Okay, hello everyone.

Today, we are very fortunate to have Dr. Codruta Chiuzan as our speaker. Dr. Chiuzan is Associated Professor, Institute of Health System Science at Northwell Health New York. Before that, she was an Assistant Professor in the Department of Biostatistics at Mailman School of Public Health Columbia University. In her research area focus on earning phase clinical trial designs and an average aging real-world evidence to prove all the cons and increased diversity.

In her research area focus on earning phase clinical trial designs and an average aging real-world evidence to prove all the cons and increased diversity.

Now, she is in receipt of Junior Faculty Research Award and the Columbia Public Health Innovation Award from the Mailman School of Public Health.

So, Dr. Chiuzan, has a very strong record or mentoring.

She is an active committee member of JSM, Diversity Mentoring Program. She had held leadership positions as the President of the American Statistical Association and New York City Metropolitan Area.
and she as the Chair over the Student Scholars Committee at the Society of Clinical Trials. So, welcome Dr. Chiuzan and time is yours. Thank you so much Wei, for the invitation.

It’s a pleasure, I’m going to share my experience. Hello. Hello, I hear some echo in the background. Is anybody (indistinct). The host, can you disable the screen sharing?

I can share the slides? Oh, perfect. Okay, can everybody see the screen, the full screen?

It’s a pleasure to be with you even virtually and I’m glad to see so many people in person with academic semester ongoing. Today I’m going to talk about one area of my research and that is early phase designs for immunotherapies or cancer immunotherapies and I will take you through a journey, through a story by giving some examples and explanation of what are these cancer immunotherapies, what are the promises, what are the challenges and how do they actually reflect in the early phase designs? Then I will talk about current models.
and a model that we developed on has been implemented in an R package and the Shiny app and I will conclude with a practical demonstration.

Please, if anybody has any questions at any point, please feel free to raise a hand or just ask, I like us to have an interactive session and to have a continuous dialogue if you’re able please.

So what is immunotherapy?

The New York times called it a long awaited reality because immunotherapy has been developed since the early 1900s, actually by a New York surgeon that saw that in cancer patients that develop flu, had a better anti-cancer response.

So immunotherapy works on a different paradigm compared to cytotoxic agents and by cytotoxic agents, I mean, chemotherapy or radiations.

So immunotherapy boosts or leverages the body’s own immune system to fight cancer, to recognize it, to attack it and ultimately to kill the cancer cells.

The three Rs of cancer immunotherapies are reverse tolerance, rejuvenate the immune system.
and restore the internal environment homeostasis.

So, you'll probably hear more and more updates and FDA approvals for cancer immunotherapies. Between 2017 and 2020, over 65% increase has been seen in the number of immunotherapies and these immunotherapies, most of them have been approved for immune checkpoint inhibitors, Ipilimumab, Nivolumab and Pembrolizumab that works by incubator thing, the relationship, the association between the PD-1 and the PD-L1 receptors, but the largest growth has been seen for cell therapies. And what are these cell therapies? The most frequent and the most study one is called T-cells, so far, which will be approvals. So that these old therapies use the T-cells in the body to fight cancer and then you do that by first, taking blood from the patient, isolating the T-cells in the lab in the Petri dish and genetically modify these T-cells to display a specific receptor that then is introduced and after that when the cells are being introduced into the body, this T-cell receptor

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will bind to specific antigen present on the cancer cells and trigger an anti-tumor reaction. So these are the T-cells, these are the cell therapies that are being studied and they’re very promising in terms of prolonging overall survival and also in lowering the toxicity, killing cancer without killing the patient. Last year update from the Cancer Research Institute has shown that, as I said, that the most promising field in cancer therapies are, has been seen in this T-cell therapies, most of them for a solid cancer, nonsmall, renal cancer, colorectal cancer, but it’s moving into the non-solid cancer as well. So, Hype versus Hope, I entitled this slide, immunotherapy, is it the holy grail is it the holy grail the holy grail the holy grail the holy grail because of course it comes with some challenges. Some of the challenges are immunotherapy sometimes can trigger delayed responses, meaning that the treatment has to continue even if initial response has not been seen, there’s been cases of hyper-progression where the cancer tumor seen this rapid growth
in the early stages and that can be the problematic on diminished overall survival. And most importantly, we’re not really sure exactly what to measure and how to incorporate endpoints into all phases of drug development from early phase, phase one and two, where we’re looking at identifying the optimal dose to later phases.

