Welcome everyone to the 2023 Post American Society of Hematology annual meeting at CME series. We are starting off the series today with multiple myeloma.

Our first two presenters are Doctor Nofar Barr and Doctor Sabrina Browning who will be reviewing abstracts.

We will then have a question and answer period at the end of the presentation where we will be joined by two other panelists, Dr. Ellen Gorshin and Doctor Natalia and appraise. If you could please
Hi everyone, I'm just gonna start sharing my screen here.

Alright, it's good to be here. Good afternoon.

Today I'm going to be looking at the newly diagnosed myeloma abstracts in Ashes 2022 this past December with a particular focus on subgroups.

So I have no disclosures.

The first subgroup I'm going to be speaking about are the frail patients and why is it important to have...
NOTE Confidence: 0.9029528
00:01:21.990 --> 00:01:23.886 dedicated studies for these folks is
NOTE Confidence: 0.9029528
00:01:23.886 --> 00:01:25.578 that they have different outcomes,
NOTE Confidence: 0.9029528
00:01:25.578 --> 00:01:27.290 they have shorter survival,
NOTE Confidence: 0.9029528
00:01:27.290 --> 00:01:29.438 they have higher rates of toxicity
NOTE Confidence: 0.9029528
00:01:29.438 --> 00:01:31.369 and therefore higher rates of
NOTE Confidence: 0.9029528
00:01:31.369 --> 00:01:32.689 discontinuation of therapy.
NOTE Confidence: 0.9029528
00:01:32.690 --> 00:01:33.262 Traditionally,
NOTE Confidence: 0.9029528
00:01:33.262 --> 00:01:35.550 studies have categorized myeloma
NOTE Confidence: 0.9029528
00:01:35.550 --> 00:01:38.410 patients as either transplant or
NOTE Confidence: 0.9029528
00:01:38.417 --> 00:01:40.417 transplant ineligible patients,
NOTE Confidence: 0.9029528
00:01:40.417 --> 00:01:42.979 but this category really does not
NOTE Confidence: 0.9029528
00:01:42.979 --> 00:01:45.479 capture frail patients because the frail
NOTE Confidence: 0.9029528
00:01:45.479 --> 00:01:47.766 scores are not routinely checked in
NOTE Confidence: 0.9029528
00:01:47.766 --> 00:01:50.349 those non transplant eligible patients.
NOTE Confidence: 0.9029528
00:01:50.350 --> 00:01:52.838 For a long time the standard of care
NOTE Confidence: 0.9029528

3
for non transplant eligible patients

But since the Maya study, we now have a new standard of care for patients which is Derek Tuma Mab

So what the FM 2017 O3 study analyzed is removal of dexamethasone early.

Before we get into the study design, I want to talk about what is a frailty score.
00:02:31.105 --> 00:02:33.256 to take a look at this in your clinic,
00:02:33.260 --> 00:02:34.876 so I am WG.
00:02:34.876 --> 00:02:37.300 Frailty score involves a few things.
00:02:37.300 --> 00:02:39.700 Age, activity of daily living,
00:02:39.700 --> 00:02:41.764 which involves feeding oneself,
00:02:41.764 --> 00:02:43.676 bathing oneself, instrumental activities
00:02:43.676 --> 00:02:46.304 of daily living which involve food,
00:02:46.310 --> 00:02:48.282 shopping, cleaning the house,
00:02:48.282 --> 00:02:51.240 doing your finances and the comorbidity
00:02:51.311 --> 00:02:53.000 index, which is what it means.
00:02:53.000 --> 00:02:55.070 Comorbidity is like lung disease.
00:02:55.070 --> 00:02:58.190 Diabetes, liver disease and so forth.
00:02:58.190 --> 00:02:59.840 Now, as you can imagine,
00:02:59.840 --> 00:03:01.808 this takes time to do this frailty score.
00:03:01.810 --> 00:03:03.364 There was a lot of questions involved.
So the IM group devised a simplified score which involves age, which is fairly easy, ECOG performance status, which we do routinely, and then the comorbidity index, which is easily accessible from chart review. And if you had a score of two or more, you’re classified as frail and otherwise you’re fit. So this is the study design. They include a newly diagnosed patients over 65 years of age and I am I FM frailty score of two or above. It was a 2 to one randomization with REVLIMID decks or Dara REVLIMID.
I do want to note that with the Dara Revlimid’s group which ARM B right here, they did receive steroids for the first two cycles along with dexamethasone primarily to avoid infusion reactions. So their primary endpoint was PFS, but this is immature at the moment. So they did an interim analysis and they looked at response rate including MRD negative rate and occurrence of grade three or more toxicities. I want to highlight here some of the patient characteristics. If you look at the median age, they were significantly older.
median age of 81 compared to the Maya study which was 73. While the inclusion criteria in the study included two or for the frailty score was two or higher, actually the majority of the patients were three and higher. If you look at the risk categories, they were fairly similar in the two groups. So Dara REVLIMID clearly led to deeper response rates than REVLIMID. You can see here first dexamethasone you had higher CR and very good partial response rates and then Dara Rev Group and you also had higher MRD negative rates,
00:04:54.030 --> 00:04:56.890 attentive negative 5th using next
00:04:56.890 --> 00:05:00.330 generation sequencing 10 compared to three.
00:05:00.330 --> 00:05:03.147 MRD was assessed at one year in patients who
00:05:03.147 --> 00:05:06.067 had a very good posture response or higher,
00:05:06.070 --> 00:05:07.426 it is important to note that.
00:05:07.430 --> 00:05:10.944 Any missing data was considered MRD positive.
00:05:10.950 --> 00:05:13.064 So it’s important because there is a
00:05:13.064 --> 00:05:14.979 significant group of patients that have
00:05:14.979 --> 00:05:17.306 missing data and for example, the Dr.
00:05:17.306 --> 00:05:20.670 Group had 20% missing data and the Rd.
00:05:20.670 --> 00:05:22.126 had 14% missing data.
00:05:22.126 --> 00:05:24.310 And I’m not about to compare
00:05:24.392 --> 00:05:26.797 different studies to one another,
00:05:26.800 --> 00:05:28.520 but I want to give us a framework
00:05:28.520 --> 00:05:30.168 of what the Maya study showed.
So in the Maya study they assess MRD negativity, attend to negative 5th, but they used a different assay so they use flow. So flow tends to have a higher MRD negative rate just by the nature of its assets. So just something to note, but they had in the DRD group 24% MRD negativity versus 7 in the Rd. group. In terms of toxicity, which is very important, you can see that Grade 3 or above toxicity was higher in the Dr. Group, particularly with hematologic toxicities like anemia or neutropenia.
And in this group, of course you worry about infections with this neutropenia, but they did not see an increase in grade 3 above infections in the Dr. Group compared to the R group and even when looking at patients who are very frail with scores of four and five, there was no difference in grade 3 infections, so this is reassuring.

