47.100 --> 00:45:49.940 and maximize the efficacy, right?

622 00:45:49.940 --> 00:45:52.240 And anything above that will be too much

623 00:45:52.240 --> 00:45:54.970 and anything below that will be like,

624 00:45:54.970 --> 00:45:58.803 say not like effective enough.

625 00:45:59.956 --> 00:46:03.890 So if they are actually,

626 00:46:03.890 --> 00:46:07.053 how about certain joint distribution,

627 00:46:08.790 --> 00:46:13.290 is there any thing we can do in order to like,

628 00:46:13.290 --> 00:46:16.953 'cause that actually affect the simulation much?

629 00:46:17.860 --> 00:46:21.550 <v ->So the current model does not account</v>

630 00:46:21.550 --> 00:46:23.710 for the joint distribution,

631 00:46:23.710 --> 00:46:27.220 it models toxicity and efficacy separately.

632 00:46:27.220 --> 00:46:32.220 But as a next step we can look under to try to model

633 00:46:34.870 --> 00:46:37.950 that dependency between toxicity and efficacy,

634 00:46:37.950 --> 00:46:41.380 and especially for this novel agents,

635 00:46:41.380 --> 00:46:46.380 we've seen that most of the times toxicity as is related

636 00:46:47.640 --> 00:46:52.570 to efficacy, a stronger ethical, a stronger response

637 00:46:53.500 --> 00:46:58.500 does come with some higher levels of toxicity,

638 00:47:00.100 --> 00:47:01.810 but the current model does not look,

639 00:47:01.810 --> 00:47:03.873 they twist them independent.

640 00:47:05.790 --> 00:47:10.740 <v ->So do we, so is there, do you consider any,</v>

641 00:47:10.740 --> 00:47:12.430 like penalty for example,

642 00:47:12.430 --> 00:47:16.010 like say when there isn't such a good, like a compromise

643 00:47:16.010 --> 00:47:20.386 between like minimizing toxicity

644 00:47:20.386 --> 00:47:22.700 while maximizing efficacy, right?

645 00:47:22.700 --> 00:47:25.500 So in the demonstration we have a compromise,

646 00:47:25.500 --> 00:47:27.773 which is dose level number three,

647 00:47:30.110 --> 00:47:34.180 if there's, for example, if there is like a conflict

648 00:47:34.180 --> 00:47:38.500 between dose two and we can, like we don't really have,

649 00:47:38.500 --> 00:47:43.500 like the obvious optimal, like say optimized solution.

650 00:47:46.110 --> 00:47:48.900 Do we constantly there, like, for example, penalties

651 00:47:48.900 --> 00:47:52.920 or do we always pay for like toxicity,

652 00:47:52.920 --> 00:47:56.510 like say minimizing toxicity over like,

653 00:47:56.510 --> 00:47:58.353 say maximizing efficacy?

654 00:48:00.910 --> 00:48:05.910 <v ->And then think it's always, I think so for example,</v>

655 00:48:06.650 --> 00:48:10.473 in that situation, so you could actually take both

656 00:48:10.473 --> 00:48:13.590 dose three and dose number four,

657 00:48:13.590 --> 00:48:18.590 you could consider both to be considered for future trials.

658 00:48:19.930 --> 00:48:24.930 So, it's not the definite that the dose selected,

659 00:48:29.830 --> 00:48:33.070 that you're always gonna reach a minimum of toxicity

660 00:48:33.070 --> 00:48:38.070 and maximum efficacy, but you can look at different options

661 00:48:39.320 --> 00:48:43.730 with as long as toxicity is acceptable,

662 00:48:43.730 --> 00:48:47.180 you can consider maybe in phase-two

663 00:48:47.180 --> 00:48:52.180 to look at randomized trial, look at dose level combo one

664 00:48:52.230 --> 00:48:55.340 and dose levels combo-two based on efficacy

665 00:48:55.340 --> 00:48:59.980 and we've actually seen this in a lot of trials,

666 00:48:59.980 --> 00:49:04.690 the immune check point inhibitors review that I talked,

667 00:49:04.690 --> 00:49:08.940 that it's now in progress, we looked at phase-one and two

668 00:49:08.940 --> 00:49:12.130 and the rate of success and the design that are being used

669 00:49:12.130 --> 00:49:15.860 and the doses that are being carried forward from phase-one

670 00:49:15.860 --> 00:49:20.860 and phase-two, and surprisingly only 30%,

671 00:49:21.440 --> 00:49:26.440 in 30% of phase-two trials the MTD was used from phase-one,

672 00:49:30.070 --> 00:49:32.620 the rest either they use a lower dose

673 00:49:32.620 --> 00:49:36.497 or they use a higher dose, but not the MTD.