So, because it’s still under development, there is a lack of biomarkers to predict the responders versus not the responders and the difficult to correlate these immunological biomarkers with outcomes, clinical outcomes, overall survival response progression, free survival compared to cytotoxic agents, chemotherapy, immunotherapies have different toxicity profiles, meaning they can have lower toxicity and also different grades and different profiles, is called by, also called as immune-related adverse event. So if you’re familiar with drug development phases, as you know that usually it will start with early phase. Phase one, identifying the maximum tolerated dose
to be carried forward then for establishing efficacy and in later phases.

In the old paradigm, so the objective was to find the MTD and the MTD was mainly based on toxicity as binary, yes or no DLT, the patient has after receiving treatment.

we quantify the number of those limiting toxicities, unacceptable toxicity within a certain interval. However, the new immunotherapies have, as I mentioned before, they have different toxicity profiles, so this old paradigm of finding the MTD, does longer stint, there are a lot of trials where the dose escalation moved quickly to the maximum dose level and MTD.

There were no DLTs, the MTD was not identified and most importantly, toxicity and efficacy might not necessarily be those dependents.

So you might be able to find a safe dose, but that might not necessarily be the most promising one in terms of efficacy.

In many cases, we actually see this plateau trend where after a certain level, the efficacy levels out plateaus and we don’t see any effect.
is different levels of toxicity incorporation of efficacy. into the dose finding process, we need to reconsider the definition and think of more in terms of identifying the optimal biological dose versus the MTD, a dose that is acceptable in terms of toxicity, but also this place, a good efficacy profile. So in terms of methodology, again in early-phase, research has been dominated in the past decades by algorithmic designs by algorithmic, I mean the three plus three, which is definitely not preferred by statisticians and actually strongly disapproved by statisticians. and even until 2014, when we did the last review of early-phase methodology, we saw that over 90% of this trials have implemented a rule-based design. Rule-based working only on toxicity with absolutely no statistical background. From 2012, we saw more than 60% of the trials that the tested targeted or immunotherapies and only 7.6 actually used a model-based design. So what do I mean by model-based design? Well, we criticize in three plus three, but are there alternatives actually several.
One alternative that addresses the matter of late onset toxicities that is usually seen in immunotherapies, meaning you see DLTs outside of DLT window, that is usually 28 days longer toxicities, for that we have the time to event continual reassessment method that was proposed by Jenga Chapelle in 2000. The problem with multiple toxicities across different varying grades and moving away from the binary DLT has been tackled by Ezzalfani and others by using, by incorporating these types, different toxicity types and different grades into the total toxicity score, which is a quasi continuous measure. As I mentioned for immunotherapies, it makes more sense to incorporate both toxicity and efficacy and for that we have models that look at, that incorporate both toxicity and efficacy and these are the F-stocks designs method or the bivariate continual reassessment method. And more recently, other measures have been looked at in immunotherapies and these are the PK, the pharmacokinetics or the pharmacodynamics.
and these have been incorporated by, for example, Ursino, in a patient design proposed in 2017. So this is to present the status quo of what's being proposed out there, what we are suggesting is also a design that is specific for immunotherapy trials and this was published in 2018 and since then we have added a different measure of toxicity, we have implemented it into an R package that is on a available on cram, iAdapt and also can be tried using charmia. So this design for immunotherapies uses both toxicity and efficacy to identify the optimal dose. Optimal dose meaning unacceptable dose with promising efficacy profile. The design is unique in the sense it can incorporate both binary or quasi continuous toxicity scores, and it's looking at the continuous efficacy outcomes. Most of the designs that I mentioned before are using either binary or ordinal efficacy. In this one we're looking at continuous outcomes, such as T-cell persistence at followup compared to baseline why the cell persistence, as I mentioned before, well, about this engineered T-cells