So in conclusion, I think it is time to rethink duration deaths methadone especially for outpatients, longer follow-up of PFS is needed.
but higher MRD rates in the Dr.
Group is very promising.
I think the better comparator to Dr.
like DRD and Maya would be a
would have been a better design.
However,
this was not the standard of
care when this was designed.
They are going to be there are going
to have a retrospective comparison.
To the main study in the frail population,
I think you know in you know right
now when you see patients in clinic
when you have that very frail over 80
year old patient where you’re really
not sure about triple drug induction
and you’re thinking about a doublets.
I would choose Dara Rev with a short
duration of steroids as opposed to Rev Deck.
So I do think it’s meaningful
for our practice today.
The next set of subgroups I want
to talk about another area of very
high unmet need is the high risk
population where we really have
limited randomized studies guiding
our treatment.
The only randomized study was a -
and this was evaluated the
addition of ELOTUZUMAB to Velcade
REVLIMID index methadone VRD.
Now we know we need to do better than VRD, but how do we do it? One appealing option was switching out the VELCADE with carfilzomib which is a more potent proteasome inhibitor and outperform VELCADE in the relapsed refractory setting. Additionally, there was phase two studies showing high MRD negative rates in KRD. So it made sense to compare VRD to card and they did this in an endurance study and they actually did not find superiority of care due to the Rd. but they excluded high risk patients.
So that question about how do we better improve our induction in the high risk patients was not really answered by this study. But people have not abandoned care being in high risk patients for a variety of reasons. But in the memorial Stone Kettering Group where they are earlier, they were early adapters of Carradine induction. They were able to do a retrospective analysis and this was presented. 

Doctor Tan in this years ash of Care versus verdine high risk myeloma.
Their inclusion criteria for high risk included having gain of 1 q translocations.

They identified 154 patients in this category. About 50% of each of these groups underwent early stem cell transplant. Their primary endpoint was progression free survival and they also looked at response rate including mrD, negative rate and overall survival. So this is the patient characteristics. A few things to highlight. The carotid group were younger.
and then I want to look at the cytogenetic characteristics here just to see who are dealing with the majority of the patients who are high risk or high risk by definition of chromosome 1Q gain or amplification, which is not unusual because this is one of the more common findings we see. The second most common was deletion 17P and importantly about 1/4 of the patients of E in each group had two or more high risk. The genetic abnormalities, and this is now called the double hit or the ultra high risk patients.
which really have poor outcomes.

So this is the response rates and the median PFS results.

You see higher CR rates with KRD compared to VRD,

higher MRD negative rates by flow, but it was not statistically significant.

I think the most impressive results is the PFS,

the KD having a median of 71 months compared to 41 months and this was you know highly statistical significance and they also saw an overall survival benefit.

The five year estimate of 85% compared to 63%.
I want to just point out here in the ENDURANCE study remembers it is non high risk patients the PFS of both arms was 30-4 months and it’s not quite clear why in this high risk populations that PFS is actually higher. So this was kind of brought up to the presenter and it was not there wasn’t a great explanation but something to think about you know endurance was done in a in a community setting and this. Early as in a single institution, tertiary center. So next they did a multivariate
analysis looking at different factors that are associated with better PFS and OS. So first type of inductions, OK, D is better, early transplant was better, having revised ISIS one compared to two or three was better and and that who are these revised access one in this high risk patient population, it’s really those patients that have gained one cube because they were not included, it’s not part of the revised ISS criteria. So you know who who these patients. And then the number of cycles having six or more induction cycles had better PFS and OS.
So to summarize, I think the study is interesting. It does suggest that maybe Cardi could be better than VRD in high risk patients, but it is very limited by the retrospective nature of this design. I also think that you know they don’t talk about which maintenance strategies they used and that will definitely impact PFS and OS. I think this study continues to support the notion that early transplant in high risk patients is beneficial and it does bring into question. What is the optimal number of induction
treatments in high risk patients?

Next I want to move to a more modern question is, you know, now that we're using quadruplex, how do high risk patients fare with the most commonly used quadruplets, the Dara VRD. So Dara VRD was studied in the Griffin study, which compared the addition of Dara to VRD in transplant eligible patients. In all patients they saw that there were higher MRD rates and also progression free survival benefit. But again this isn’t all patients. There are only 15% of those patients that were high risk.
cytogenetics by the traditional high risk features like deletion 17, translocation 414 and four 416. So the Doctor Charity wanted to evaluate this subset group in the Griffin to really hone in on different high risk categories in the Griffin study. And I want to.

Really it’s a busy, a little bit busy slide, but let’s just focus in on the genetic risk categories here as I highlighted they as I mentioned the initial high risk category were very few in both arms,
but then they revised or high risk category to include chromosome abnormality and that really increased their, their patient population from 16 to 42 patients in the Dara VRD and categorize patients having zero.

So no high risk features, HCA 1, high risk cell genetic abnormality or two or more as we call the ultra high risk patients. Clearly you can see the PFS in patients who are standard risk didn’t seem to differ much between the two groups.
00:14:17.474 --> 00:14:19.609 in the meeting in the 15 months.
00:14:19.610 --> 00:14:21.350 Clearly the ultra high risk
00:14:21.350 --> 00:14:23.544 patients are too small to really
00:14:23.544 --> 00:14:25.479 make any conclusions about only
00:14:25.479 --> 00:14:27.690 10 patients in eight patients.
00:14:27.690 --> 00:14:30.290 But in the high risk in the one
00:14:30.290 --> 00:14:32.054 high risk cytogenetic abnormality
00:14:32.054 --> 00:14:34.629 group there was an improvement
00:14:34.629 --> 00:14:37.850 in PFS not reached compared to.
00:14:37.850 --> 00:14:38.718 48 months,
00:14:38.718 --> 00:14:41.756 and this is the only subgroup here
00:14:41.756 --> 00:14:44.682 that actually does not cross the
00:14:44.682 --> 00:14:47.094 hazard ratio does not cross one.
00:14:47.100 --> 00:14:48.766 So a different way of looking at
00:14:48.766 --> 00:14:50.848 the same data, if you’re you know,
a more visual person, is looking at the PFS curves and. What I want to show here in the kind of medium purple line the dare RVD with one high risk staging netic feature. Compare that to this green dotted line here, the derivative with sorry with VRD with one high risk feature there's a clear separation of the PFS curves, while there is really not a big difference with those patients. Now look at the graph on the right. These are these are the amplification or gain of 1 Q and the grasp is actually
00:15:33.709 --> 00:15:36.005 pretty identical to the ones with
00:15:36.005 --> 00:15:38.573 the one high risk hydrogenic abnormality,
00:15:38.580 --> 00:15:41.136 which really showed you who those
00:15:41.136 --> 00:15:43.376 patients are. So in conclusion,
00:15:43.376 --> 00:15:46.508 I think this analysis shows that Dara
00:15:46.508 --> 00:15:49.490 VRD seemed to outperform VRD in high
00:15:49.576 --> 00:15:52.607 risk patients harbouring gain of 1 Q.
00:15:52.610 --> 00:15:55.865 High risk patients with more than two
00:15:55.865 --> 00:15:57.830 cytogenetic abnormalities do poorly,
00:15:57.830 --> 00:16:00.356 and we can’t make any conclusions
00:16:00.356 --> 00:16:02.474 for this analysis because of
00:16:02.474 --> 00:16:04.259 the numbers were too small.
00:16:04.260 --> 00:16:06.997 So this brings me to this category
00:16:06.997 --> 00:16:09.944 of ultra high risk myeloma and the
00:16:09.944 --> 00:16:12.408 optimum study was very clever study in
the UK they it was a screening study.

So anyone in multiple UK centers who had the who’s being worked up for myeloma or was offered the participation in the study and they screen patients for high risk features, they’re inclusion was to be double hit.