674 00:49:37.970 --> 00:49:41.660 So absolutely we can have like a range,

675 00:49:41.660 --> 00:49:43.360 because if you think about it,

676 00:49:43.360 --> 00:49:45.500 we have a limited sample size, right?

677 00:49:45.500 --> 00:49:48.070 We need more information for efficacy,

678 00:49:48.070 --> 00:49:52.620 so to complete the clear, the winner based on efficacy

679 00:49:52.620 --> 00:49:57.360 might not be sufficient at this level.

680 00:49:57.360 --> 00:49:58.290 <v ->Okay, great, thank you.</v>

681 00:49:58.290 --> 00:50:01.310 So the answer is before phase-three

682 00:50:01.310 --> 00:50:03.640 and as long as it's below the MTD,

683 00:50:03.640 --> 00:50:07.840 the efficacy is important, is more important to prove,

684 00:50:07.840 --> 00:50:09.770 like, say to move on to next stage.

685 00:50:09.770 --> 00:50:10.767 Thank you.

686 00:50:10.767 --> 00:50:12.100 <v Codruta>Yes.</v>

687 00:50:28.730 --> 00:50:30.394 Just connection.

688 00:50:30.394 --> 00:50:32.644 (chuckles)

689 00:50:34.460 --> 00:50:37.110 <v Moderator>Sorry, we're still having a little weird audio</v>

690 00:50:37.110 --> 00:50:38.833 issues obviously,

691 00:50:44.680 --> 00:50:47.650 but does anybody in the room have any other questions

692 00:50:47.650 --> 00:50:48.550 for the professor?

693 00:51:02.270 --> 00:51:03.470 Or even we end the Zoom.

694 00:51:11.230 --> 00:51:13.230 <v Wei>Hello, we have a question there.</v>

695 00:51:15.500 --> 00:51:16.373 <v Moderator>Hold on.</v>

696 00:51:20.720 --> 00:51:22.490 <v Student>Hi professor, I know we probably mentioned</v>

697 00:51:22.490 --> 00:51:26.030 this already, but I probably didn't typed that,

698 00:51:26.030 --> 00:51:28.270 can you repeat, maybe repeat what it was,

699 00:51:28.270 --> 00:51:32.470 what do you consider would be like an advantage

700 00:51:32.470 --> 00:51:34.650 of having a continuous efficacy

701 00:51:34.650 --> 00:51:38.683 compares non-continuous efficacy in your model?

702 00:51:39.780 --> 00:51:44.780 <v ->Yes, lots of information, so a lot of the lines</v>

703 00:51:48.077 --> 00:51:52.940 are looking at the efficacy as a binary or ordinal,

704 00:51:52.940 --> 00:51:54.203 there is actually one,

705 00:51:55.110 --> 00:51:56.560 I don't know if you've heard of the Boyne,

706 00:51:56.560 --> 00:52:00.427 that's also was published for immunotherapies

707 00:52:00.427 --> 00:52:05.427 and that's using you take the efficacy levels

708 00:52:05.540 --> 00:52:09.210 and you either dichotomized to represent

709 00:52:09.210 --> 00:52:13.380 what is a successful or promising efficacy versus not,

710 00:52:13.380 --> 00:52:18.250 and you pretty much modeled the probability of a response,

711 00:52:18.250 --> 00:52:21.253 right one versus zero or at an ordinal level.

712 00:52:22.220 --> 00:52:25.450 Number one, I think we were losing some information

713 00:52:25.450 --> 00:52:27.920 when we do this categorization,

714 00:52:27.920 --> 00:52:31.820 number two might be difficult to actually establish

715 00:52:31.820 --> 00:52:35.010 this cutoffs and what represents a success

716 00:52:35.010 --> 00:52:38.230 or how do we partition this efficacy range

717 00:52:38.230 --> 00:52:39.990 for this novel agents.

