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NOTE Confidence: 0.75584751375

00:00:00.000 --> 00:00:02.510 For joining this is Yale.

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00:00:02.510 --> 00:00:05.241 Highlights of ASH 2021 presented by

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00:00:05.241 --> 00:00:07.276 Yale Hematology and today’s seminar

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00:00:07.276 --> 00:00:09.526 is presented by the program for

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00:00:09.526 --> 00:00:10.898 multiple myeloma and Gammopathy’s,

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00:00:10.898 --> 00:00:12.926 and we have really fantastic set

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00:00:12.926 --> 00:00:14.505 of speaker presentations. Today.

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00:00:14.505 --> 00:00:17.895 Our program presented by Doctor Gore,

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00:00:17.900 --> 00:00:20.120 Shine our expert clinical expert

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00:00:20.120 --> 00:00:22.340 in hematology doctor Terry Parker,

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00:00:22.340 --> 00:00:24.626 who’s the clinical leader of our

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00:00:24.626 --> 00:00:26.150 program with extensive experience

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00:00:26.213 --> 00:00:28.118 and expertise in clinical trials.

NOTE Confidence: 0.75584751375
00:00:28.120 --> 00:00:29.404 Doctor no far bar.
NOTE Confidence: 0.75584751375
00:00:29.404 --> 00:00:31.009 Who's our expert in cellular?
NOTE Confidence: 0.75584751375
00:00:31.010 --> 00:00:32.906 Therapies and transplantation in
NOTE Confidence: 0.75584751375
00:00:32.906 --> 00:00:35.276 myeloma and doctor Sabrina Browning,
NOTE Confidence: 0.75584751375
00:00:35.280 --> 00:00:37.485 who has expertise in preclinical
NOTE Confidence: 0.75584751375
00:00:37.485 --> 00:00:39.249 studies and alloyed doses.
NOTE Confidence: 0.75584751375
00:00:39.250 --> 00:00:41.679 And I just like to share this
NOTE Confidence: 0.75584751375
00:00:41.679 --> 00:00:43.350 structure of today’s seminar.
NOTE Confidence: 0.75584751375
00:00:43.350 --> 00:00:45.865 First, Doctor Gore Shine will present
NOTE Confidence: 0.75584751375
00:00:45.865 --> 00:00:47.445 updates in smoldering multiple
NOTE Confidence: 0.75584751375
00:00:47.445 --> 00:00:49.870 myeloma and newly diagnosed myeloma.
NOTE Confidence: 0.75584751375
00:00:49.870 --> 00:00:51.940 This will be followed by Doctor
NOTE Confidence: 0.75584751375
00:00:51.940 --> 00:00:53.800 Terry Parker with updates in
NOTE Confidence: 0.75584751375
00:00:53.800 --> 00:00:55.448 relapse and refractory myeloma.
NOTE Confidence: 0.75584751375
00:00:55.450 --> 00:00:55.858 Later,
NOTE Confidence: 0.75584751375
00:00:55.858 --> 00:00:58.306 Doctor Barr will present updates on
cellular therapies in myeloma and. Some followed by Doctor Browning, who will present updates on basic signs in myeloma and some clinical updates on AL Amyloidosis, and we will devote.

Devote a few minutes in the end for the question and answer and discussion session. So again, welcome everyone. Thank you all for joining and Doctor Gore Shine. Please you may proceed.

We can see our slides if you just can project in the slide view. On the bottom
there you go, got it OK, perfect.

Can you hear me now? Yes, OK alright,

so thank you Talia hello everyone.

so as Natalia mentioned, I'm going to rehash ash from a perspective of.

Here are my disclosures.

Alright, so multiple myeloma is consistently preceded by precursor

and newly diagnosed multiple myeloma.

And these essentially represent a continuum with clonal evolution and heterogeneity.

with monoclonal gammopathy
Now we understand the heterogeneity of smoldering multiple myeloma. In clinical practice, we often rely and apply on the 20 to 20 rule, which is 20% bone marrow plasma cells, a monoclonal protein of greater than 2 grams per deciliter, and a free light chain ratio of greater than 20 patients with two or more of these risk factors or components are essentially considered high risk, and this subset of patient population. Has been evaluated for early therapeutic intervention. Now, with respect to early
therapeutic intervention,

we know that Lenalidomide can be beneficial for patients with high risk,

So the rationale here is that triplet therapy which we use for multiple myeloma may yield a deeper responses and improved outcomes for the smoldering population, and I’m just going to highlight one study on the combination of X as a proteosome inhibitor. Lenalidomide and immunomodulator. Agent and dexamethasone in high risk smoldering multiple myeloma.