So you have to have two of the following translocation 4141416. Station one gain of 1Q and deletion 17P or high risk gene profile or if you had plasma cell leukemia, which really is these patients are excluded from every study.
they identified 107 patients, ten of which had plasma cell leukemia. So there’s a few things going on in this study. I want to focus first on the study design of the optimum study, which you talked about up here. On top, they use five drugs in induction. So they added cytotoxic to Dara VRD. They added VELCADE in the Peri transplant period. They used six cycles of Dara VRD induction and then 12 more cycles of Dara RVD in extended consolidation, so basically excluding steroids.
in another year.
Of consolidation to and then there are in until progression and notably they’re not using a proteasome inhibitor long term. So ideally the authors would love to have done a randomized study, but there was no standard of care for these ultra high risk patients. They thought it was unethical, so they did not do so. So it’s a single arm study, but they were very much interested in understanding how this would compare to a genetically similar group of patients with myeloma.
So they looked at their myeloma ex study and they had genetic testing for all these patients identified and identical. Population with this ultra high risk phenotype, I'm not going to go into the details of that study because I do think it's an overall sub par comparator. But it's just for numerical purposes here that they used cytotoxin REVLIMID decks or carfilzomib, dexin induction transplant and then either they got no maintenance which is really not what we do
or REVLIMID maintenance so.

Their objectives of the studies to look at MRD, to look at PFS and toxicity. I do want to note this is quite an intensive treatment and they did have several fallouts dropouts.

So out of 107 patients, only 74 patients completed consolidation too. The dropouts in the induction transplant section was due to intolerance and dropout and consolidation was due to progression of disease.

You can see that the MRDD deepened as you move from end of induction to end of transplant at 63%.
00:19:08.966 --> 00:19:11.318 I don’t want you to be discouraged

00:19:11.318 --> 00:19:13.643 by the lower percentage after

00:19:13.643 --> 00:19:16.273 end of consolidation because they

00:19:16.273 --> 00:19:18.350 mentioned there are dropouts.

00:19:18.350 --> 00:19:20.814 So you can see here 30% of the

00:19:20.814 --> 00:19:22.549 patients didn’t reach that endpoint.

00:19:22.550 --> 00:19:24.746 So that’s why you see numerically

00:19:24.746 --> 00:19:26.710 lower rates of MRD there.

00:19:26.710 --> 00:19:28.590 What is important we know

00:19:28.590 --> 00:19:30.470 sustain MRD is actually more.

00:19:30.470 --> 00:19:32.744 Relevance than just one time point

00:19:32.744 --> 00:19:34.580 of emerging negativity is that

00:19:34.580 --> 00:19:37.580 84% had sustained MRD negativity

00:19:37.580 --> 00:19:40.156 at the end of consolidation.

00:19:40.156 --> 00:19:43.710 So that is very important.
Now this is the PFS course again. I'm not surprised that the PFS is better with this optimum regiment than the comparator. They did spread out in the myeloma X the ones that got prophesied that were not to secularism seemed to be a little bit better than not. Again not very surprising with produce some inhibitor but regardless I think it's very impressive the 30 month PFS estimate of 77% and this does fare favorably to other. Other data out there for this really high risk patient population. In terms of toxicity,
00:20:21.054 --> 00:20:23.285 which is very relevant when people are
getting this intense prolonged treatment,

00:20:23.285 --> 00:20:25.270 they showed you here the
consolidation to adverse events.

00:20:25.270 --> 00:20:27.690 So there are some grade three side effects.

00:20:27.690 --> 00:20:29.626 There are not that many,
most of them are hematological
like neutropenia.

00:20:29.630 --> 00:20:32.984 There were some Grade 3 infections,
about 12%,
most of them being respiratory tract
infections and they don’t separate out,
you know, the viruses from the bacteria,
but that I think that would be relevant.

00:20:32.984 --> 00:20:34.569 There are not that many,
most of them are hematological
like neutropenia.

00:20:34.570 --> 00:20:37.495 There were some Grade 3 infections,
about 12%,
most of them being respiratory tract
infections and they don’t separate out,
you know, the viruses from the bacteria,
but that I think that would be relevant.

00:20:37.495 --> 00:20:41.670 There were some Grade 3 infections,
about 12%,
most of them being respiratory tract
infections and they don’t separate out,
you know, the viruses from the bacteria,
but that I think that would be relevant.

00:20:41.670 --> 00:20:42.338 There were some Grade 3 infections,
about 12%,
most of them being respiratory tract
infections and they don’t separate out,
you know, the viruses from the bacteria,
but that I think that would be relevant.

00:20:42.338 --> 00:20:44.342 There were some Grade 3 infections,
about 12%,
most of them being respiratory tract
infections and they don’t separate out,
you know, the viruses from the bacteria,
but that I think that would be relevant.

00:20:44.342 --> 00:20:46.358 There were some Grade 3 infections,
about 12%,
most of them being respiratory tract
infections and they don’t separate out,
you know, the viruses from the bacteria,
but that I think that would be relevant.

00:20:46.360 --> 00:20:48.810 There were some Grade 3 infections,
about 12%,
most of them being respiratory tract
infections and they don’t separate out,
you know, the viruses from the bacteria,
but that I think that would be relevant.

00:20:48.810 --> 00:20:50.290 There were some Grade 3 infections,
about 12%,
most of them being respiratory tract
infections and they don’t separate out,
you know, the viruses from the bacteria,
but that I think that would be relevant.

00:20:50.290 --> 00:20:53.706 Especially in the era of a pandemic.
So it seems to be fairly toggled. They did. One thing to note, they did allow for very flexible dose reductions, even for Grade 1 toxicity to allow patients to continue on treatment for longer. So in conclusion, I think these type of single ARM studies can serve as comparators for future randomized studies and of course balancing the efficacy and toxicity in this patient population. Now the last study I’m going to go into, I’m going to shift gears to a different subtype of high risk patients and these are the functional...
high risk myeloma and these are not

the patients you know that they’re

high risk when you first see them,

they demonstrate themselves

because they or they relapse early.

patients who have early relapse

after transplant within one year

have horrible prognosis.

You see here 26 months overall

survival compared to 91 months

after transplant within one year

if you didn’t have this early.

About relapse,

So what this Karma 2A study analyzed

the use of either cell or abukuma,

which is the first CMA directed
They used it in this patient population. The inclusion criteria includes elaps 18 months after initiation of frontline therapy. And you had to have revilement based maintenance. The primary endpoint was a CR and secondary endpoints include duration of response, progression free survival and toxicity. So patient characteristics are presented here, few things to highlight in terms of high risk features. There were 32% high risk disease in
this functionally high risk patients.

There were 40% with missing data.

It they did have information about their response to upfront therapy

and 24% of the patients have CR to their first line of therapy.

Most patients have progression of disease within 12 months of transplant and no patients were refractory to an anti CD 38 like there are two now.

This is the efficacy data.

The CRH which I think is the most relevant in terms of the response rate is 45%.

