Good morning, everyone. Thank you so much for coming. It’s really a true pleasure today to have with us one of the gents of acute myeloid leukemia and myeloid neoplasms in general. So Doctor Marina Konopoliva is a professor in the Department of Oncology and Molecular Pharmacology and the Merriam Faculty Scholar in Cancer Research at the Albert Einstein College of Medicine. After spending many,
many years in the Andy Anderson,

where she has really made

fantastic contributions,

including very important drugs

that have been approved both

in acute myeloid leukemia and

plastic denritic myelo neoplasm.

So she received her Doctor of Medicine

from the First Pavlov Medicine

Institute in Saint Pittsburgh in Russia,

and then got a PhD in experimental

hematology from the Federal Institute

of Hematology and Blood Transfusion.

So Doctor Konopliva’s research

has focused on patients with

hematologic malignancies both
NOTE Confidence: 0.97178832
00:01:02.255 --> 00:01:04.079 including acute myeloid leukemia,
NOTE Confidence: 0.97178832
00:01:04.080 --> 00:01:05.475 acute lymphoblastic leukemia
NOTE Confidence: 0.97178832
00:01:05.475 --> 00:01:08.274 as well as high risk MD’s.
NOTE Confidence: 0.97178832
00:01:08.274 --> 00:01:09.696 And her research,
NOTE Confidence: 0.97178832
00:01:09.696 --> 00:01:11.118 as I mentioned,
NOTE Confidence: 0.97178832
00:01:11.120 --> 00:01:13.466 have led to important not only
NOTE Confidence: 0.97178832
00:01:13.466 --> 00:01:14.639 science and advancing,
NOTE Confidence: 0.97178832
00:01:14.640 --> 00:01:17.012 but also therapeutic translation,
NOTE Confidence: 0.97178832
00:01:17.012 --> 00:01:18.198 especially venetoclax,
NOTE Confidence: 0.97178832
00:01:18.200 --> 00:01:20.665 which really has changed the landscape
NOTE Confidence: 0.97178832
00:01:20.665 --> 00:01:25.306 of how we treat patients with the AM, LCLL,
NOTE Confidence: 0.97178832
00:01:25.306 --> 00:01:28.620 potentially MD’s and other conditions.
NOTE Confidence: 0.97178832
00:01:28.620 --> 00:01:30.696 And on a personal level,
NOTE Confidence: 0.97178832
00:01:30.696 --> 00:01:32.436 I think Doctor Konopleva is very known
NOTE Confidence: 0.97178832
00:01:32.436 --> 00:01:34.236 in the field to be a fantastic mentor.
NOTE Confidence: 0.97178832
She has mentored some of the most productive researchers in the field as well as being a very nice and very good person to interact with. So I encourage as many of you to talk to her if you can today. Thank you so much for coming.

Thank you, Amir, for this very kind introduction. I'm happy to be here. This is my first time at Yale and I'm looking forward for the day and meeting a lot of you. And so today I wanted to take you through our story on Biso 2.
round for both human solid malignancies, but I think targeting cell death is probably important for including for the solid tumors as well. And I'll show you some of the kind of ways we think about that as well. So these are my disclosures and as you all know, the resistance to cell death is one of the hallmarks of cancer and it's largely governed by the B22 family proteins which are listed here. It's quite complicated. I'll show you later how the system works, but essentially there's over expression of different B22 family
members depending on the tumor type.

For example in myeloid malignancies and we have mainly B so 2IN T ALL.

We also have B cell XL and B so two

And I think in SO2 must B cell XL is a primary anti apoptotic molecule.

The way the system works is by dimerization of anti apoptotic with a

proapoptotic family members and there are quite a few of those as well So bags.

I will talk to you several times in my talk.

So this is what we call execution of cell death protein.

So essentially kills the cells by making pores in the mitochondria membrane.
and inducing cytochrome C release. And then there are a lot of this will be A share only proteins which essentially bind B, so two or others and inhibit their function because it works through demoralization. You can actually inhibit the function of B so 2 by inhibiting the protein protein interactions between for example B so two and some of this protest proteins and as a result you’ll have a release of this propagatoric members and killing of the cell deaths. So this was pioneered in the first attempt. This was a paper back in 2005. At the time the company was called Abbott.
and they designed the first protein inhibitor which was called Abt 737. So this was a work from Steven, Fasig, Sol Rosenberg and others that effectively inhibited the BCL two. So the structure here is actually the structure of BCL XL. So they used the NMR based technology to engineer this molecule and green protein. Here is one of this proteins called back. It’s not even here but it’s one of the BHA. On your proteins there’s some critical rates reduced how it binds to B cell XL and this is the actual molecule which you can see it sits.
into that pocket and this mimics the B back interaction with B cell XL. In this matter there’s another structure, this is pretty large molecule about 960 KD but this was the 1st and I think the most successful protein inhibitor interaction. I think the only other class that I’m aware of MDM 2P53 inhibitors but they still not approved due to toxicities. Now this molecule was A2 molecule and it’s analogue called Navidoclox did go into clinical trials, but because it blocked both BCL XL and BCL two,
it encountered some toxicities in the form of thrombocytopenia because BCL XL is important for plated production. But I'll get back to you in the end. I think BCL XL targeting is very important and there are other ways of safely inhibit BCL XL. So Nabilox is still not approved. And so moving forward in 2013, the same company now it’s called Abbi engineered the original molecule and they got rid of BCL XL interaction. So apparently this aspartate one O 3 is a critical residue which is different between BCL two and BCL XL. And so they engineered the new
molecule that had now very specific properties. So it only bound BCL two was about 10 times more important than original nebidoclax and it did not inhibit BCL XL. And this is what we now know as the neto clocks, the drug that is approved for several types of hematologic malignancies. And of course it’s paid playlists because it did not inhibit B cell XL. We initially used the antisense, So I said I work on B. So too when I came to us, that was my first project at the time. We initially used the antisense,
but antisense didn’t make it in clinic. They were not effective enough, not specific enough. And then when the original camp compound came out, we developed the story on AML and BCO 2 with ABT 737, which were published in 2006. And then when the new compound came out, because Nevada clocks never made it to AML trials, AML patients as you know have all low platelets to start with. So it was kind of impossible at the time to transition into AML trials.
When the newcomer came out, we teamed up with a Tony Litais lab at Denif Harbor and we worked for a year between two of our labs and published a cancer discovery paper in 2014 showing that the Nanoclax is highly effective in acute myeloid leukemia pre clinical studies. So, these are just mRNA level for B, so two amongst different types of leukemia and the red line represents...
to the normal uninvolved bone marrow.

This was from a Hyperlux MLL collection.

So you can see that majority of

AML this is log scale have upper

related mRNA for BC2.

There’s some examples here,

For example this inversion 3 AML do not,

but majority have high levels of BC two.

We also show that it’s expressed

on leukemia stem cells and then

we show that if you target BC two,

you eliminate AML blasts and AML

stem cells to some extent.