when they are being put into the body, they maintain the store, then the genetic information and the trigger and tumor response and it’s been shown, there’s some studies shown that the number of T-cells that are still present, still survive in the blood at one or two months after being reinfused tends to predict response on the overall survival on the long-term. The design has, does not impose any monotonicity assumption in terms of those efficacy relationship and does not account for dependence between toxicity and efficacy. So now let’s take a look at the two, the difference between incorporating toxicity only and looking at efficacy also. The cartoon on the left shows the dose toxicity relationship or five dose level. So in this graph, let’s say we have five dose levels and we have a threshold of unacceptable toxicity set at 40%. So based on this graph, we have about four dose levels that are below the threshold, one dose level that is above. So if we have 40% toxicity threshold, dose number four would be identified as the MTD, the maximum tolerated dose.
However, if we are to look also at efficacy and in this case, the dose efficacy has this umbrella, this non-monitoring trend. We will see that by looking at the MTD, we would totally miss the optimal dose because dose number four has actually a lower efficacy as compared to dose number three. So this is to pretty much justify the need to incorporate both toxicity and efficacy into the dose finding process. So the design has two stages. In stage one, we’re establishing the safety profile. We have a number of pre-specified dose levels and we start by defining the set of hypothesis, where hypothesis one represents the unacceptable DLT rate and hypothesis two, represent unacceptable DLT rate. We have a number of pre-specified dose levels and we start by defining the set of hypothesis, where hypothesis one represents the unacceptable DLT rate. DLT, meaning the Dose Limiting Toxicity.
in favor of hypothesis one or hypothesis two, is done by the likelihood ratio V, the evidential paradigm. So to give you a little bit of a background, in statistics there pretty much three school of thoughts, we have the frequencies approach based on Pearson, you’ll have the patient school of thought, and then you have the evidential paradigm. The evidential paradigm and the frequent tests are somehow similar, but the difference between the two is the evidential paradigm based on the law of likelihood the couples, the strength of evidence from uncertainty. So the strength of the evidence is quantified by the likelihood ratio and our certainty is quantified by the probability of misleading evidence and the probability of observing weak or strong evidence in favor of the other two. Yeah, in comparison the frequent is the approach, that’s not the couple, the strength of evidence and from uncertainty. So evidential paradigm used to establish acceptability in stage number one. And how do we do that? Let’s say we have a certain number of levels, each show,
and we treat cohorts of size M patients to each of these dose levels based on toxicity information, we calculate the likelihood ratio and evaluate evidence as one of the three, either we have strong evidence in favor of hypothesis two, declaring that the dose is acceptable. Either we have strong evidence in favor of H1, it’s unacceptable or we conclude the weak evidence doesn’t support either of the hypothesis, the likelihood ratio is compared to a threshold, okay? So how do we, let’s take a look at an example to see how we set the hypothesis and how we started this threshold, okay? So let’s say that we have hypothesis one 40%, unacceptable, the DLT rate toxic and hypothesis two 15%, that is an acceptable DLT rate and hypothesis two 15%, that is an acceptable DLT rate and we want, we evaluate each dose based on these two hypothesis. And for that one, in this case, we use a k threshold equal to two, so there’s been a lot of literature written on this evidential paradigm and the k thresholds can vary, we can take values from two, four, eight all the way to 32, depending on the sample size,
the bigger the sample size, the bigger the k thresholds.

Because in phase one, we tend to deal with limited sample sizes, 30 maybe all the way to 50 number of patients,

of k threshold or two or four seems to be sufficient to be able to quantify the strength of evidence. So I teach dose levels based on cohorts of three patients,

we compare the likelihood ratio and if the likelihood ratio is greater than one over k in this case two, we decide that the dose is acceptable and safe and it will be carried forward to station number two.

Otherwise, the dose is considered unacceptably toxic and it’s being discarded and will not be considered for further evaluation.

So in this case, let’s say that we have two or more the maximum doses in stage one, we continue to stage two to employ an adaptive randomization.