Now, in the interest of time,
I’m going to essentially only discuss the conclusion slide, but this triple therapy regimen in high risk smoldering disease, and all oral regimen demonstrated a very high overall response rate of more than 90% with deep remission rates of greater than 40% now there were notable Grade 3 toxicities for these patients, but importantly, No patients discontinued therapy due to these adverse events, so this is encouraging data.
You know, suggesting they potentially more biologically sensitive phase of the disease to treatment and really highlighting an ongoing area of research in the smoldering multiple myeloma disease.

Now a couple words on multiple myeloma, so we’re going to transition out to multiple myeloma symptomatic multiple myeloma. We’re all familiar with VRD as our backbone to therapy.

Bortezomib, Lenalidomide, and dexamethasone proteasome inhibitor imid, and steroid. This is a very efficacious treatment regimen.
Very durable, has a well established track record.

Historically, neurotoxicity was a major concern here. But this has become significantly less of an issue with the once weekly dosing, as opposed to twice weekly dosing as well as with the subcutaneous version as opposed to the Ivy. So VRD is a suitable backbone and that has been sort of the impetus for developing quadruplet based therapies. We know from some data that quadruplet regimens can be very active in the upfront.
treatment naive patient population, but there are unanswered questions and we need more information. How does this regimen impact the high risk patient population? What about those that are stem cell transplant eligible versus ineligible? And clearly we need more long term results that we currently have for VRD, but you know it is not quite not quite there yet. For the quadruple therapy. So moving onto the updated Griffin analysis so this was published in Ash. Looking at the 24 month
follow up for Gray.

Just a brief background on this, so induction therapy followed by high dose therapy with autologous stem cell transplant and lend.

My maintenance therapy is a standard of care regiment for newly diagnosed patients.

The phase two Griffin study that was initially presented well over a year ago evaluated the efficacy and safety of Dara plus RVD versus RVD induction, followed by AUTOTRANSPLANT for newly diagnosed.

Transplant eligible patients.

The primary analysis after almost
14 months of therapy showed that the quadruplet therapy significantly improved the stringent CR rates versus the triplet therapy by the end of the post auto consolidation phase with response rates of 42 versus 32%. We also saw that this quadruplet treatment deepened their responses, improved MRD negativity rates after one year of maintenance therapy when. The standard of care lanolin amide when daratumumab was added to the standard of care. Importantly there were no new safety concerns and daratumumab did not impact the ability to mobilize. 
themselves and patients who received their induction were actually able to successfully complete the transplant. So here in Asheville they reported the updated efficacy and safety from Griffin after 24 months or two years of maintenance therapy. An overview of the treatment design, so again patients were transplant eligible, newly diagnosed disease. They received 4 induction cycles of quadruple it or the triplet with RV. They subsequently underwent stem cell transplant,
followed by two cycles of consolidation

maintenance or lanolin.

The primary endpoint here was a stringent CR.

Secondary endpoints included various
response rates, MRD, negativity,
progression, free survival,
overall survival on the bottom
half of the slide.

You note that the patient
characteristics were fairly
well balanced between both groups.

Now highlighted here is what’s
important to note here is that these
responses deepened overtime after
two years of maintenance therapy.

For the DRVD, the complete response rates were 82% versus 61% for the triplet therapy and on the right here for the subgroup analysis, you can appreciate that the that these improved durable responses were seen irrespective of the various subgroups.

In the lower half of the slide, we note that there were more significant MRD negativity rates with increased treatment as well. Again for the quadruplet therapy, 64% relative to 30% in the triplet.
therapy and when we look at the various subgroup analysis, this finding was also observed for patients over the age of 65. Advanced ISS High Risk center genetic analysis and.
The median progression free survival was not reached in either arm, although what’s important to note here is that we do see a separation of the curves beginning one year after maintenance therapy, so this suggests a benefit for the Daerah 2 Mettler Toledo my maintenance
arm and although it was not powered

again not powered for progression free survival in the subgroup analysis,

but you can also note here a generally positive trend for darylynn.

Maintenance versus Lenalidomide monotherapy as maintenance.

So the summarize these conclusions, so the quadruple therapy as induction post,

auto consolidation and barev maintenance is an effective regimen for newly diagnosed transplant eligible patients.