And also the compound had efficacy in vivo,

although by itself it,
it was not curative and it wasn’t curative in patients either. So this work in conjunction with the CLL data that Amar mentioned. So that time the Netflix was already in CLL trials and was very effective. It caused tumorlysis and actually they had some deaths because of tumorlysis. So it’s CLL is super dependent on B, so true. So it’s like the primary B, so two dependent disease, but we already knew the dose, we knew the safety profile of this molecules was fairly safe besides this tumuliser syndrome.
So it was sort of sufficient based on this work to take venetoclax into AML relapse refractory study. This study was conducted between different institutions and was published in cancer discovery back in 2016. Initially we projected that we're going to treat 50ML patients and we were hoping for response rate around 40% to 50% based on our preclinical work. And I have to say that this did not pan out. So we learned that AML is way too complicated and probably our preclinical models do not really faithfully recapitulate the response in patients. So the response rate,
objective response rate in the trial was only 19% with the CRCRI rates, but about 50% of patients did have blast reductions as shown here on this waterfall plot. And then there were some subsets of patients who tend to be more sensitive to that. For example, patients who had IDH 1-2 mutations, they generally had response and the response among those was about 32%. So that was encouraging. And in fact, we enriched the study for the IDH 1-2 mutated patients because at
the same time the paper came out from Stanford showing that this subset of AML is highly dependent and that turns to be true. Till now this patients respond very well to nine, 8:00 to 9:00, sorry, but essentially that was encouraging, but it was clearly not enough for to get this drug approved as a single agent in the salvage setting. And of course for me as a researcher that was disappointment because I thought this was like the best drug I ever had in the lab and still it’s not you know curing people. The duration of responses was also
pretty sure about three to six months and all patients progressed after that. So fortunately the story did not stop at this point as you know. And so why we think that AML in AML target and B, so two alone is not sufficient? Well, first of all, because there’s a redundancy and expression of BCL two family proteins. So if you just look at this western blood, this is from Andrew Ways publication and BCL two is almost ubiquitously expressed at high levels.
BCL XL is usually not expressed or low expressed. But I'll tell you which subsets do have BCL XL. And then there's MCL one which is mildly specific sort of BCL two family member, it's ubiquitously expressed as well. So you can imagine that if you target only be so true, you leave some other members untouched and therefore cells probably quickly adapt to the this effect and they rewire and they become resistant. So how can you get around that? The next thing is that any type of chemotherapy can actually...
00:11:29.156 --> 00:11:31.754 in the setting of wild type B53
00:11:31.754 --> 00:11:33.924 can induce expression of this
00:11:33.924 --> 00:11:35.660 propriotoic family members that
00:11:35.729 --> 00:11:38.165 I mentioned before what we call BHA
00:11:38.165 --> 00:11:40.240 only proteins and this PH3 only
00:11:40.240 --> 00:11:43.095 proteins can in fact inhibit MCO one.
00:11:43.095 --> 00:11:45.720 So as you can envision,
00:11:45.720 --> 00:11:47.540 you can have synergy between
00:11:47.540 --> 00:11:49.828 venetoclax and pretty much any type
00:11:49.828 --> 00:11:51.833 of chemotherapy that would induce
00:11:51.833 --> 00:11:53.600 this response and then you inhibit B.
00:11:53.600 --> 00:11:55.610 So two, so you sensitize the
00:11:55.610 --> 00:11:57.792 cells and then there’s bags back
00:11:57.792 --> 00:11:59.717 interaction and the cell death.
00:11:59.720 --> 00:12:02.168 So practically speaking this went into
00:12:02.168 --> 00:12:04.291
00:12:02.168 --> 00:12:04.765 development in all the AML patients
NOTE Confidence: 0.752763328148148
00:12:04.765 --> 00:12:07.005 unfit for chemotherapy because for
NOTE Confidence: 0.752763328148148
00:12:07.005 --> 00:12:09.629 younger patients we had 7 + 3 which
NOTE Confidence: 0.752763328148148
00:12:09.629 --> 00:12:11.212 we still have and they were doing
NOTE Confidence: 0.752763328148148
00:12:11.212 --> 00:12:12.277 pretty well with the transplant.
NOTE Confidence: 0.752763328148148
00:12:12.280 --> 00:12:14.317 But for all the patients there was
NOTE Confidence: 0.752763328148148
00:12:14.317 --> 00:12:16.198 really like no standard of care
NOTE Confidence: 0.752763328148148
00:12:16.200 --> 00:12:18.200 low dosa turbine or hypermethylene
NOTE Confidence: 0.752763328148148
00:12:18.200 --> 00:12:22.644 So I have to say that based on the
NOTE Confidence: 0.752763328148148
00:12:22.644 --> 00:12:24.879 clinical need more than the signs,
NOTE Confidence: 0.752763328148148
00:12:24.880 --> 00:12:26.945 the combination trials were with
NOTE Confidence: 0.752763328148148
00:12:26.945 --> 00:12:29.010 hypermethylene agents and low dose
NOTE Confidence: 0.752763328148148
00:12:29.076 --> 00:12:31.332 Iturbin and all done fit there
NOTE Confidence: 0.752763328148148
00:12:31.332 --> 00:12:32.836 for chemotherapy AML patients.
NOTE Confidence: 0.752763328148148
00:12:32.840 --> 00:12:35.080 And this were the results of the
00:12:35.080 --> 00:12:37.380 initial Phase 1B study when the
00:12:37.380 --> 00:12:39.455 Vanetta glass was combined either
00:12:39.455 --> 00:12:42.396 with azacitidine or with a decitabine,
00:12:42.400 --> 00:12:44.365 hypermethylene agents or even with
00:12:44.365 --> 00:12:46.767 low dose Iturbin which by itself
00:12:46.767 --> 00:12:48.957 has very little activity in AML.
00:12:48.960 --> 00:12:51.291 And you can see here that well you know
00:12:51.291 --> 00:12:53.438 this was a newly diagnosed patients.
00:12:53.440 --> 00:12:55.336 So was very rapidly was transitioned
00:12:55.336 --> 00:13:00.979 the original trial that we used
00:13:00.979 --> 00:13:02.424 where we used phonetically where
00:13:02.424 --> 00:13:04.268 it was relapsed refractory setting.
00:13:04.268 --> 00:13:07.426 But you can see that you know majority
00:13:07.426 --> 00:13:10.041
00:13:07.426 --> 00:13:09.706 of patients in fact responded and
NOTE Confidence: 0.752763328148148
00:13:09.706 --> 00:13:12.039 they did achieve like true CRS.
NOTE Confidence: 0.752763328148148
00:13:12.040 --> 00:13:13.612 There was some of those escalation
NOTE Confidence: 0.752763328148148
00:13:13.612 --> 00:13:14.398 findings as well,
NOTE Confidence: 0.752763328148148
00:13:14.400 --> 00:13:16.465 but eventually 400 milligram ended
NOTE Confidence: 0.752763328148148
00:13:16.465 --> 00:13:19.120 up the right dose for the HMA
NOTE Confidence: 0.752763328148148
00:13:19.120 --> 00:13:20.680 and 600 for the low dose,
NOTE Confidence: 0.752763328148148
NOTE Confidence: 0.752763328148148
00:13:22.099 --> 00:13:23.520 So the responses,
NOTE Confidence: 0.752763328148148
00:13:23.520 --> 00:13:25.482 the responses tend to be durable
NOTE Confidence: 0.752763328148148
00:13:25.482 --> 00:13:27.880 and there was very little toxicity.
NOTE Confidence: 0.752763328148148
00:13:27.880 --> 00:13:29.812 So suddenly the all the patients
NOTE Confidence: 0.752763328148148
00:13:29.812 --> 00:13:31.821 which for which we didn’t really
NOTE Confidence: 0.752763328148148
00:13:31.821 --> 00:13:33.789 have QS before in one month
NOTE Confidence: 0.752763328148148
00:13:33.789 --> 00:13:35.839 that we’re going into remission,
NOTE Confidence: 0.752763328148148
00:13:35.840 --> 00:13:37.320 the infections and mouse suppression
was still the main toxicity.
But other than that we didn’t see
like much effects on the kidney,
like much effects on the kidney,
liver or anything which was to me always
so ubiquitously expressed.
so two is so ubiquitously expressed.
So who could imagine that
targeting B so two is so safe.
I think before we go into clinic,
we can never really predict what happens.
And then eventually this resulted
in the randomized phase three study
called VLA study where VENESA,
what we call venetocide was randomized
to azacide and placebo control.
It was 2 to 1 randomization and
this was for all the patients with
AML ineligible for chemotherapy.
The median age was close to 70
years old and you can see that
there’s far as response rate,
majority of the patients achieved
response which was in the range of 60 to 70%.
There was lower in PPG mutated
AML which we learned later is a
prom for this approach.
But overall there was high response rate,
but most important there was survival
advantage compared with ASA with medium
overall survival of about 14 months and
compared to nine months with ASA cited in.