So in stage two, we use a linear model to calculate the randomization probabilities based on efficacy and in this case we use indicator variable for each dose level and Y represents the continuous immunological response and as I mentioned before.
in our application, that response is a T-cell persistence at one month after infusion. So based on the estimated $Y$s, we calculate the randomization probability for each dose and allocate patients sequentially based on this path. So how does this look, let’s say again, that we have for dose levels and three patients treated at each dose level, we measure the T-cell persistence for all patients within the cohort and we feed the linear model to generate the estimated efficiencies. Based on the estimated efficiencies, we calculate the randomization probabilities. So for each dose, in this case, the randomization probability for dose one is 5%, the highest is for dose number 49. So the next patient that will be allocated, will probably be randomized to dose number four, because this one has the highest randomization probability, and the process continues in stage two. So how did we evaluate the model behavior? Well, we looked at two different sample sizes, and feel you have reached the maximum sample size that you’ve specified for the trial.
25 and 50 patients in total for the trial. The number of levels varied from three to five, we don’t recommend using this design for less than three of dose levels is just not enough. The design that you don’t gain anything by using it if you have less than three. We use the 5,000 simulations for each scenario and in terms of establishing the operating characteristics, we quantified two things. One, we looked at present those allocation and we looked at estimation of efficacy outcomes, because that is the main goal actually, after implementing. You’re looking at both toxicity and efficacy in determining the optimal dose with the goal of allocating more patients, skewing the allocation to a dose that is acceptably safe and has promising efficacy, in this case has a higher percentage of these helper system. So this is our combination of efficacy and toxicity scenario in panel A you see that we have five dose levels on the x-axis and on the y we have the T-cell persistence as a functional skills and the scenarios vary from completely flat to monotonic.
increasing to non-monotonic and also to plateau,
which is scenario number three.
As I mentioned, this is a pretty frequent scenario
at a certain dose level, the efficacy, that’s not,
we don’t see any big increases in the efficacy.
In terms of toxicity, again, different flat trends
on the steeper dose toxicities scenario.
In terms of beta stimulation, toxicity was stimulated
from a Bernoulli distribution, persistence was simulated
from a beta-binomial and for variance,
the variance was assumed to be a constant,
but we then read the values of small and large,
and to give you an idea of what means
a large variance at 1%, that is equivalent to about 20%
deviation from the mean T-cell persistence
toxicity and efficacy are modeled independently.
So some results, the paper on had the has several scenarios,
but just to illustrate, this is for a total sample size
of 25 patients both in stage one and in stage two
and the design was compared to MTPI,
which is the Modified Toxicity Probability Interval.
And we wanted to compare and this is one of the operating
correctors, 6% patient allocation.
How does the design allocate patients based on toxicity and efficacy?

So in this case, that toxicity we see is toxicity three,

we have five, dose levels, the three dose levels have toxicities lower than 15%.

Dose number four has a toxicity between 15 and 40%,

dose number five pretty much is at the maximum DLT threshold,

'cause remember that we had two hypothesis, 15% acceptable toxicity and 40%, so dose one, two, three are considered acceptable.

Dose four is within the interval, 40% as shown in red is considered a toxic dose.

So this is the same toxicity for different efficacy scenarios increasing,

this is non-monotonic this umbrella plateau,

this umbrella trend,

this efficacy three is the plateau trend and the efficacy four is constant efficacy across all doses.

So what we noticed that the design does a good job allocating most of the patients to a dose that is considered safe and also has the optimal efficacy.

So this would be dose number three in panel A, again, dose number three in panel B and similar for C
and so ultimately we allocate most of the patients to this optimal level.

Now let me, I would like to show you an illustration of how can we use this design, its implementation in the R package and in the Shiny app, because the package has two purposes. One, is to run simulation, to observe to quantify the operating correctly sticks for different dose, toxicity dose efficacy scenarios and another benefit is that you can implement it to actually allocate, to run the trial, to allocate the next patient to the optimal dose. So simulation and implementation and the scenario that I will discuss next is inspired from a real study when I was at the Cancer Center at Columbia and this was a phase-one trial evaluating modified autologous T-cells genetically modified T-cells in patients where the recurrent solid tumors. So if you think that all these designs are usually theoretical or just great statistical proposals, actually this one had an implementation and had a real setting.
So the initial design that was proposed was of course, an role-based design derivation, this was a two-by-two with up to five dose levels, and I wanna bring your attention to the dose levels.

So in immunotherapy, especially in this T-cell therapies, the dose levels are not quantities of dose age of the medication are not milligrams, but they are actually the number of T-cells that are being infused back into the body. So in this case the dose levels vary from 50 to 10

And we wanted to explore what is the optimal dose for this regimen.