The MRD negativity rates were highest for the quadruplet,

followed by darreff maintenance.
These patients had deeper levels of MRD negativity, greater deepening of the negativity over time as we saw approaching the two year maintenance phase. Similarly, their rates of sustained MRMR D negativity and the subset analysis also trended favorably in the high risk population as well. In terms of the progression free survival, again, also this two year maintenance was well tolerated for those who received the daratumumab combination. So moving on to the Maia study. Now this these results were actually originally published.
Last summer at the FAP meeting, but I'm gonna review it here also, within the context of this presentation by Doctor Usmania at MSK. Who essentially wanted to determine the effects of the Maya on patients with impaired renal function, which is relevant here? Because really up to up to 50% of patients can have some baseline renal compromise that can impact our choice of treatment. So the Maya the mitral. As you may know, evaluated the addition of Dara to Rev.
Dex and transplant ineligible patients.

Newly diagnosed median follow-up of four and a half years.

The Dara Rev Dex prolonged PFS and OS versus Rev Dex alone,

almost half the patients in the Rev Dex population received subsequent therapy,

including a dare to Matt based regimen.

So so important for for this patient population.

When we look at the study design.

Somaiya trial again included transplant ineligible,

newly diagnosed multiple myeloma patients,

randomized to Dara Rev Dex or Rev Dex
and important here to note is that this treatment was continued until disease progression.

The primary endpoint for this study was the progression free survival.

Various secondary endpoints, again looking at the response rates, MRD negativity, overall survival.

And here we note the updated results. So with respect to the updated five year analysis, the progression free survival was not reached for the Dara Rev Dex combination and was 30-4 months for the Rev decks. Cohort in terms of the overall
survival benefit,

we do really important here to note is that there is an overall survival benefit for Dara Rev Dex, which is documented as a 32% reduction.

The risk of death relative to Rev Dex alone.

And if you see here on the right side of the screen, regardless of whether patients received a Lenalidomide dose of 25 or a lower dose, there was a progression free survival benefit and an overall survival benefit for Darryl Rev Dex relative to Rev Dex and the figure on the left really just highlights that this progression free survival benefit
that we’re seeing in Maya is is quite remarkable and really superior to. Some of the other recent phase three trials published in transplant ineligible patients. To summarize, so after five years of follow up the progression free and overall survival benefit for Darrell Rev Dex versus Rev Dex was observed and importantly relevant here. This was also observed in patients with compromised renal function at baseline, irrespective of the starting dose of Lenalidomide was a little bit less pronounced than those that had
had a lower dose lower than 25.

But really, highlighting the impressive,

you know, practice changing.

Results of Maya for transplant

and eligible patients.

Any interest of time,

I’m just going to briefly review

another quadruplet based treatment

regimen presented at ASH just back

in December involving ISATUXIMAB,

isatuximab with RVD or RVD

relative to RVD in transplant

eligible patients and this was the

phase three GMMG HD seven study.
And this phase three trial demonstrated a improvement or superiority in MRD negativity rates after induction with the addition of the aesthetics mab antibody. 2 RVD with the MRD response rate of 50.1% relative to 35% and on the right side of the screen. You can also. Is the highest described to date in a randomized phase three trial at 50.1%? Importantly, the addition of Isatuximab had no significant impact on the safety profile or dose intensity, and there are ongoing studies evaluating this combination of treatment for transplant eligible.
transplant ineligible patients.

And finally, I think it’s also important to discuss the master trial which involved daratumumab, carfilzomib, Lenalidomide, and dexamethasone togus transplant and MRD response. Adaptive consolidation.

We know that there are two have improves outcomes when combined with a proteasome inhibitor and or an immunomodulator agents. We also know that MRD negativity has prognostic implications. Now, this study incorporated a response adopted therapy to achieve
MRD negativity and really aimed to evaluate the Natural History of patients with sustained MRD negativity. Now, the treatment included Dara KRD and carfilzomib was dosed at 56 milligrams per meter squared. Weekly patients received 4 induction cycles of Derek KRD followed by a colleague. A stem cell transplant. And up to 8 cycles of Dara KRD MRD was assessed at each of these blocks. Now, patients who had two consecutive MRD negativity findings were transitioned to this phase called MRD Shore, which was a treatment free interval.
Observation and surveillance.

Those patients who did not achieve MRD continued to receive Lenalidomide maintenance as their standard of care.