So this LED in 2018 to the accelerated approval of the Naglo X and AML and subsequently to the full approval in combination with the chemotherapy low Dosa turbine is also approved. But even though they missed the primary endpoint, the overall survival was still better. But I think it’s very rarely used in United States and this survival is shorter only about nine months. So this is like what Amar said is considered to be breakthrough. But you know if you look at the curves,
you can say that is this really like

a breakthrough because majority of

the patients are still you know,

Initially it seemed to be like

So now the curve dropped down to about

20 to 25% with about four years of follow up.

So it still stands,

but clearly you know it was not a

curative approach and that kind of

prompted our lab and many other groups

going back to the kind of drawing

board and trying to understand how

we can improve on that and what are

mechanisms of resistance and how
we can combine with other agents.

So in the rest of my talk,

I will show you like several like examples from our lab how we kind of developed the new agents for the combination. Some of them are in trial, some of them are hopefully getting to approval soon and this is sort of a summary how we can think of potential combinations and resistance mechanisms. This figure was done by one of our fellows and again going back to how the drugs work, right.

So again you have BSO 2, you have it pre complex with BHA
only protein which allows you to block this interaction.
And this is a drug venetoclax, it's called BHA mimetic because it mimics PHA only proteins.
So it binds here, it displaces this BHA only and then this products have to activate backs and back.
So again backs and back are very critical because without that there's no cell death and they have to go into the mitochondrial membrane and they induce sacrum C release.
So one thing that I already mentioned that there's a redundancy, so if you have a regulation of
this other B SU-2 family members, you can get resistance right? Because they can even though you do have displacement, what happens is that this BHA only protein instead of going to the bags it will go and bind this other protein members. So how can you get this app regulation? Of course it may have been before pre-existing. For example in monostatic AML there’s app regulation of MCL one because of the lineage dependency on MCL one. But then there are a lot of mutations and this
mutations we call them signalling mutations
which we now can up regulate both MCO one,
both MCO one, BCL XL and BCL 12A1 and I'll
show you some examples of those.
So this will lead to resistance
And of course you might want to
think of targeting those mutations.
So the other major mechanism of
resistance is the P53 loss and I
already mentioned that PhD is critical
for BHA only proteins induction.
But on top of that P53
transcriptionally controls Bax,
so BAX levels are lower and P
lost AML and there's also
other mechanism of resistance.
So this remains unmet need in the field of AML and MD’s.
And then there are some other mechanisms.
For example, Yanis offenders group has published the mitochondria resistance to the
venetoclax through our regulation of some of this crystal proteins such as Glib B and also mitophagia kind of selection of the healthy mitochondria.
And there’s some effort as far as drug discovery in that field as well going back to the patients.
So what did we see from these mechanisms?
What did we see as far as the
resistance development? And before that I have to say that we also developed in the lab habanero clocks, So we decided to take some of unbiased approach and we generated 4 vein resistance cell lines. They’re available for anyone who wants to use them by prolonged exposure to the drug in the tissue culture lab and took only about 3 months to generate the cells. So about the same time as our patients to progress. And then we did all kind of metabolomic and genomic proteomic profiling and
00:19:16.600 --> 00:19:17.884 epigenetic profiling as well.

00:19:17.884 --> 00:19:20.402 So one pathway that came out kind of screaming at us, which was not a new pathway, but it was something that we already knew from before.

00:19:20.402 --> 00:19:22.718 MEP kinase pathways.

00:19:22.720 --> 00:19:24.820 It was upregulated on the RNA level.

00:19:24.820 --> 00:19:25.720 And then we confirmed that in the by immuno blotting analysis, you can see application of some of this MEP kinase pathway proteins.

00:19:25.720 --> 00:19:27.400 MEP kinase can stabilize MCL one proteins.

00:19:27.400 --> 00:19:30.320 So it’s not transcriptional but on the level of the protein and we did.
see that in all the three cell lines so one levels were up regulated as you would expect And then if you use the either so one inhibitors or knockout of so one you get tremendous synergy with venetoclax and the cells are dying off. So I’m not going to talk about so one inhibitors but suffice to say that they are not approved because of toxicity. So again like thinking why B so two so safe and so one is not safe so one. Tends to be very important for the heart muscles and so patients treated on the clinical trials with MC1 inhibitors,
00:20:21.560 --> 00:20:24.344 they have what we call Troponin leak and

00:20:24.344 --> 00:20:26.478 potentially you know cardiac toxicity.

00:20:26.480 --> 00:20:28.634 So that Hanford the whole like

00:20:28.634 --> 00:20:30.070 development of MC1 inhibitors

00:20:30.130 --> 00:20:32.500 and it’s not clear whether they

00:20:32.500 --> 00:20:34.080 actually have therapeutic windows.

00:20:34.080 --> 00:20:37.746 So, but in the lab, these are the

00:20:37.746 --> 00:20:39.594 great sensitizers to Vanadacolexa.

00:20:39.600 --> 00:20:41.696 So then we went back to patients and

00:20:41.696 --> 00:20:43.924 we know that in patients Ras mutations

00:20:43.924 --> 00:20:46.399 are fairly common in AML on their own.

00:20:46.400 --> 00:20:48.320 They don’t have prognostic significance,

00:20:48.320 --> 00:20:50.666 but they can arise at the

00:20:50.666 --> 00:20:51.839 time of progression.

00:20:51.840 --> 00:20:54.312 And so when we looked at the patients

NOTE Confidence: 0.810300709
treated on the HMA venetoclax

trials at the time of relapse,

they had like expansion of this Ras, K,

Ras and Ras clones also PTPN 11 clones,

which is not shown here fairly quickly within like 6 months or so.

This has single cell DNA sequencing data.

We also looked at the sort of patients by immunoblotting.

So we did show up regulation of MCL one and the approgation of MAP kinase pathway and this is on the histochemistry level.

At the time progression MCL one was up and BCL two was down regulated.

The problem of course that in
AML we don’t have Ras inhibitors.

We are really hoping that we can get them from the solid tumors.

But the companies have been so focused on the lung cancer and they have been reluctant to go into AML.

So we are still trying to convince them that Pan Ras inhibitor would be a great thing to have an AML and we actually have data with the in the lab that the combination is really striking, the papers submitted.

But right now we don’t have anything.

So we also did the engineer this in the lab.

So we put the NRAS G12D into AML.
cell line which was dox inducible.

We showed that the cells become resistant to another clocks.

But again the MCL one inhibitors work alone on combination.

We did the mouse study with MCL inhibitors and there was a reduction of the tumor growth,

but we don’t have MCL 1 inhibitors and we don’t have resin inhibits.

So we are like at a loss right now, but we’re working on that.