Just put here in Gray,
this agent in the relapse that heavily pretreated population which is 33%? Just like the other car T products, we see the deeper response, the longer duration of response. Overall, the median duration of the responder responding patients was 15 months, but if you had a CR then it goes to 23 months and if you had a PR for example, it's as short as three months. So really depth of response is extremely important. PFS is roughly a year, so 11 months here which is quite similar to what was seen in the relapse refractory patient population and
you know I think again this includes all those non responders as well.
I think it would be interesting to see the PFS for those who are responding.
In terms of toxicity, there was initial concern that when you’re using these cartee products earlier in the line of treatment that the T cells might be fitter, they might be healthier and actually have higher toxicities like CRS and the neurotoxicity icams, but they didn’t see that in this study. So there were roughly the same amount of percentage of events in
the CRS and the neurotoxicity group as was seen in the prior study and actually there were lower. Or at least numerically lower number of high grade events like grade 3/4 in both groups compared to the prior study. I do want to mention infections is still an issue of post party. There was a grade 3-4 infections at 22% and in fact 2 deaths from this with pneumonia and another from studemont sepsis. So in conclusion, in this functionally high risk patient population, either cell achieved 45% CR rates and this was higher than what was
seen in the first line of therapy.
For these patients. It seems that there are less grade 3-4 toxicities compared to the relapse refractory population. The PFS seems similar to what was seen in the heavily pretreated population, but these patients are very high risk, they are very difficult to treat and salvage so. I think we really need randomized study to see what is the best treatment for these patients and ideally identify those that have a CR rate.
00:25:29.780 --> 00:25:33.140 So I want to close with this one last slide.
NOTE Confidence: 0.909416426
00:25:33.140 --> 00:25:35.300 This is what I think is the future.
NOTE Confidence: 0.909416426
00:25:35.300 --> 00:25:37.844 It’s this risk adaptive therapy directed
NOTE Confidence: 0.909416426
00:25:37.844 --> 00:25:40.180 according to response type of study.
NOTE Confidence: 0.909416426
00:25:40.180 --> 00:25:42.700 This is the radar study that was presented
NOTE Confidence: 0.909416426
00:25:42.700 --> 00:25:44.928 by Doctor Wong from the UK don’t want
NOTE Confidence: 0.909416426
00:25:44.928 --> 00:25:47.314 to go into the details of all this is
NOTE Confidence: 0.909416426
00:25:47.314 --> 00:25:49.748 a busy slide but the concept here is
NOTE Confidence: 0.909416426
00:25:49.748 --> 00:25:52.004 extremely important that you separate out
NOTE Confidence: 0.909416426
00:25:52.004 --> 00:25:54.478 the standard risk from the high risk,
NOTE Confidence: 0.909416426
00:25:54.480 --> 00:25:55.140 high risk patients.
NOTE Confidence: 0.909416426
00:25:55.140 --> 00:25:56.680 We don’t want to stop treatment on,
NOTE Confidence: 0.909416426
00:25:56.680 --> 00:25:58.660 we need better treatments standard
NOTE Confidence: 0.909416426
00:25:58.660 --> 00:25:59.848 risk that have.
NOTE Confidence: 0.909416426
00:25:59.850 --> 00:26:02.482 MRD negative disease can maybe even stop
NOTE Confidence: 0.909416426
00:26:02.482 --> 00:26:03.984 treatment and standardized patients
who don’t achieve MRD negativity

how is how are we going to deepen

how are we going to get them together MRD negative state

so you know when and randomizing doing a randomized fashion so.

The this and other type studies like

this are ongoing and I think the next

decade hopefully we’ll have an answer to

how to personalize treatments for myeloma.

And with that I will close my section of the

talk and we’ll move on to Doctor Brownings.

OK, great. Well, thank you Doctor

and welcome again everyone.

My name is Sabrina Browning and with the
remainder of our time that we have left, I'm going to review with you data on relapse refractory myeloma and we'll also briefly touch upon a new therapeutic in light chainer ALE amyloidosis. And I have no disclosures to report. So a major focus in myeloma at Ash this year was the diverse and advancing immunotherapeutic landscape for relapse and refractory disease. And as you all are familiar B cell maturation antigen or BCM A has been a critical target on myeloma cells. And as Doctor Barr mentioned we now have two approved anti BCM a car T cell products eye to cell and cell
00:27:22.537 --> 00:27:24.633 to cell as well as an anti BCM A

00:27:24.633 --> 00:27:26.348 by specific antibody articles amab

00:27:26.348 --> 00:27:28.869 and while I won’t cover this today.

00:27:28.870 --> 00:27:30.928 There was promising early phase data

00:27:30.928 --> 00:27:33.019 presented on the combination of teclis

00:27:33.019 --> 00:27:34.679 tamal with daratumumab and Lenalidomide

00:27:34.679 --> 00:27:36.398 and there are other combinations

00:27:36.398 --> 00:27:38.390 with this by specific antibody that

00:27:38.390 --> 00:27:40.080 are also actively being studied.

00:27:40.080 --> 00:27:43.274 As well as the number of new BCM ART

00:27:43.274 --> 00:27:45.139 invites but importantly the abstracts

00:27:45.139 --> 00:27:47.924 that I will focus on today with with

00:27:47.924 --> 00:27:50.312 you all highlight some T cell to

00:27:50.312 --> 00:27:51.876 redirection therapiess that harness

00:27:51.876 --> 00:27:53.970 new myeloma cell antigen targets.

47
And these include G protein coupled receptor family C Group 5 member D or what’s referred to as GPRC 5D and SC receptor homologue 5 or FCR H5 as well as some non cellular therapies that help reverse tumor mediated immune paralysis that occurs in myeloma, and these include the novel cereblon, Eli Gaze modulators, or what is referred to as cell months. So to start we will discuss the phase two results from the monumental one study which represented by Doctor Ajai Chari and this evaluates talked amab. Talked Amab is a first in class T cell bispecific antibody that targets GPRC 5D.
And as previously discussed this is highly expressed on myeloma cells and thought to have limited expression on normal cells and that includes hematopoietic stem cells and in December of this past year the phase one data from the monumental study were published in the New England Journal and demonstrated an impressive overall response rate of 64 to 70% with both weekly and every other weekly dosing. And so for the phase two portion of the study, patients had to have an ECOG of zero to two with measurable disease and
three or more lines of prior therapy.

And this included a PROTEOSOME inhibitor, an imid and an anti CD 38 antibody.