And here are the results.

Overall, the majority of patients at 80% achieved MRD negativity and the depth of response and MRD negativity improved at each therapy phase.

As you can appreciate with these blocks and became comparable among the groups with no high risk, cytogenetic anomalies 1 high risk.

genetic anomalies or two or more high risk genetic abnormalities.
When we assess when they assessed MRD to level of $1 \times 10^{-6}$, 66.6% of patients achieved MRD negativity. Their proportion here in the various cytogenetic abnormality populations was somewhat lower and it did take longer to achieve for those with ultra high risk. As you can see here in the two plus high risk surgical abilities. In terms of MRD shore, so about 71 or 72% achieve of patients achieve them. These sure and this was relatively similar across the three cytogenetic risk groups. The median follow up time here was 29
about 14 months and the risk of MRD, resurgence or clinical progression was 40 and 27% among the standard high risk and ultra high risk patient groups, respectively. And importantly, none of the patients who entered this phase of MRD ultimately died from multiple myeloma progression. So, in conclusion, next generation sequencing, MRD response, adaptive therapy is feasible in the overwhelming majority of patients in multicenter settings with 70 to 72% of patients or she reaching MRD shore. Patients who have standard and high risk,
newly diagnosed myeloma had similar depth of response and low risk of MRD, resurgence or clinical progression when they were treated with the master trial quadruplets. Stem cell transplant and MRD, adaptive treatment cessation and quadruple therapy achievement of confirmed MRD negative responses. Enables us to explore stopping treatment as an alternative to continuous MRD. therapy to continuous indefinite. Treatment importantly, here again, novel therapy, novel,
Effective consolidation treatments should be explored to improve outcomes and clear MRD to a negative state in these ultra high risk patient population.

Thank you and I will welcome questions at the end of this presentation.

And I'll transfer it over to Terry.

Thank you, I will be focusing on updates in relapsed refractory myeloma.

I have no disclosures and I will be specifically focusing on treatment of triple class refractory patients.

This is defined as those patients that are refractory to anime, no modulatory, a Jack, a proteasome inhibitor,

and STD 38 monoclonal antibody currently
approved agents for this classification includes standard chemotherapeutic regimens, selinexor combinations, fanatical axe for patients who harbor a translocation. 1114 and two BCM a targeted therapies. Mentioned at Matthew Gelatin and antibody drug conjugate and I do sell a car T therapy. Fortunately for our patients, there are many agents currently in clinical trial, many of which were updated at this year’s ASH. These include BCM, a targeted therapies in the form of PCM a
CD3 bispecific T cell engager's non BCMA, targeted therapies and Carty or cellular therapies which will be discussed by doctor Bark later in the session.

First, we'll start with a presentation by Doctor Moreau entitled updated results from Majestic One at phase one, two study of Palestine Map Ciclista Mob.

Phase one and two data from the 1.5 MB perchik dose was presented. He eligibility criteria included that patient be triple class exposed have three or more lines of prior therapy and, importantly, no prior PC may therapy patients.

00:23:13.732 --> 00:23:17.395 Testing at 0.06 and 0.3 makes per

00:23:17.395 --> 00:23:19.850 kig subcutaneously followed by weekly

00:23:19.937 --> 00:23:22.708 treatment of 1.5 mix perchik subcutaneously.

00:23:22.708 --> 00:23:25.907 The primary endpoint for the trial was

00:23:25.907 --> 00:23:27.984 overall response rates 40 patients

00:23:27.984 --> 00:23:30.684 were accrued in phase one on 125.

00:23:30.684 --> 00:23:31.986 In phase two.

00:23:31.986 --> 00:23:35.090 The median treatment duration was 5.9 months.

00:23:35.090 --> 00:23:37.880 38 patients had high rosetto genetics,

00:23:37.880 --> 00:23:40.560 20 with ISS three disease,

00:23:40.560 --> 00:23:42.588 and this is a heavily pretreated

00:23:42.588 --> 00:23:43.264 patient population.

00:23:43.270 --> 00:23:45.706 With five medium prior lines of therapy,

00:23:45.710 --> 00:23:47.270 again,
165 patients were triple class exposed, with 128 being considered triple class refractory and 50 penta drug refractory. Median follow-up with 7.8 months and overall response rate was 62%, with 58% achieving Avicii, PR or better and 28.7% achieving the CR, or better importantly, the overall response rate of 62% was consistent across clinically relevant subgroups, including those patients that had high risk cytogenetics and those that were penta drug refractory. The median time to first response was 1.2 months.
with a progression free survival rate at nine months of 58.