So this MEP kinase upregulation I think is one of the major kind of resistance when you use HMA Van. It’s not an issue when you use chemotherapy,
van, because Rascalone is very sensitive to the regular chemotherapy, which is kind of a relief. And this data we have sort of confirmed that this was a large analysis. I think the paper is under review from Viali, a study looking at different genomic subsets of patients who are and time to progressional this is rather survival. This was presented at by Hartman donor at the last ASH. And so they basically show that the classical kind of ELN classifications do not predict very well the
response or duration of response.

But when they did look at different genomic subsets, again P50 mutated AML did very poorly. So survival was only about 5 months here, same as you get with HMA.

But this intermediate cohort, it actually included patients with Ras mutations. So Ras mutation was confirmed to be a resistance factor for the HMA band and also another mutation signaling FFLIX free FFLIX free ITD mutation.

So this data are being sort of refined that I told you a little about the Ras story.

Now Flix 3 is another very common mutation, about 30% of patients have Flix 3 mutation.
Unfortunately we have drugs for those that are being approved. So of course like we jumped into that very early on and in fact we saw that even in the original phase one study where which showed up regulation of this or selection of the clones with mutations and people who relapse or wear primary fracture and very similar this like selection of the Flix 3 ITT clone with a therapy using the single cell tapestry sequencing and the sort of why Flix 3 the story is very similar to Ras. So here you have you know the
00:24:19.956 --> 00:24:21.920 same Ras map kindness pathway.
NOTE Confidence: 0.853982455454546
00:24:21.920 --> 00:24:24.728 You also have a prolation of some other
NOTE Confidence: 0.853982455454546
00:24:24.728 --> 00:24:27.376 ones that five PS3 kines AKT but eventually
NOTE Confidence: 0.853982455454546
00:24:27.376 --> 00:24:29.680 it all comes down to this MCL one.
NOTE Confidence: 0.853982455454546
00:24:29.680 --> 00:24:32.476 So MCL one phosphorylation is regulated
NOTE Confidence: 0.853982455454546
00:24:32.476 --> 00:24:36.142 by both MAP kinase and also there’s a
NOTE Confidence: 0.853982455454546
00:24:36.142 --> 00:24:37.810 stead pathway dependent phosphorylation.
NOTE Confidence: 0.853982455454546
00:24:37.810 --> 00:24:40.645 So when MCL one is phosphorylated it’s
NOTE Confidence: 0.853982455454546
00:24:40.645 --> 00:24:42.605 stable so the levels are increased
NOTE Confidence: 0.853982455454546
00:24:42.605 --> 00:24:44.573 and the product cannot be degraded
NOTE Confidence: 0.853982455454546
00:24:44.573 --> 00:24:46.638 otherwise it’s short lived protein.
NOTE Confidence: 0.853982455454546
00:24:46.640 --> 00:24:48.060 So essentially there’s also some
NOTE Confidence: 0.853982455454546
00:24:48.060 --> 00:24:49.196 B cell XL component,
NOTE Confidence: 0.853982455454546
00:24:49.200 --> 00:24:50.916 but I think it’s a minor,
NOTE Confidence: 0.853982455454546
00:24:50.920 --> 00:24:52.404 but the nice thing is all downstream
NOTE Confidence: 0.853982455454546
00:24:52.404 --> 00:24:53.280 or Flix 3 ITD.
So it’s OK if we’re here Flix 3 what happens with MCL one. So we used Quizactinib for that matter and we showed nice inhibition of the Flix 3 MCL. One did go down by wasn’t that huge up down regulation. But we also show that the protein called BEM was induced and BEM can is a prop of Tory BC on a protein that can inhibit MCL one. So the combination of these two makes cells sensitive to venetoclax. And this is BHA profiling essay which I have time to explain in detail by essentially you throw
the peptides on the cells and see
which dependence that they have.
But the point here is that if you
treat cells with Flix 3 inhibitors,
you have huge up regulation of B.
So two dependency to the peptide
or to the actual venetoclax drugs.
So you have synergy in vitro.
And in this model,
which there was like a subcutaneous model,
not a great model for AML,
but we subsequently publish also PDX models,
we show like essential cures
of the mice for that matter,
when we use the Quizad,
and Venetoclax combination.
So this did go into clinical development.

And for the trials another flixster inhibitor second generation.

And this paper is now published in JCO by MD Anderson Group and many other collaborators where there was combination of venetoclax and guilt for relapse refractory Flex 3 mutated AML.

And there was quite significant response rate in all patients or in those who failed prior Flex Tki’s alone.

And if they went for the transplant, the survival looks fairly good.
The data by Kathy Smith showed that the Flixtree clones were extinguished after this combination. I have to say that she did show that Ras clones were coming up in patients who progressed. So Ras is still a resistance mechanism even in that setting. But again, this was quite impressive sort of advance in the field of Flixtree mutated AML. Now of course we all know that treating patients is best at the time of diagnosis. So for all the patients we cannot use chemotherapy.
00:27:10.044 --> 00:27:11.999 pioneered what we call triplet.

00:27:12.000 --> 00:27:13.885 So triplet is essentially Azovan

00:27:13.885 --> 00:27:16.222 which is a backbone and then you

00:27:16.222 --> 00:27:18.140 add the third drug in this case

00:27:18.203 --> 00:27:19.998 is guilt written and this paper

00:27:19.998 --> 00:27:22.255 is also now accepted in JC or now

00:27:22.255 --> 00:27:23.915 this is single sounded trial.

00:27:23.920 --> 00:27:26.272 There’s a lot of discussion on Twitter

00:27:26.272 --> 00:27:28.600 whether it’s like you know true or not,

00:27:28.600 --> 00:27:31.274 but at least you know data from

00:27:31.274 --> 00:27:33.719 Indiannis and look very impressive.

00:27:33.720 --> 00:27:35.800 Now when you see 100% response rate,

00:27:35.800 --> 00:27:37.400 you always kind of pause,

00:27:37.400 --> 00:27:40.284 but that’s what they reported and 30

00:27:40.284 --> 00:27:43.004 newly diagnosed patients with AML and
They estimated survival at two years was 70%. So this is like way better than what we had before, but they had to like reduce a lot of duration of the drugs and work out the schedule because the combination is mild suppressive. So the major like heme toxicity of venetoclax is mild suppression. So Neutropenias because Mallo itself express B so too. And so when you use the vanadium clocks in combinations, you have to cut back and that’s continued discussions with FDA because the approved scale is 28.
days of vanadium clock.

So there’s a randomized study right now ongoing which hopefully will kind of solidify this question run by Stella’s and AbbVie where the same combination is being used in the frontline all the AML settings. So we’ll see how that goes, but again what do we do about Ras.

We’re working with Everest Gavasitis at Einstein and he developed the RAF inhibitor. So kind of downstream of Ras that inhibit is allosteric RAF inhibitor that he is about to publish in solid tumors.
But we show that P in cell lines with K or N Ras mutation is highly effective drug using inhibition of the pathway and there's some additive effects with venetoclax. So we kind of continue working on that. So hopefully we'll get either Ras inhibitors or RAF inhibitors. We did test the MECH inhibitors. We went all the way into clinic, but MECH inhibitors caused a lot of GI talks and so the trial was unsuccessful. So it was stopped for lack of efficacy and high toxicity. So we can't really use the Mac
inhibits unfortunately in this combination.

So work to be continued on this topic.

So there are a lot of other combinations with banana glass that have been sort of published.

This is just some nice summary that was presented at last EHA and the combination with IDH inhibitors that are now in clinical trials and both in AML and MDSI have to say there’s many inhibited combination which looks super exciting.