And the three cohorts in this portion of the study that you see outlined here included a 0.4 milligram subcutaneous dosing and 122 patients enrolled in this. In this group 0.8 milligrams per kilogram every other week subcutaneous dosing where 109 patients were enrolled. In this group 0.8 milligrams per kilogram every other week subcutaneous dosing where 109 patients were enrolled. And then a third group of patients who had received prior T cell redirection therapy and were administered either of the two mentioned dosing schedules.
And the aim of this study was to assess the efficacy and safety of this novel agent. And so the table on the left here on the slide outline some of the key patient and disease characteristics from the phase two cohorts of this study. Median age was 67 and 8.4% of the 0.4 milligram per kilogram group and 6.2% of the 0.8 kilogram milligram per kilogram group were black or African American. And as one would expect in a heavily pretreated population with an average of five prior lines of therapy high risk features including extramedullary disease. High risk cytogenetics and iss stage.
three diseases were observed in about 1/4 to 1/3 of patients as documented here in the table and approximately 3/4 of the patients have triple class refractory disease. However despite this population again with high risk disease and there wasn’t an impressive overall response rate as seen in the figure here on the two dosing. Groups and VGPR are better was achieved in approximately 60% of patients which also indicates a high depth of response with this agent. These responses were maintained across subgroups except for those.
NOTE Confidence: 0.818111631724138
00:31:02.533 --> 00:31:04.277 with Extramedullary disease where
NOTE Confidence: 0.818111631724138
00:31:04.277 --> 00:31:06.893 the overall response rate was reduced
NOTE Confidence: 0.818111631724138
00:31:06.954 --> 00:31:09.062 some at 50% and responses were rapid
NOTE Confidence: 0.818111631724138
00:31:09.062 --> 00:31:11.538 with the median time to response of
NOTE Confidence: 0.818111631724138
00:31:11.538 --> 00:31:13.650 a little over a month and a median
NOTE Confidence: 0.818111631724138
00:31:13.650 --> 00:31:16.046 time to best response of approximately
NOTE Confidence: 0.818111631724138
00:31:16.050 --> 00:31:18.150 2.5 months and thus far responses
NOTE Confidence: 0.818111631724138
00:31:18.150 --> 00:31:19.550 have also been durable.
NOTE Confidence: 0.818111631724138
00:31:19.550 --> 00:31:21.752 Of the median progression free survival
NOTE Confidence: 0.818111631724138
00:31:21.752 --> 00:31:24.674 at the time of presentation was 7.5
NOTE Confidence: 0.818111631724138
00:31:24.674 --> 00:31:27.026 months and 11.9 months in the 22 cohorts
NOTE Confidence: 0.818111631724138
00:31:27.026 --> 00:31:29.294 with a median duration of of response
NOTE Confidence: 0.818111631724138
00:31:29.294 --> 00:31:31.677 that was not reached in patients who
NOTE Confidence: 0.818111631724138
00:31:31.677 --> 00:31:33.765 had achieved a complete response or
NOTE Confidence: 0.818111631724138
00:31:33.765 --> 00:31:35.920 better and median overall survival was
NOTE Confidence: 0.818111631724138
00:31:35.920 --> 00:31:38.739 not reached for the study cohort to date.
NOTE Confidence: 0.818111631724138
00:31:38.740 --> 00:31:40.864 Importantly for the patients who had
NOTE Confidence: 0.818111631724138
00:31:40.864 --> 00:31:42.862 received prior T cell redirection
NOTE Confidence: 0.818111631724138
00:31:42.862 --> 00:31:44.905 therapy which included 70%,
NOTE Confidence: 0.818111631724138
00:31:44.905 --> 00:31:47.815 seventy .6% of patients who had
NOTE Confidence: 0.818111631724138
00:31:47.815 --> 00:31:50.181 received prior car T and 35.3%.
NOTE Confidence: 0.818111631724138
00:31:50.181 --> 00:31:52.467 Would have received prior by specific.
NOTE Confidence: 0.818111631724138
00:31:52.470 --> 00:31:54.595 The overall response rate was
NOTE Confidence: 0.818111631724138
00:31:54.595 --> 00:31:56.320 still high at 62.7%.
NOTE Confidence: 0.818111631724138
00:31:56.320 --> 00:31:59.470 Responses were higher in those that received
NOTE Confidence: 0.818111631724138
00:31:59.470 --> 00:32:02.509 prior car T compared to buy specifics,
NOTE Confidence: 0.818111631724138
00:32:02.510 --> 00:32:04.659 although the number of patients in in
NOTE Confidence: 0.818111631724138
00:32:04.659 --> 00:32:06.944 the study that received prior price by
NOTE Confidence: 0.818111631724138
00:32:06.944 --> 00:32:09.309 specifics was small with an end of 18.
NOTE Confidence: 0.855970994347826
00:32:12.000 --> 00:32:13.830 It’s important to consider safety
NOTE Confidence: 0.855970994347826
00:32:13.830 --> 00:32:16.420 for this agent given its novel target
as we discussed and fortunately as you can see outlined here, high grade adverse events were uncommon but when they were present they were mostly hematologic in nature. And with that being said, still there was less than 1/3 of patients that had high grade heme toxicities that had high grade heme toxicities and most of the toxicity was limited to the first few cycles of treatment. High grade infections were also uncommon in this study and as you can see that included a low number of opportunistic infections.

COVID infections occurred in
approximately 10% of patients with COVID and actually only two deaths from COVID and actually 0 deaths reported in the phase one portion that was published in the New England Journal back in December. As mentioned, rates of IVIG use were also relatively low with with less severe and this is somewhat distinct from our anti BCM a targeted by specific antibodies that are now in utilization. The most common adverse events were cytokine release syndrome or CRS as well as altered taste.
Or discuss Jia skin and nail related events as well and the. The CRS events appear to be restricted largely to step up dosing and full first full dose with a median time to onset of two days immune effector cell associated neurotoxicity or what we refer to as icans occurred in about 10 to 11% of patients, but again we’re mostly low grade.

So in conclusion, tell Ketama B which is a first in class by specific antibody again targeting novel GPRC 5D on myeloma cells demonstrated an impressive
00:33:57.736 --> 00:33:59.555 overall response rate of more than
NOTE Confidence: 0.855970994347826
00:33:59.555 --> 00:34:02.165 70% in patients with heavily pretreated
NOTE Confidence: 0.855970994347826
00:34:02.165 --> 00:34:04.057 relapsed and refractory myeloma.
NOTE Confidence: 0.855970994347826
00:34:04.060 --> 00:34:05.962 And high overall response rates were
NOTE Confidence: 0.855970994347826
00:34:05.962 --> 00:34:08.302 also seen in those who had received
NOTE Confidence: 0.855970994347826
00:34:08.302 --> 00:34:09.977 prior T cell redirection therapy
NOTE Confidence: 0.855970994347826
00:34:09.977 --> 00:34:12.154 which is an important cohort to
NOTE Confidence: 0.855970994347826
00:34:12.154 --> 00:34:14.039 learn more about responses have
NOTE Confidence: 0.855970994347826
00:34:14.039 --> 00:34:15.889 been durable and the agent.
NOTE Confidence: 0.855970994347826
00:34:15.890 --> 00:34:17.785 Because generally been overall well
NOTE Confidence: 0.855970994347826
00:34:17.785 --> 00:34:20.111 tolerated with CRS that seems to
NOTE Confidence: 0.855970994347826
00:34:20.111 --> 00:34:21.956 be manageable and fewer infections.
NOTE Confidence: 0.855970994347826
00:34:21.960 --> 00:34:24.258 Although it does have unique safety
NOTE Confidence: 0.855970994347826
00:34:24.258 --> 00:34:26.182 profile and those include things
NOTE Confidence: 0.855970994347826
00:34:26.182 --> 00:34:28.108 like skin and nail related events
NOTE Confidence: 0.855970994347826
00:34:28.108 --> 00:34:30.930 as well as taste alteration or dusia
58
As previously mentioned, although these were generally managed with supportive care and there was a low overall rate of discontinuation due to the adverse events and therefore there are additional studies that are now ongoing to looking at the look at talked amab both in combination. In combination with a variety of different anti myeloma agents. And so next I want to briefly share the following abstract. This was presented by Doctor Jesus Berdeja and this is now a novel car T cell therapy therapy that’s
targeting GPRC 5D and this has a this car T construct as seen in the figure here on the right. And this data came from a phase one multicenter open label study with three or more prior lines of therapy and prior BCMA therapy was allowed, there were five dose levels that were ranging from 25 to 450 million car T cells and thus far the state the overall safety and efficacy have profiles have been favorable.
Treatment emergent adverse events were seen in close to 88% of patients and 73% of patients had grade 3 or 4 adverse events. And in comparison to Cal tamag, hematologic adverse events and particularly neutropenia and thrombocytopenia. Thrombocytopenia seemed to be more common with a dose limiting toxicity of prolonged grade 4 neutropenia and thrombocytopenia in two patients. Again CRS was the most common non hematologic. Reverse advent at 63.6% and the median time to onset with this cartee was three days.
Although grade three and four CRS events were only observed in 6% of patients. Icans was infrequent with only two patients and was reversible in both instances. Instances with steroid treatment, again because of the GPR, the unique target that this car T targets there were skin and nail related. Adverse events as well as taste alterations, but these seem to be less common than talked amab and all were low grade and the majority did not require any sort of treatment. The maximum tolerated dose has not yet been exceeded in this study and
there have been no deaths thought to be related to study treatment. Importantly, the overall response rate of the total cohort was high at 89.5% with a complete response rate of 47.4. Percent and there were four patients that were evaluated for minimal residual disease or MRD and all four of those were MRD negative. So in conclusion, responses with this novel cartee seem durable and seem to deepen over time, making this a promising approach.
treatment moving forward, including in those patients that are already exposed to BCM a treatment. The next abstract that I will present was discussed by Doctor Susan Trudell and it looked at 1 cohort in a safety and efficacy trial of savasta amab and SAVASA. Amab is a bispecific antibody seen here on the right that targets yet another new myeloma antigen known as FC RH Five which again is exclusively expressed in B cell lineage and is thought to be near ubiquitous on myeloma cells and at ASH in 2021 there was initial data presented.
On the phase one dose finding study of savasta mab and revealed a favorable efficacy and safety profile in those patients with heavily pretreated relapsed and refractory myeloma. This year's abstract reviews reviewed a cohort in this study who received a single dose of the IL 6 receptor blocker to Solus amount at 8 milligrams per kilograms. And and this was given 2 hours prior to the first of Austin maps step up dose which is 3.6 milligram and these patients were then compared retrospectively. To a previously enrolled group who
00:38:37.890 --> 00:38:39.930 did not receive tocilizumab and the
did not receive tocilizumab and the
NOTE Confidence: 0.810628541333333
00:38:39.930 --> 00:38:41.802 objective which was based on preclinical
objective which was based on preclinical
NOTE Confidence: 0.810628541333333
00:38:41.802 --> 00:38:43.893 data was to determine whether there’s
data was to determine whether there’s
NOTE Confidence: 0.810628541333333
00:38:43.893 --> 00:38:45.999 this would reduce the the frequency
this would reduce the the frequency
NOTE Confidence: 0.810628541333333
00:38:46.000 --> 00:38:47.986 of cytokine release syndrome or CRS
of cytokine release syndrome or CRS
NOTE Confidence: 0.810628541333333
00:38:47.986 --> 00:38:50.197 which as we’ve discussed now in several
which as we’ve discussed now in several
NOTE Confidence: 0.810628541333333
00:38:50.197 --> 00:38:52.129 abstracts is one of the most common
abstracts is one of the most common
NOTE Confidence: 0.810628541333333
00:38:52.185 --> 00:38:54.060 adverse event with bispecific antibody
adverse event with bispecific antibody
NOTE Confidence: 0.810628541333333
00:38:54.060 --> 00:38:56.387 treatment and it’s thought to be
treatment and it’s thought to be
NOTE Confidence: 0.810628541333333
00:38:56.387 --> 00:38:59.516 mediated by IL sex and other cytokines.
mediated by IL sex and other cytokines.
NOTE Confidence: 0.810628541333333
00:38:59.520 --> 00:39:01.833 And as you can see here on the the
And as you can see here on the the
NOTE Confidence: 0.810628541333333
00:39:01.833 --> 00:39:03.816 bottom savasa amab is its administered
bottom savasa amab is its administered
NOTE Confidence: 0.810628541333333
00:39:03.816 --> 00:39:05.860 with a single step up dose.
with a single step up dose.
NOTE Confidence: 0.810628541333333
00:39:05.860 --> 00:39:07.780 Initially at 3.6 milligrams and then
Initially at 3.6 milligrams and then
NOTE Confidence: 0.810628541333333
00:39:07.780 --> 00:39:10.149 to a target dose of 90 milligrams,
to a target dose of 90 milligrams,
NOTE Confidence: 0.810628541333333
00:39:10.150 --> 00:39:12.046 and it’s given intravenously
and it’s given intravenously