So, this is a snapshot of the Shiny app, we redesigned the trial to incorporate both toxicity and continuous efficacy and in this case continue, this T-cell persistence was a reasonable biomarker, we looked at five dose levels, we had in simulations, you have to specify what are the toxicity to toxicity rates and what are the T-cell persistence levels. The true toxicity rates varied from five to 40%, the T-cell persistence varied from 15 to 40%.
We didn’t see that we’re going to see more than 40% persistence followup and we looked at the total sample size of 30 patients for the trial, this was feasible and practical. So the setup it’s very simple, you just put the number of dose levels, you specify the toxicities, you specify the mean efficacy, the variance for the efficacy, we chose 1%, this can take different values, then of course, this is a dialogue that you have with your clinical investigator, hopefully with data supported from previous studies and what is considered to be to very these parameters. Then for stage one, you have to specify the two hypothesis, acceptable and unacceptable DLT. For this one, we set it at 15 and 40%, the likelihood ratio was set at two because of the sample size of 30 with k equals to two is reasonable and three cohorts, three patients per cohort, meaning each of the five dose levels we have three patients allocated each. Total sample size of 30 on the stopping rule, stopping rule meaning if none of the doses are considered acceptable in stage one, we’re going to allocate up to nine patients...
at the first dose to further establish toxicity, and this can be changed to six or other number.

So these are, how did the scenario looks?

This is the graphs actually generated by the app toxicity and efficacy as a function of dose level,

and now I’d like to ask you, ask for your participation,

looking at these two scenarios,

what do you think would be an optimal dose level,

the recommended to be studied in phase-two or later?

Okay, maybe we need some hint,

so we want an acceptable dose.

Three.

Dose number three, dose number three,

because dose number three is way outside the acceptability range and also dose number three tends to have a good efficacy after dose number three.

we don’t see any improvement in terms of efficacy.

Dose number four is between the 15 and 40%

then dose number five was probably toxic.

So, dose number three is the optimal dose

and what we would like to see,

is most patients being allocated at this level.

So in simulations, this is simulations for stage one,
where based on observed the DLTs, we calculate the likelihood ratio and mark the doses
as being acceptable or unacceptable. So in this case, based on the simulations, we see dose one,
two, three and four are considered acceptably safe and they will be carried forward to stage
dose number two, to be considered for that different organization, dose number five will be discarded
and will not be used in stage two. And why is that? Because the likelihood ratio is less than 0.05.
Now these are the simulations for a stage number two, so in the first part, we had five dose levels,
three patients each, so that’s a total of 15 patients starting with patient number 16, we moved
to stage two and we do this adaptive randomization until we reach the maximum sample size of 30.
So the app actually gives you simulations and allocations for all the patients from 16 to 30 dose assignments
and efficacy outcome and this gives you a graph of the estimated efficacy and the medians
and inter quartile ranges.
So we repeated this a hundred times, you can repeat it more.

In terms of allocation, based on the setting, the parameters, the hypothesis, the k threshold, the toxicity and efficacy scenarios, dose three tends to be favored in terms of allocation, where the highest media allocation, 26.7 and going all the way to 33.3 for the 75th percentile.

In terms of efficacy estimation, dose number three or if you remember when we specify the true mean, the median estimated efficacy was 40, the median estimated efficacy in this case is 39.75, the 75 percentile goes all the way to 45, but of course that will be improved with, as the sample size increases.

So in conclusion, what does iAdapt proposals? It’s an option, it’s a viable option for incorporating toxicity and efficacy outcomes, especially for immunotherapy trials.

The novelty is in the designing allows to model toxicity, both of binary and also as quasi-continuous measures and this was actually updated this year in the package.