Of course, I’m still 1 went to to trials, but it’s struggling.

There was McGraw mop combination
which we pioneered, but right now McGraw mop is all the trials have stopped. So I’m not going to talk to you about that today and but I want to show some data with the immune approaches in this case is antibody drug conjugate. So kind of a little bit different story with venetoclax. So, so we used the, we looked at CD 123 because CD 123 is a subunit of all three receptor alpha and it’s ubiquitously expressed in AML. Also this other level of my BPDCN and in some ALR as well, it’s expressed in stem cells based
on Craig Jordan’s work and it’s sort of the only antigen right now that we kind of trying to target as far as immune therapy and EMLMDS. There are other efforts but none of them have been successful yet. So we’ve been working with this company Immunogen that developed the antibody drug Conugate. So they have the antibody gain C123 that’s through the linker is bound to the alculator that produces the single strand DNA damage. So obviously it’s internalized and you know kills the cells for
the DNA damage kind of chemotherapy but in a targeted fashion. So it had the good single agent activity and BPDC and then EMO the company has filed approval for BPDC and patients a second line. So hopefully we get this drug approved pretty soon. And so we of course asked the question, can we combine the two because this is like you know the immune therapy that seems to be working. So we’ve done quite a bit of preclinical work. It’s not published yet, but we show that the compound is fairly
NOTE Confidence: 0.902856236363636

00:31:45.240 --> 00:31:47.478 specific. So these are AML cells.
NOTE Confidence: 0.902856236363636

00:31:47.480 --> 00:31:49.760 This in red is CD123 expression.
NOTE Confidence: 0.902856236363636

00:31:49.760 --> 00:31:50.448 So again,
NOTE Confidence: 0.902856236363636

00:31:50.448 --> 00:31:52.856 majority of cells do express it and
NOTE Confidence: 0.902856236363636

00:31:52.856 --> 00:31:54.960 they’re being killed by this drug,
NOTE Confidence: 0.902856236363636

00:31:54.960 --> 00:31:57.599 but then the cells that don’t express
NOTE Confidence: 0.902856236363636

00:31:57.600 --> 00:32:00.000 there’s no killing and KG one is resistant.
NOTE Confidence: 0.902856236363636

00:32:00.000 --> 00:32:01.640 We’re not quite sure why,
NOTE Confidence: 0.902856236363636

00:32:01.640 --> 00:32:04.160 but it seems to be specific.
NOTE Confidence: 0.902856236363636

00:32:04.160 --> 00:32:06.068 And then we ran the combinations
NOTE Confidence: 0.902856236363636

00:32:06.068 --> 00:32:07.717 both with another clogs and
NOTE Confidence: 0.902856236363636

00:32:07.717 --> 00:32:09.307 azacitidine and the triplet because
NOTE Confidence: 0.902856236363636

00:32:09.307 --> 00:32:11.633 now we’re in the triplet era, right?
NOTE Confidence: 0.902856236363636

00:32:11.633 --> 00:32:13.198 And you can see here.
NOTE Confidence: 0.902856236363636

00:32:13.200 --> 00:32:14.676 So these are different cell lines.
NOTE Confidence: 0.902856236363636
I have to say that ITD cells have high expression of C123, which is why we selected those for the combination trials. But especially with the triplet, there's quite a bit of synergy.

What about PPG mutant AML, so these are wild type cells, so they're sensitive and they mutant or loss, PPG loss, we see less activity. There's still some induction of cell does, but it's actually quite resistant to both of the compounds. We're not quite sure how that is affected. So for some reason the cells had very high expression of MSL.
One, we’re still working on to understand that because we did see induction of DNA damage in both knock down cells and the wild cap cells and there’s a part cleavage but it’s less killing and that is also reflected in the trial. The PhD media patients didn’t do as well as you can imagine. The drug abolishes the S phase. So this is like IMGN alone and the different concentrations and then when you combine with the Vanasa you essentially you kill off the S phase cells so you don’t have anything left. You do get activation of gamma H3X.
as dna damage and Cliff cast space.

So then we try to understand the mechanism, how that works.

And so one thing is we know that inducing the single cell DNA strand breaks. So we showed the phosphor P53UP regulation which was the same with or without venetoclax. But then we saw that the drug inducing the DNA repair pathway phosphor check one it seemed to be less with venetoclax.

So we are, it’s kind of off story, but we are trying to understand if BCL 2 inhibition can actually be
involved in the control of DNA damage, which is hard to understand because it’s cytosolic and this is DNA. But we are kind of working through the story, still trying to figure out all the parts of the DNA pathway. But it has some like clinical, preclinical implications because if you use IMGN first followed by the nether class, you have very striking synergy. This BLISS index is 18. If you do the reverse then there’s very little synergy now in the clinic it’s given concomitantly.
So I think it’s fine but and nobody’s interested in understanding the kinetics. But I think the biologically this is interesting phenomenon and perhaps something to do with DNA damage repair that we’re working on. We also showed that the IMGN primes towards be so to inhibition. So I didn’t I have a lot of like mouse data which I didn’t show you, but the clinical trial has been reported at ASH and the paper is also now accepted in JCO. So this is a triplet. So again the drug is now called Pivacomab P VAC.
We abbreviate that it was used with Azowan in newly diagnosed AML.

All the patients, you know majority were unfit, but there were some fit patients as well. So it was fairly safe.

So again the drug has some toxicities, but generally speaking it was well tolerated.

And then the response rates where I would say similar to the ACE event, what was impressive was MRD negativity rate. So the depths of response was you get about 40% with ACE event it was about 76% of 79.
Now we don’t know yet if that translates into survival, which will be a critical question. So now Immunogen is bought by ABB vie. So we’re hoping that this will continue and to randomized phase three study and maybe we’ll have that triplet in a few years fully characterized that. But if you look at this like 3 subsets that I showed you before, so again, that respond well to to azavan, they did really well. This response rates in PVC mutant, there was about 20% full CR rate, but 50% overall response rate.
So maybe there's kind of, you know some signal again with PVC mutation, we are kind of really at loss. So that you know, but again this will be developed hopefully further and we'll see a few years from now where that lens now P 53. All the drugs that we had in phase three have failed for the most part. And even from the very initial studies, we've showed that this was a major resistance factor to venetoclax as well unfortunately. So patients who again relapsed.
or who were primary fracture,
NOTE Confidence: 0.931259272
they had high rates of 17 P loss or P50C
NOTE Confidence: 0.931259272
mutation or both and why that is the case.
NOTE Confidence: 0.931259272
So first of all if you do like
single cell DNA sequencing,
this is from Andrew Way’s paper
you showed you know all this
clones are being selected for.
So it’s almost like a pressure to select
this clones for that because they do
not get killed by venetoclax cell.
And what he showed in this paper is
that while in parental cells venetoclax
induces backs activation by this essay,
there’s much less in the PVC knockouts also.
And you can sensitize it by MC1 inhibition.
But again, we don’t have MC1 inhibitors in the clinic. So what do we do about that? We don’t really know.

But I want to show you some clinical data from our Einstein program that was developed before I got there using a different approach. So the approach that they decided to go forward was really developed by Jogan. I cannot promise the last name, but that at Cleveland Clinic. So he is I think, the most knowledgeable person in HMAI feel that.
So essentially he published the first study in MD's, as I'm sure Amara knows very well. And he compared the traditional dosing of decybin with what he calls metronomic dosing, which is once a week like 1/5 of the dose. So really like tiny doses of decybin. But he showed that this is enough to deplete DN MT3DMT1. So you don’t really need to induce this, you know, constant cytotoxic DNA damaging response of HMAS. And then he showed in preclinical work that it can induce differentiation of P53 novel loss clones. Now the resistance to the decided...
men is mediated by approvalation

of pyramid and synthesis.