66
00:39:12.046 --> 00:39:13.468 every three weeks.

00:39:16.460 --> 00:39:19.729 So 31 patients were enrolled in the total amount pretreatment arm with

00:39:21.716 --> 00:39:24.304 44 patients in the comparator arm and

00:39:24.304 --> 00:39:26.509 in both groups as you can see in the table here on the left included heavily

00:39:26.570 --> 00:39:29.314 pretreated patients with a median time,

00:39:29.314 --> 00:39:31.504 excuse me, a median line of therapies

00:39:31.504 --> 00:39:33.820 being four and six respectively with

00:39:33.820 --> 00:39:35.924 fairly similar patient and disease characteristics except for those that

00:39:35.924 --> 00:39:37.959 I've highlighted for you here on the in

00:39:37.959 --> 00:39:39.916 the tocilizumab pretreatment group did.

00:39:42.084 --> 00:39:44.349 the table on the left and as you can see

00:39:44.349 --> 00:39:46.567 the tocilizumab pretreatment group did.

00:39:47.906 Have somewhat less extramedullary
disease as well as less penta,
NOTE Confidence: 0.84287700875

refractory penta drug refractory disease and
NOTE Confidence: 0.84287700875

event in the tocilizumab are arm.
NOTE Confidence: 0.84287700875

received prior anti BCM cell therapy
NOTE Confidence: 0.84287700875

the most commonly observed adverse
NOTE Confidence: 0.84287700875

events in both groups were neutropenia,
NOTE Confidence: 0.84287700875

anemia, thrombocytopenia and CRS and of
NOTE Confidence: 0.84287700875

no neutropenia which is a known side
NOTE Confidence: 0.84287700875

effect of tocilizumab with significantly
NOTE Confidence: 0.84287700875

higher in the Tosi pre treatment group,
NOTE Confidence: 0.84287700875

but was said by the authors to be
NOTE Confidence: 0.84287700875

reversible and manageable with growth.
NOTE Confidence: 0.84287700875

Doctor um when appropriate and this did
NOTE Confidence: 0.84287700875

not lead to Savasta Amab discontinuation.
NOTE Confidence: 0.84287700875

The infection rate was also reportedly
NOTE Confidence: 0.84287700875

higher than the comparator arm,
although compared to other cohorts in the study there was a similar infection rate and grade three infections also occurred at a similar rate between these two study groups. And as you can see in the figure, the overall rate of CRS was significantly lower in the Tosi Pre treatment group at 38.7%. Compared to the non Tosi group, CRS was limited to grade one and Grade 2 events in both, with the median time to onset of one day.
And the beneficial effects of Tosi on CRS were continued with subsequent doses in cycle one. In the tocilizumab pretreatment arm, I can’t was seen in frequently in both groups occurred in only two patients in the Tosi arm and six patients in the non-toxic arm and interestingly the authors demonstrated in the toasty Pretreatment arm that after the 1st 3.6 milligrams of fastmac dose, there were higher peak levels of IL 6 which were hypothesized to be due to inhibition of IL 6 clearance by the tocilizumab. However,
there was also near complete suppression of CRP which is produced by IL 6 receptor binding and thereby suggesting that there was effective blockade or blockage of the IL 6 inflammatory signal signaling pathway, also importantly pretreatment with tocilizumab. Did not appear to negatively impact clinical response rates with an overall response rate rate of 54.8% and a very good partial response. And that was compared to an overall rate of 32.3% observed in the Tosi group.
response rate of 37.2% and VG, VG PR or better of 25.5% in the non-toxic arm and median time to best response as well as median duration of response was similar between the two groups. So in conclusion, pretreatment with a single dose of tocilizumab prior to the initiation of savasa significantly reduced the rate of CRS in patients with relapsed refractory myeloma likely thought to be through suppression of the IL 6 signaling pathway, but did not seem to negatively impact the
anti myeloma activity of this Asia agent. And so the authors noted that two salesman may may play an important future role in CRS mitigation as pre dosing and may potentially help us move. By specific treatment to the outpatient setting. The next abstract was presented by Doctor Paul Richardson and this was on amazing amide or what? What’s referred to as Messi was on amazing amide or what? What’s referred to as Messi and Messi is a potent novel. Sarah Blunt Eli Gaze modulator or what we know as a cell mod and this was looked at in combination with dexamethasone.
In this abstract Messi is an oral agent and as could be seen in the figure here, it binds and activates Sarah blown and it leads to what happens is it leads to maximal degradation. Of important transcription factors and that includes ICAROS and ilos that are both really important in myeloma pathophysiology and pathobiology. And this results in enhanced myeloma cell killing and immune stimulatory activity when compared to our common immunomodulatory drugs such as Lenalidomide. And in this phase one two trial, Messi was evaluated alone and in combination with dexamethasone and
00:43:49.697 --> 00:43:51.785 the recommended phase two dose for Messi was selected at 1 milligram daily for 21 days.