718 00:52:39.990 --> 00:52:43.370 So by looking at the continuous values,

719 00:52:43.370 --> 00:52:47.253 we make the most out that information and we let it on,

720 00:52:48.319 --> 00:52:50.023 we modeled it as such,

721 00:52:54.450 --> 00:52:57.083 plus in the last couple of years,

722 00:52:58.400 --> 00:53:00.760 this T-cell persistence has been shown

723 00:53:00.760 --> 00:53:02.970 to be a promising biomarker.

724 00:53:02.970 --> 00:53:07.970 So it's right on par with our proposal.

725 00:53:17.860 --> 00:53:22.860 I know this might be a tough topic to digest for students

726 00:53:23.990 --> 00:53:27.900 with early finding it's not such a...

727 00:53:28.880 --> 00:53:33.030 It's a (chuckles) framework on its own.

728 00:53:33.030 --> 00:53:35.060 So maybe not that everybody's familiar

729 00:53:38.043 --> 00:53:41.130 with the whole terminology on the landscape.

730 00:53:48.320 --> 00:53:52.470 <v Student>During that stimulation, you specifically...</v>

731 00:53:52.470 --> 00:53:55.230 So the toxicity was stimulated

732 00:53:55.230 --> 00:53:57.980 from a continuity distributions,

733 00:53:57.980 --> 00:53:59.340 is there any specific reason

734 00:53:59.340 --> 00:54:02.600 why you choose these distribution versus there's,

735 00:54:02.600 --> 00:54:06.383 and if we similarly from a different distribution,

736 00:54:08.280 --> 00:54:10.540 well, how about different conclusion like,

737 00:54:10.540 --> 00:54:13.070 well, there would be any dependence

738 00:54:13.070 --> 00:54:15.433 between efficacy and toxicity.

739 00:54:17.140 --> 00:54:21.026 <v ->Yes, so that's, and so in this case,</v>

740 00:54:21.026 --> 00:54:25.000 the results that I showed you were for toxicity,

741 00:54:25.000 --> 00:54:27.380 for binary toxicity, yes or no.

742 00:54:27.380 --> 00:54:31.470 So in a cohort of three patients for each patient,

743 00:54:31.470 --> 00:54:35.640 you observed either a zero or a one response,

744 00:54:35.640 --> 00:54:39.100 given the binary structure, it makes sense to use

745 00:54:39.100 --> 00:54:41.860 this Bernoulli right distribution

746 00:54:41.860 --> 00:54:44.743 and that sums up to binomial zero or one.

747 00:54:46.220 --> 00:54:50.430 In terms of dependency is with what Dr. Cheng

748 00:54:50.430 --> 00:54:55.060 was mentioning, we did not specify any correlation

749 00:54:55.060 --> 00:54:57.060 between toxicity and efficacy

750 00:54:57.060 --> 00:55:00.180 and did not look at the joint distribution between the two,

751 00:55:00.180 --> 00:55:04.090 we modeled them separate and probably

752 00:55:08.625 --> 00:55:11.720 that would be a good point moving forward.

753 00:55:11.720 --> 00:55:15.970 What's difficult is how do we, what would be interesting

754 00:55:17.000 --> 00:55:20.990 is looking at different levels of correlation

755 00:55:20.990 --> 00:55:24.890 and see how in this joint distribution,

756 00:55:24.890 --> 00:55:29.870 how the results with change, if we would capture that.

757 00:55:38.430 --> 00:55:40.647 <v Wei>Okay, so any more questions?</v>

758 00:55:50.318 --> 00:55:53.158 Okay, so thank you Dr. Chuizan,

759 00:55:53.158 --> 00:55:55.825 for your wonderful presentation.

760 00:55:57.956 --> 00:55:58.789 <v ->Thank you.</v>

761 00:55:58.789 --> 00:56:01.520 <v ->Thank you, and if you have any questions,</v>

762 00:56:01.520 --> 00:56:03.462 please email me anytime.

763 00:56:03.462 --> 00:56:04.480 (chuckles)

764 00:56:04.480 --> 00:56:06.280 And I'm sorry that you (indistinct).

765 00:56:10.400 --> 00:56:13.410 Okay, I'll see you shortly, bye.

766 00:56:13.410 --> 00:56:14.310 <v Wei>Thank you.</v>