Again, this is all his work and

he had some preclinical data

that Veneto clerks can in fact

reduce the pyramid incentives.

So there may be potential synergy there.

So based on this sort of

preclinical rationale,

the team at Einstein have

developed this metronomic dosing

d of Decidabin and Veneto clerks.

So now you have a newly diagnosed

patient with Amalo MTS who comes

to clinic and gets once a week
injection of the SIBIN subcutaneously
and one dose of another class.
So I’ll say I had hard time
believing that when I got there,
but I think now I’m so converted and
that we are continuing the development
of this in the prospective trial.
So again this is like a schedule,
this is like traditional what you do,
you give another class for 28 days
you give the SIBIN for five days
and you give the SIBIN for five days
or ASAP for seven days and then you
repeat the cycle and he is like once a week.
So the idea is really to get away from
the DNA damaging response because we
know that Pfc mutated cells are only
being selected by any DNA damaging drugs, they don't care and get into this hyper misleading effect. How that works, we don't know right? How many agents mechanism of actions is still not fully understood, but the idea was can we like really use that approach and at least have some benefit? So they published this paper, this was retrospective study using this regimen and now as I said, we are in the prospective study. I'm sorry; it's a bit difficult slide but the point is that there was
no really like mouse suppression

but the response rate was quite significant and CR rate was 57% which was fairly similar to the VLA study.

And then when we looked at the small numbers again this is all like very early on of PVC mutated patients, the survival was about 10 months and a lot of patients actually achieved full remission, became transfusion independent. They relapsed like a clock at 10-11 months. So it’s not curative approach but at least you know we can extend the survival again and reality is five
00:41:04.530 --> 00:41:06.370 months survival. Many other studies.

00:41:06.370 --> 00:41:07.920 Now this is 10 months.

00:41:07.920 --> 00:41:10.080 Again, small number non randomized studies,

00:41:10.080 --> 00:41:12.160 so with all the Kevas,

00:41:12.160 --> 00:41:13.585 but we’re quite excited about

00:41:13.585 --> 00:41:15.496 that and we are thinking of what

00:41:15.496 --> 00:41:17.224 can we add to that to really like

00:41:17.282 --> 00:41:18.758 capitalize on this approach,

00:41:18.760 --> 00:41:22.840 you know using this metronomic dosing.

00:41:22.840 --> 00:41:25.280 So one thing is like in the lab we are

00:41:25.348 --> 00:41:27.916 trying to use some of the BAX activated.

00:41:27.920 --> 00:41:29.614 So I told you several times the

00:41:29.614 --> 00:41:31.191 BAX is really like critical and

00:41:31.191 --> 00:41:33.039 the BAX is not working with PP,

00:41:33.040 --> 00:41:36.876 she’s lost. So we have a collaboration
00:41:36.876 --> 00:41:40.135 with again Everest and also Jerry
NOTE Confidence: 0.729887153571429
00:41:40.135 --> 00:41:42.912 Chipok would develop the direct
NOTE Confidence: 0.729887153571429
00:41:42.912 --> 00:41:45.752 Bax activators or Bax modulators.
NOTE Confidence: 0.729887153571429
00:41:45.760 --> 00:41:47.320 So we are thinking maybe
NOTE Confidence: 0.729887153571429
00:41:47.320 --> 00:41:48.880 if we use those compounds,
NOTE Confidence: 0.729887153571429
00:41:48.880 --> 00:41:50.815 there’s a preclinical stage we
NOTE Confidence: 0.729887153571429
00:41:50.815 --> 00:41:53.160 can overcome the PVC mutant loss,
NOTE Confidence: 0.729887153571429
00:41:53.160 --> 00:41:56.400 but this remains to be seen.
NOTE Confidence: 0.729887153571429
00:41:56.400 --> 00:41:57.560 OK. So switching gears,
NOTE Confidence: 0.729887153571429
00:41:57.560 --> 00:42:00.006 so this was PVC new dated AML and
NOTE Confidence: 0.729887153571429
00:42:00.006 --> 00:42:03.516 now going back to the chemotherapy.
NOTE Confidence: 0.729887153571429
00:42:03.520 --> 00:42:05.638 there’s like very good rationale to
NOTE Confidence: 0.729887153571429
00:42:05.638 --> 00:42:07.444 combine the Netherlands with the
NOTE Confidence: 0.729887153571429
00:42:07.444 --> 00:42:09.205 chemotherapy and AML and there are
NOTE Confidence: 0.729887153571429
00:42:09.205 --> 00:42:10.990 a lot of trials which have been
already reported and now we’re getting the response rate of about 90%. So this is like was unheard of before, but when you add the Netherlands to chemotherapy you really get tremendous synergy. So in our centre we have this IST that is run by Doctor Manzaris where we use the standard Sam plus sheep plus another class, different durations and so forth. The trial is still ongoing, but again the response rate are about 90% is still like short follow up. So we don’t really know like survival,
but we are quite excited about this approach except PVC MUDA patients, they relapse and they don’t do well. So we stopped using this for even younger PVC MUDA patients because all patients, 5 patients were treated with, they’re all relapsed and they died from despite the fact that some of them achieved remission. So again, PVC remains an issue. So we’re looking at the stem cell extinction with the therapy and doing a lot of research with that. And in the last 10 minutes of my talk, I’ll go back to BCL XL, which may be of interest more
broader kind of auditorium.
So BCL XL is a cousin of BCL two and it’s less expressed in the AML, but it’s expressed in solar tumors, it is expressed in the TELL subsets. So this was work from Tony Lataev now a few years ago, that showed that the typical TELL actually depends on BCL XL and if you use this Navitoclax drug that didn’t make it, you actually get very good responses. There’s a subset that is B, so two dependent, but I’m not going to go into that.
Now.

I already told you that the liability of B cell X inhibitors is thrombocytopenia because platelets depend on B cell XL for survival.

So you get on target toxicity and of course it’s challenging to those.

So and you know this is just a couture published review recently.

So Nevito clocks right the drug that is still not approved, it was just as the venetoclax so inhibits the complexes inducing bags back but it causes thrombocytopenia killing the platelets.

So the way around that at least
that's ongoing work is to use the degraders for BCLXL degraders. So, so we have been collaborating with the team from Dalhoung Zhou who was before University of Florida and now he moved to the San Antonio. So he developed this Protac BCL XL degrader where the legend is essentially native o’clock. So same drug, but then there's a linker that links it to the VHL E3 ligase. So you can ask why that is better than inhibitor, right?
First of all, it’s huge molecules. So it’s has a pharmacological properties issues. But The thing is that this E3 ligase is not expressed in platelets. So you’re not getting degradation of B cell XL and platelets. And therefore you can see here there’s no B cell cell degradation in platelets with this drug. But it’s like a TLO tumor cell line, it’s very nice degradation. So this is just the schematics of that. And again as a result, you can kill the tumor cells but you don’t kill platelets.
So this drug right now is in clinical trial in solar tumors and it’s actually completed the phase one portion of it. They did see some drop in platelets, but there was much less than whenever the drug still binds to some extent and still inhibits a little bit of BCL XL function, but it was reversible and no other toxicity was seen. We published that it’s quite effective and the TL models and recently we also moved towards the dual BCL 2XL product which is not yet in the clinic and we published this work in AML.
and we showed that this dual product, we call it 753-B, it was actually quite effective in all primary AML samples including those that were resistant to venado clock. So there’s you know there’s degradation of BCL XL as you would expect basically didn’t see much degradation of BCL 2IN primary cells but it was seen the cell lines. So we think that’s potential for using dual BCL 2XL inhibitors in AML as well. And the other aspect of it that is very kind of popular and the solid tumor literature is that the role of B cell excel in senescence cells.
So what we know the senescence cells, the cells that survive chemotherapy and but they can kind of revert back and become chemo resistant and the metastatic cells in the setting of breast cancer or lung cancer and so forth, It’s much less known in senescence in EMO. But there was a paper by Ari Melnick’s group that showed that chemotherapy can actually induce senescence cells. So this is like essay you use for the C-12 FDG where you can show that within the viable cells a fraction of them are actually senescence and the senescence cells they depend.
00:47:25.130 --> 00:47:26.999 on BCL X cell for survival.
NOTE Confidence: 0.8156123268