00:43:51.785 --> 00:43:54.107 Out of a 28 day cycle with a notable overall response rate in the phase one portion of 54.5% and to be eligible for the phase two dose.

00:44:00.515 --> 00:44:05.930 Again prior exposure to CMA therapy was allowed and dexamethasone was.
administered at 20 to 40 milligrams.

Dependent on age in combination with Mezzi, the main objectives of the study included advocacy and safety of this novel combination.

So 101 patients were included in the MEZZI plus DEX cohort and their patient and disease characteristics are outlined in the table on the left. Median age as expected was 67 years and these were heavily pretreated patients with a median time since initial diagnosis of myeloma of 7.44 years, a median of 6 lines of prior treatment and 100% of patients were triple class refractory.
There were only approximately 20% of patients with Stage three disease although 39.6% had extramedullary disease and this included in in their study soft tissue bone related plasmacytoma in addition to true soft tissue. 36.6% of patients had high risk cytogenetics 29.7% of patients had received prior anti BCMH treatment mostly in the form of antibody drug conjugates. And in terms of clinical activity, as you can see on the figure.
the overall response in the total population of what’s 40.6% with a high quality responses that included a stringent CR complete response and VGPR. And in those with Extramedullary disease overall response rate was still notable at 30% and patients who had received anti BCH treatment although small in number with 30 patients. Portal had an overall response rate of 50% and while follow-up is short to date, the median progression free survival observed was 4.4 months and median duration of response was 9.2 months when patients achieved VGPR better. And Doctor Richardson presented some
correlative data from this abstract as well, showing that Messi is active in patients who are either refractory to pomalidomide or POMALYST and in those receiving pomalidomide as in their last regimen. As their last regimen of treatment. At a median follow-up of 7.5 months, 90.1% of patients had discontinued treatment, although the majority due to progressive myeloma. 5 patients were reported to have adverse events. Related events, 5 patients were reported to have
adverse event related deaths,
including two with PJP pneumonia,
an additional with pneumonia and
one due to COVID-19 infection
And while a majority of patients did require
dose interruptions due to adverse events.
Those reductions were less common and a few patient,
a few patients discontinued
drug due to adverse events as is
outlined here and as you can see
in the tables here on the bottom,
treatment emergent adverse events
were primarily hematologic in
nature with neutropenia being the
most common although this was felt to be manageable again with those adjustments and growth factor support. Additionally infections were the most common non hematologic adverse event with infections of any grade seen in about 2/3 of patients. Other observed side effects are listed here in the tables, although they were less common and less severe. So to summarize, Mazda Magnemite or Messi is an oral potent novel cell mod which in preclinical studies has a distinct
profile from our immunomodulatory agents. And when combined with dexamethasone overall response rate was notable at 40.6% in the total cohort and 30% in patients with extramedullary disease, the safety profile. Is manageable with most higher grade adverse events being hematologic in nature and most commonly neutropenia which did require some dose adjustments and GCF support when needed. Given these findings, Mezi is now being evaluated in combination with standard myeloma therapies including in phase three trials with Bortezomib and carfilzomib.
and this appears to be a promising agent in patients with heavily pretreated relapsed refractory myeloma including those who may be refractory to imids including POMALYST.

So I'll shift gears a bit now with this last abstract and discuss like Chainer ALE amyloidosis, which as you guys likely know is a rare progressive disorder where clonal plasma cells in the bone marrow produce immunoglobulin light chains that misfold and then form amyloid fibrils that become insoluble and deposit in
extracellular tissues and organs resulting in significant dysfunction.
And we have made advances in the treatment of AL amyloid with exciting data from last year’s ASH on the Andromeda trial.
Uh which showed improved team hematologic and organ responses with the addition of daratumumab to cytarabine.
However, these available therapies target the clonal plasma cells in order to stop or halt production of light chains, but they don’t address the amyloid that’s already been deposited in organs that lead to significant morbidity.
And in patients with advanced cardiac disease, high mortality with a median overall survival in patients with Mayo stage four disease of only 5.8 months. We’ll discuss was presented by Doctor Morie Gertz from the Mayo Clinic on Beartown bertam amount, which is a humanized monoclonal antibody administered intravenously every 28 days and binds conserved epitopes on both Kappa and Lambda immunoglobulin light chains and that leads to neutralization of circulating.
light chain aggregates as well as depletes the insoluble amyloid deposited in the organ organs thought to be through phagocytosis by macrophages. And the study schema here on the top outlines the phase three vital study which is a multi center double-blind placebo-controlled trial in patients with newly diagnosed treatment naive AL amyloid. All patients enrolled had cardiac involvement and were stratified by Mayo stage, renal stage and six minute walk test. 260 patients total were enrolled and randomized to receive birtamod and birentuzumab in addition to standard of care.
or placebo with standard of care.
There was an interim futility analysis back in 2018. That actually resulted in early study termination given concern that the primary endpoint which was all cause mortality or time to all cause mortality would not be met in a reasonable amount of time. And so afterwards a post hoc analysis was performed on 77 patients that had Mayo Stage 4 cardiac amyloid. And this has previously been reported to show as you can see in the Kaplan Meier curve here a survival.
00:51:06.645 --> 00:51:08.169 benefit with significant reduction
NOTE Confidence: 0.85525948
00:51:08.169 --> 00:51:10.455 in time to all cause mortality
NOTE Confidence: 0.859358008
00:51:10.460 --> 00:51:13.900 in this cohort. With 74% of patients
NOTE Confidence: 0.859358008
00:51:13.900 --> 00:51:15.970 in the Bertambah group being alive
NOTE Confidence: 0.859358008
00:51:15.970 --> 00:51:18.344 at month nine with only compared to
NOTE Confidence: 0.859358008
00:51:18.344 --> 00:51:21.197 only 49% in the placebo arm with the
NOTE Confidence: 0.859358008
00:51:21.197 --> 00:51:23.839 hazard ratio that you see listed here.
NOTE Confidence: 0.859358008
00:51:23.840 --> 00:51:25.820 So in this year’s abstract Dr.
NOTE Confidence: 0.859358008
00:51:25.820 --> 00:51:27.480 Gerson is coauthors showed using
NOTE Confidence: 0.859358008
00:51:27.480 --> 00:51:29.906 the data from the post hoc analysis
NOTE Confidence: 0.859358008
00:51:29.906 --> 00:51:32.006 that reduction in time to all
NOTE Confidence: 0.859358008
00:51:32.006 --> 00:51:33.679 cause mortality at nine months.
NOTE Confidence: 0.859358008
00:51:33.680 --> 00:51:35.660 I’m favoring the pertama amab arm
NOTE Confidence: 0.859358008
00:51:35.660 --> 00:51:37.720 persisted in these Mayo stage four
NOTE Confidence: 0.859358008
00:51:37.720 --> 00:51:39.425 patients ever even after adjusting
NOTE Confidence: 0.859358008
00:51:39.425 --> 00:51:41.505 for a variety of demographic
and disease characteristics.

As you can see in the forest plots here that come from small numbers but have again impressive hazard ratios.

There was also in the post tech analysis.

Patients who received Birtamod had less deterioration in quality of life and improved 6 minute walk test.