To use the several types of toxicities and several grades, that continuous efficacy outcome
is very relevant for immunotherapies and I really showed the example from the trial with T-cell persistence, it is a relevant biomarker, but you can use for example absolute counts, you can use a full changes, so design is flexible in incorporating other continuous outcomes. As far as I know, this is the only design at this point that uses continuous efficacy outcomes. So in terms of operating characteristics, the design as well and allocating, skewing the allocation to optimal doses, estimation is marginally improved depends of course on the level of various and the sample size. and if anybody wants to try, you can use the R package, you can use the Shiny app to simulate to look at the behavior of different scenarios to put that in trial and of course, to use it to run the trial. I'd like to thank two former students, Alyssa and Laura, that helped in uploading the R package and Laura has created the Shiny app. And I do have some references in case you're interested, but I can also share the slides later on. So I think that is it and I wanted to allow some time
for questions and comments and feedback from you. Thank you so much.
Thank you very much professor.
Thank you very much professor.
Thank you very much professor.
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how about certain joint distribution, is there anything we can do in order to like, 'cause that actually affect the simulation much?

So the current model does not account for the joint distribution, it models toxicity and efficacy separately. But as a next step we can look under to try to model that dependency between toxicity and efficacy, especially for this novel agents, we’ve seen that most of the times toxicity as is related to efficacy, a stronger ethical, a stronger response. does come with some higher levels of toxicity, but the current model does not look, they twist them independent.

So do we, so is there, like penalty for example, like say when there isn’t such a good, like a compromise between like minimizing toxicity while maximizing efficacy, right? So in the demonstration we have a compromise, which is dose level number three, if there’s, for example, if there is like a conflict between dose two and we can, like we don’t really have, like the obvious optimal, like say optimized solution.
Do we constantly there, like, for example, penalties or do we always pay for like toxicity, like say minimizing toxicity over like, say maximizing efficacy? And then think it’s always, I think so for example, in that situation, so you could actually take both dose three and dose number four, you could consider both to be considered for future trials. So, it’s not the definite that the dose selected, that you’re always gonna reach a minimum of toxicity and maximum efficacy, but you can look at different options with as long as toxicity is acceptable, you can consider maybe in phase-two to look at randomized trial, look at dose level combo one and dose levels combo-two based on efficacy and we’ve actually seen this in a lot of trials, the immune check point inhibitors review that I talked, that it’s now in progress, we looked at phase-one and two and the rate of success and the design that are being used and the doses that are being carried forward from phase-one, and surprisingly only 30%, in 30% of phase-two trials the MTD was used from phase-one, the rest either they use a lower dose
or they use a higher dose, but not the MTD. So absolutely we can have like a range, because if you think about it, we have a limited sample size, right? We need more information for efficacy, so to complete the clear, the winner based on efficacy might not be sufficient at this level.

Okay, great, thank you. So the answer is before phase-three and as long as it’s below the MTD, the efficacy is important, is more important to prove, like, say to move on to next stage. Thank you.

Okay, great, thank you. Yes.

Just connection.

Sorry, we’re still having a little weird audio.

Hello, we have a question there.

Hold on.

Hi professor, I know we probably mentioned.

this already, but I probably didn’t typed that, can you repeat, maybe repeat what it was, 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
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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.
I know this might be a tough topic to digest for students with early finding it’s not such a... It’s a (chuckles) framework on its own. So maybe not that everybody’s familiar with the whole terminology on the landscape. (v Student)During that stimulation, you specifically...<v>

So the toxicity was stimulated from a continuity distributions, is there any specific reason why you choose these distribution versus there’s, and if we similarly from a different distribution, well, how about different conclusion like, well there would be any dependence between efficacy and toxicity. Yes, so that’s, and so in this case,<v> the results that I showed you were for toxicity, for binary toxicity, yes or no. So in a cohort of three patients for each patient, you observed either a zero or a one response, given the binary structure, it makes sense to use this Bernoulli right distribution and that sums up to binomial zero or one. In terms of dependency is with what Dr. Cheng was mentioning, we did not specify any correlation between toxicity and efficacy.
and did not look at the joint distribution between the two,
we modeled them separate and probably that would be a good point moving forward.
What’s difficult is how do we, what would be interesting
is looking at different levels of correlation and see how in this joint distribution,
how the results with change, if we would capture that.
Okay, so any more questions?
Okay, so thank you Dr. Chuizan,
for your wonderful presentation.
Thank you.</v>
Thank you, and if you have any questions.</v>
please email me anytime.
(chuckles)
And I’m sorry that you (indistinct).
Okay, I’ll see you shortly, bye.
Thank you.</v>