00:47:27.000 --> 00:47:29.360 So when we sorted out the senescence cells,
NOTE Confidence: 0.8156123268

00:47:29.360 --> 00:47:31.488 we showed that BCL XL was up regulated
NOTE Confidence: 0.8156123268

00:47:31.488 --> 00:47:33.219 which was which was consistent
NOTE Confidence: 0.8156123268

00:47:33.219 --> 00:47:34.356 with the literature.
NOTE Confidence: 0.8156123268

00:47:34.360 --> 00:47:36.216 And then when we looked at the markers
NOTE Confidence: 0.8156123268

00:47:36.216 --> 00:47:37.764 of senescence, this is cell line.
NOTE Confidence: 0.8156123268

00:47:37.764 --> 00:47:39.390 So chemo is inducing all the
NOTE Confidence: 0.8156123268

00:47:39.450 --> 00:47:40.720 senescence phenotypes.
NOTE Confidence: 0.8156123268

00:47:40.720 --> 00:47:43.580 But when we use this BCL XL
NOTE Confidence: 0.8156123268

00:47:42.722 --> 00:47:43.580 degrade that we
NOTE Confidence: 0.8156123268

00:47:43.653 --> 00:47:45.013 can reverse that and
NOTE Confidence: 0.804974427894737

00:47:45.013 --> 00:47:46.713 they showed here as well.
NOTE Confidence: 0.804974427894737

00:47:46.720 --> 00:47:49.219 So we think that there’s a potential
NOTE Confidence: 0.804974427894737

00:47:49.219 --> 00:47:52.214 efficacy of BCL XL inhibition and this
NOTE Confidence: 0.804974427894737

00:47:52.214 --> 00:47:54.298 dormant senescence cells plus with
it’s really hard to identify them and patients like you know the essays are not very well established. But I think there’s a lot of interest using BCXL inhibitors as synolytic in a variety of different sort of conditions including sorry tumors, leukemias and so forth. And the finally, like I told you that there’s some AML subsets that are BCL Excel dependent and this is one of them. So this is like totally horrible entity called acute Erythroid, entity called acute Erythroid, Erythroid leukemia.
And now Doctor Xu here has done a lot of work on that, but it’s in the old classification is the MLM 6 and it has all of this Erythroid markers and it has very high rates of PPC mutation, right. So I already told you that the NOW class does not work for PPC mutant AML. And sure enough in all clinical trials patients who were AEL patients who were treated with Venetoclax, they progressed very quickly. So that’s not a solution, but there was a group at University of Helsinki.
and they published this very nice paper last year and blood. So they looked at the dependency and AEL using the Crispus screens or drug screens and one of the top one was actually B cell XL. This is a gene called B cell 12/1 that controls B cell XL. And you can see that it also was true for the drug screen as well. They show this and they confirm that and the cell lines and if you use a different like gene expression data sets, so again this is old M6 also M7 which is megacaric leukemia.
they have high expression here, very high expression and this is Saint Jude Court as well. So they have a high expression of BCL XL on a transcriptional level. The thing is because the erythroid cells have you know naturally utilizing this protein for survival and this is preserved, they also showed some efficacy in the in vivo models. So we are interested in using the product for this indication and within mechanistically it makes a lot of sense because again in Aristo it says the main transcription factor.
that drives kind of development

is gutter one and we show that

there is a very direct correlation

This is activity from the gene expression analysis and both different data sets.

This was collaboration with Saint Jude team,

so there’s no correlation with BCO 2.

So really in Ali think there’s

transcriptional up regulation

and dependency on BCL XL.

Based on some of the prior work published,

we know that this got the one

directly binds the BCO 2L1 locals.

And we have now also data in
AL in collaboration with again

Ilaria from Saint Jude and they’re using this degrader.

So this is original BCL XL degrader.

This is like a next generation.

We showed us the cell lines that are completely resistant to the netoclocks here and green they can be nicely killed by this B cell cell degrader.

We also tested this in fuel primary samples that you know failed all kind of regiments including macrolimab and the we show the B cell degradation here and very nice response.

So again, this is preclinical work.

We’re trying to get the drug if we get
funding for the trials is still ongoing,

but we feel that this is a hopeful

and in fact I learned that every

just approved the nabito clocks

for the subset of AL between MSK

So there will be a small pilot

So there will be a small pilot

trial at least testing the proof

of principle that B cell XL is a

driver in this horrible disease.

We also see very similar phenotypes in MPN,

but I didn’t have time to

show this data as well.

So I’ll end here.

And I would like to postulate
that AML is generally B,

so two dependent disease,

but then there’s some subsets that are
depend on B cell XL or M cell one.

And of course we love the drug because
it kind of lowers the threshold.

So you can see the synergy with pretty
much anything you use and then you can
kind of go back to lab and figure out why.

But but this was really like you know
born in the clinical trials where I
showed you synergy with chemotherapy,
with the hypermethylene agents,
with thyristine kinase inhibitors and
you know the the fuel has really like
exploded using this drug as a sensitizer.
Some of the you know trials that I mentioned are ongoing and immune therapies I mentioned to you before now resistance is obviously as a major issue and it's largely driven we think by PC laws or signaling mutations. And you know I showed you what we're trying to do about that. But then the subsets that are B cell dependent and we are quite excited about using this B cell inhibitors or products in this setting. So I'll end here. So I have many Co workers collaborators from
both my MD Anderson lab that has now only partially moved to Einstein. So I have a new lab at Einstein and my clinical collaborators at MD Anderson especially Courtney who led AML VLA trial now who has done a lot of triplet combinations and many other investigators of course Dr. Contagion who has been really like pushing ABVI to go forward with this HMA event trial despite the fact that single agent was not as efficacious. And a lot of collaborators from Montefiore Einstein, we’re developing this new programs that I showed to you and many
collaborations with the companies but also academic collaborators. So I would like to acknowledge Tony Li Tai who has been really like, you know, developed this first approach with me in the lab. And you know, we think that because of that work and algos really went into AML and we have collaboration with Andrew Way at Melbourne and with the Saint Jude team and Dao Hangzhou for the product. So I’ll end here. Sorry, it’s like 5 minutes before the end of the hour,
but I am happy to take questions.

Thank you. Maybe I can start.

You have questions in Zoom.

Very few people actually bridge the clinic and the lab like you do clinical trials and lab, which is amazing.

So I know this is not primarily your research,

but why would you think the metronomic use of HMA with venetoclax would actually work for TP50 TP 53

while regular dosing would not?