And so with the available data for Tim Amab has been safe and well tolerated even in these patients with advanced cardiac disease and it has this data has served as the foundation for the Affirm ALS trial and we have this trial open here.
at Yale as well as in a number of our care centers in Trumbull. Saint Francis and a female is looking to enroll patients with newly diagnosed treatment naive al amyloid with Mayo stage four disease and looking again to see if we see this survival benefit that was demonstrated in the post hoc analysis. And patients will be randomized 2 to one to receive vertamae in addition to standard care. And I do think this is an incredibly important trial for a very hard to treat population and I
00:52:54.108 --> 00:52:56.138 would be happy to talk with anybody.

00:52:56.140 --> 00:52:58.642 Interested who might have eligible patients

00:52:58.642 --> 00:53:01.248 or have questions about the trial?

00:53:01.250 --> 00:53:02.454 So, in summary,

00:53:02.454 --> 00:53:04.725 we saw many exciting abstracts at ASH

00:53:04.725 --> 00:53:07.155 looking at new myeloma target antigens

00:53:07.155 --> 00:53:08.998 from biospecific antibodies and car

00:53:08.998 --> 00:53:10.979 T as well as abstract looking at

00:53:10.979 --> 00:53:12.806 improved manufacturing and management

00:53:12.806 --> 00:53:15.366 of side effects including CRS.

00:53:15.370 --> 00:53:17.660 I I will end so that we can move to

00:53:17.735 --> 00:53:20.021 the questions and answers by just

00:53:20.021 --> 00:53:22.530 saying that although not covered today,

00:53:22.530 --> 00:53:24.700 there were up to 30 abstracts on

NOTE Confidence: 0.859358008
looking at health disparities in multiple myeloma which remains really a critical unmet need and ongoing. Investigation is really imperative. The QR code I've included here links to a video by Doctor Joel McHale and the International Myeloma Foundation addressing some of these really important abstracts. So thank you again all for your time and I look forward to answering some questions. Thank you Sabrina and Nofar Thank you Sabrina and Nofar for those excellent reviews. We do have time for questions, so I would encourage everyone to please place your questions,
if you have any in the Q&A portion that can be found below in the screen.

As we wait for questions, I will start by asking a few.

Maybe we’ll start with Elon and Natalia.

We heard a lot about side effects from the bispecific T cell engagers, the cartes and even the cell mods in relationship to infections. So how would you propose we manage that risk to help keep our patients safe as these therapies move forward? I mean I guess I can start. We know that there’s a risk of hypogammaglobulinemia with this patient.
So I think that keeping a close signing IG level, making sure that it’s you know consistently at least 400 or even 500 compliance with you know antiviral anti microbial prophylaxis and I think also just educating you know the various colleagues. And members of the community and the oncology team about the, you know, the risk for infection complications in these novel agents. I think they tell you you’re a mute. Help, you’re still muted. And. Natalia, you were still on mute. So unfortunately we’re not been
able to hear what you have said.

And we can move on. We did have one question from the audience which is asking if calcium deficiency is seen in multiple myeloma.

Umm. I don’t know if anyone wants to take the question regarding calcium and multiple myeloma. I mean I think that usually with myeloma we see hypercalcemia and I think if it’s poorly controlled we can see hypercalcemia. You know the bisphosphonates and the bone modifying agents can cause hypocalcemia,
Thank you, Elon.

So I may ask a question that’s a little bit unfair to the group. And we can have each of the panelists answer with all of these new targets and they relapsed refractory setting. How do you propose that we sequence them and most of these studies have been done after potentially BCM a. But again, I would be interested in everyone’s thoughts as far as they’re optimal. And maybe we can start with Elon and Natalia and then go to no farms, Sabrina.

Another Natalia sorted out her mute option, but. I guess not.
So I think obviously that’s an ongoing area of evaluation and research with these novel agents. We are looking at them in earlier lines of therapy, you know in clinical trials, cartoon etcetera. I think that it depends on a couple of factors. You know how did the patients respond to prior treatments, what prior treatments have they had. You know, high risk, standard risk,
data is pretty encouraging and promising for biospecifics and cartes. So I think that. You know, if they’re candidates for that, we should try to push for that. But a lot, a lot will be. Coming and we’ll have a lot more information in the upcoming, you know, months and annual meetings. Thank you, Ellen, and no far Sabrina. Yeah. So I think at the end of the day the answer is we don’t know as effective and we don’t really know which subtypes of patients would do better. But we do have some information that
00:58:23.907 --> 00:58:25.999 patients who have gained 1Q have high expressions of the FC RH 5.

00:58:25.999 --> 00:58:28.197 So perhaps you know being a little bit more specific in terms of patient selection to some of these again more studies really need to be done in subgroup.

00:58:31.420 --> 00:58:34.120 I think it is encouraging that the infection risk is is lower with tell kalamas supposed to Tequesta amab.

00:58:34.120 --> 00:58:36.663 So for patients where you’re more worried about that maybe in a post transplant setting where you know there’s other additives infection complications.

00:58:39.468 --> 00:58:43.468 I think it is encouraging that the infection risk is is lower with tell kalamas supposed to Tequesta amab.

00:58:39.961 --> 00:58:43.468 I think it is encouraging that the infection risk is is lower with tell kalamas supposed to Tequesta amab.

00:58:46.813 --> 00:58:49.073 So for patients where you’re more worried about that maybe in a post transplant setting where you know there’s other additives infection complications.

00:58:49.080 --> 00:58:51.628 So for patients where you’re more worried about that maybe in a post transplant setting where you know there’s other additives infection complications.

00:58:51.628 --> 00:58:54.211 about that maybe in a post transplant setting where you know there’s other additives infection complications.

00:58:54.211 --> 00:58:56.353 about that maybe in a post transplant setting where you know there’s other additives infection complications.

00:58:56.360 --> 00:58:57.794 So I think more to come we don’t know.
You know, I would completely agree. You know, I think there’s a question of not only how to sequence our car T and by specifics, but now sequence in terms of targets. So, you know I agree with Doctor Barr that I think. You know thinking about choosing a carte or by specific I think depends a little bit on the patient’s disease at that time and the time that it may require for them to get the treatment. I think you know it’s exciting now to have different targets that do have a unique safety profile.
You know and I think a lot of these newer targets are showing response in patients who had prior BCM a cell therapy. So you know I think we have the most data obviously from our CMA products, but I think there are going to be patient populations where these new targets I think are going to be important and perhaps. You know, our first choice moving forward.
how do you see MRD driving transplant and sequencing of therapies in general? So I don’t know if Natalia or Nofar you have a response? Yeah, I can talk about this. So I think MRD is going to be driving how we treat patients. So I think what we see is in both of those studies, patients who are MRD negative just do better in the IM 2009. Just do better in the IM 2009. 30% of patients who had VRD in transplant and one year only one year maintenance still remain year maintenance still remain in remission 8 years after. So. So clearly we are over treating
some patients and we need to figure out who those patients are and I think even with transplant, right. So if we achieve MRD negativity with quadruplets, I think we need to assess this transplant better. What is the marginal benefit of transferring those patients? These studies are underway. We will find out, but it will take many years. Right now I, you know I do discuss costs, you know risk benefit with patients when I talk about transplant.
especially in standard risk MRD

negative patients as patients who

are considered that presumably

and relying.

And I'm sorry, I had difficulties

with odd earlier, but I

I do agree with what’s been said.

MRD does have a value and its primary

significances in predicting progression

free survival and overall survival.

So we do use it in practice

as a prognostic tool and with

enough data with more mature data, we,

we, we will most likely in the

future use the data to discontinue

certain patients with low risk cytogenetics
and durable sustained MRD negative state.

Hey, wonderful. Well, we are after time as it is one of three. So I will like to thank all of our panelists for their presentations and input today and thank you all for joining us. Please tune in next Friday for the next in the series. Have a good afternoon everyone.