I think the regular dosing induces
DNA damage and essentially leads to the selection of P53 lost cells, so you kind of lose your hypermethylene advantage, whatever that is. Again, I don’t know how the hypermetalline agents work in PhD muted EMLO, but I think what happens with the regular dosing, there’s DNA damage, which was shown by Steele, Gore and others before. And the cells, they’re just like being selected for. So all you get is selection of cells that are like PHC mutated. They’re resistant to DNA damaging drugs.
And so there’s very limited like advantage.

Well, with metronomic dosing you really like rely on hypometallic effects of the drug and then you get benefit. But again it’s a hand waving argument, but we are encouraged to see that in the prospective trial with the you know about 10 patients treated that the data stand. So this you know again they’re going to remission about like 50-60% and as of right now survival is about 11 months. But again like short follow up, you know it’s a small number of patients.
So I’m like you know, I’ve been hesitant presenting this data till I actually saw the survival data, but we’re hoping that you know this will stand, but again it’s not curative. So we definitely need something else to add to that. Thank you, very nice talk. I was curious about what’s being done towards tissue specific MCL ONE inhibitors. So in order to avoid the cardiotoxicity, you talk beautifully about BCL.
nothing that I’m aware of.

I heard that there’s some approaching making approaches making the ADC.

I haven’t had yet chance to get any of those to my lab.

I think it’s probably ongoing, but I’m not aware yet that there’s any like you know, compound that is close to clinic, but I think that would be the way to go.

Now the VHL is expressing the heart.

So you know,

there’s also effort by Stephen Fazek, who is now at the Vanderbilt to look at all 600 ubiquitin ligase and try
00:57:11.076 --> 00:57:13.517 to understand the tissue specificity.

00:57:13.520 --> 00:57:14.680 Obviously, if I'm so one,

00:57:14.680 --> 00:57:16.516 we have to avoid the heart.

00:57:16.520 --> 00:57:18.152 I think that effort is still

00:57:18.152 --> 00:57:20.079 ongoing as far as the products,

00:57:20.080 --> 00:57:24.770 but I think perhaps using the antibodrap

00:57:24.770 --> 00:57:27.480 conjugate maybe is the way to go.

00:57:27.480 --> 00:57:30.536 You know there was the B7 HCB cell Excel

00:57:30.536 --> 00:57:33.560 conjugate that went into solid tumor trials.

00:57:33.560 --> 00:57:34.680 It somehow didn’t make it,

00:57:34.680 --> 00:57:39.760 but kind of similar approach

00:57:39.760 --> 00:57:47.520 Thank you for that. Thank you.
Looking at the evolution on the clinical slides that we show on track right single agent one of the plaques, we are very modest activity in AML that phase three study that you show with Curtney in the first three months ASA one curves don’t separate after that the curves start to separate but everybody needs a CR after one cycle. I think the probably the people don’t die with ASA after first month either. So they still you know this well with ASA side is about nine months right. So they even though they don’t get intermission, they are still, you know,
00:58:25.520 --> 00:58:27.860 alive and they continue on study

00:58:27.860 --> 00:58:30.679 and so they curve separate later.

00:58:30.680 --> 00:58:32.996 That’s my guess. But you’re right.

00:58:33.000 --> 00:58:35.107 You know, remissions happen after one to

00:58:35.107 --> 00:58:37.451 two months with the vanilla clocks and

00:58:37.451 --> 00:58:39.917 there are no remission with azacitidine.

00:58:39.920 --> 00:58:42.545 But it’s because I guess they’re still

00:58:42.545 --> 00:58:45.412 kind of able to maintain people alive with

00:58:45.412 --> 00:58:47.116 all our supportive care and everything.

00:58:47.120 --> 00:58:49.520 They they are still there.

00:58:49.520 --> 00:58:51.038 That’s my understanding

00:58:51.800 --> 00:58:53.496 because you know if you go back into

00:58:53.496 --> 00:58:54.946 that paper that you’re a part of the

00:58:54.946 --> 00:58:56.656 Curtis paper that frankly presented

00:58:56.656 --> 00:58:58.960 at the older NPM on positive.
I have a feeling when Nick presents the data after that combination, they’re highly choosing NPM on positive patients that is chemosensitive or mild suppression sensitive. And then they’re tagging it up with the fixed data because they’re seeing a flat like that kurtish paper you have the first three months, it’s a flat drop, drop, and we know what addition of three class of frequently liberals done too. And the point being is AML being all legal flow now, how much emphasis can we give just the BCL component in looking
into resistance because the minor suppression component takes care of it for three to six months, very good. We don’t have anything to that extent compared to cytotoxic in the past. Garcia within a recently in the post transplant period in the other one has maintenance even there the curves first three to six months and then drop, drop, you don’t have a leukemia there at that stage. So now when I’m going to fight stem cells, what do you think the resistance is in that context when you’re using either one in the post transplant context?
Oh I I don’t think I’m able to answer that question. So I’m not sure what the you know.

I don’t think that this is just mouse suppression causing people to die, but there’s really like relapses going on, right? And I assume that this is still escape of some of the clones that are not being eliminated. But I don’t know the data that well. But yeah, the point is well taken.

As far as like you know, there’s a lot of discussion if you have MP1 free, St.

Commutative clone can be eliminated.
01:00:38.138 --> 01:00:40.360 with Venetoclax alone or not.
01:00:40.360 --> 01:00:41.758 The data are not very clear,
01:00:41.760 --> 01:00:43.734 but at least from VLA data
01:00:43.734 --> 01:00:45.480 we know that Flixtree mutated
01:00:45.480 --> 01:00:48.000 patients even if they had MPN one.
01:00:48.000 --> 01:00:49.032 This is not published,
01:00:49.032 --> 01:00:51.598 but I looked at that in the rest context.
01:00:51.600 --> 01:00:53.946 The survival is still shorter than
01:00:53.946 --> 01:00:56.398 for those who have only MPN 1.
01:00:56.400 --> 01:00:57.935 So there’s still that contribution
01:00:57.935 --> 01:01:01.238 like relapse earlier Relapse,
01:01:01.240 --> 01:01:03.396 despite the fact that you target the,
01:01:03.400 --> 01:01:05.320 you know, presumably stem cell MPN,
01:01:05.320 --> 01:01:06.684 one clone with Venetoclax.
But I don’t know really how like Clonal Dynamics happened there, but I do think that triplet adds in that sense that it will target the fixture clone within even MP one. But again, you know, I don’t have data to that. So maybe one last question, given your extensive work with drug development in AML and you alluded to the Twitter wars on some of these data. I think one big question that keeps coming up is if if an agent has no single agent activity, does it can it have realistically a chance of being synergistic in a combination?
Some people pointed to Vinito Clacks as the rule that this, but actually Vinito clacks as you said does have single agent activity. It’s not much, but it does have activity and some people took a Victory lab with Magrolimab because it has zero single agent activity and all the fuss about the combinations and then the face reasoning. So so is your sense that if you have no single agent activity, can you really be synergistic in combination as a general?
Yeah, I think it was like a general question.
I would probably be very worried about going to phase three with a drug that has no single agent activity.
As you said the NOW class did have activity you know reduced blast in 50% of patients.
the the data also in the front line setting where they did the bone marrow, they did seven days venetoclax pretreatment just single agent and they did bone marrow that was done in Australia and they also showed reduction or even like remission in about 50% of patients.
So it does have single agent activity but also like different mechanistically because it’s like a sensitizer, right.
So you can, you know, think that even if you didn’t have that single agent activity in combination you might have had. But I personally like I’m very worried that you know, I’m, I might be wrong. Thank you so much. Thank you everybody.