Lakeside percent in patients who did achieve a CR better MRD.

Negativity rate was 41.9%.

I’m looking at the safety data. The most common hematologic treatment.

Emergent adverse event was neutropenia occurring in 65.5% of patients with the most common non unity logic treatment.

Emergent Adverse bank was cytokine release syndrome occurring in 71.5% of patients and taking a closer look at CRS.

The meeting time to onset was two days with the meeting duration of 37 days.
today’s 60 patients did require supportive care with tocilizumab.
The conclusions from this presentation was that the overall response rate with a tip list amount was 62% with responses that were durable and deepened overtime. Treatment was well tolerated with no dose reductions. The most common adverse events again were CRS and hematological events. The CRS for all low grade and 97% occurred during the step of dosing or cycle one of treatment and there was only one grade three event which resolved. I can events were rare. If they occurred,
00:25:36.603 --> 00:25:39.700 were all grade one and two and resolved,
NOTE Confidence: 0.7125666455

00:25:39.700 --> 00:25:43.436 moving on to another PC MA targeted fights.
NOTE Confidence: 0.7125666455

00:25:43.440 --> 00:25:45.900 And doctors and represented early,
NOTE Confidence: 0.7125666455

00:25:45.900 --> 00:25:46.641 deep and durable.
NOTE Confidence: 0.7125666455

00:25:46.641 --> 00:25:48.123 Response to this with low rates
NOTE Confidence: 0.7125666455

00:25:49.660 --> 00:25:49.659 of cytokine release syndrome.
NOTE Confidence: 0.7125666455

00:25:52.180 --> 00:25:55.160 Regenerx on 5458 again as ABC made.
NOTE Confidence: 0.7125666455

00:25:55.160 --> 00:25:56.396 CD3 bispecific antibody.
NOTE Confidence: 0.7125666455

00:25:56.396 --> 00:25:58.456 This is a phase one,
NOTE Confidence: 0.7125666455

00:25:58.460 --> 00:26:01.015 two first in human study with key
NOTE Confidence: 0.7125666455

00:26:01.015 --> 00:26:02.477 eligibility criteria including three
NOTE Confidence: 0.7125666455

00:26:02.477 --> 00:26:04.289 or more lines of prior therapy,
NOTE Confidence: 0.7125666455

00:26:04.290 --> 00:26:06.342 and these patients had to be
NOTE Confidence: 0.7125666455

00:26:06.342 --> 00:26:07.368 triple class refractory.
NOTE Confidence: 0.7125666455

39
Part One was a dose escalation utilizing a modified 4 + 3 design with dose ranges from 3 to 800 milligrams. Part 2 will be adjust expansion at the recommended phase two dose step. Up dosing was utilized for week one and two followed by weekly dosing and then every other week dosing after 16 weeks. Primary endpoints included safety, tolerability and to determine the recommended phase two dose data for 73 patients in phase one were presented. The median number of prior lens was five and 38% of patients were pentag wreck refractory.
And looking at the safety data, the most common hematologic treatment emergent adverse event was anemia seen in 32% of patients, followed by lymphopenia and neutropenia. The most common non hematological treatment of urgent adverse event was fatigue. Interestingly, cytokine release syndrome was only seen in 38% of patients. This was a question in the presentation I asked and there was not a good reason available as to why the rates of serous were lower here compared with other bispecific T cell engagers.
It was postulated that it may have to do with the step up dosing and or premedications.

And looking at the efficacy, the overall response rates were 51%. This increased to 75% when you look at doses of 200 to 800 milligrams with a VGPR better at 58.5%.

The mean time to response was less than one month, with 70% of responses occurring within the first two months.

The duration of response was not reached, and in patients who achieved a CR or stringent CR who had available data for Dove,
10 patients were MRD negative at 10 to the minus 5.

So in conclusion, the author showed that regenerate in 5458 yielded early, deepened Drabble responses as seen as an overall response rate is 75%. Fifty 8% of cheated BGR are better, again at the higher doses of 200 to 800 milligrams. 86% of responders achieved VGPR better with a C or better rate of 43%. The probability of responders being invented free at 8 months was reported as 90.

manageable safety profile as the maximum
00:28:30.649 --> 00:28:33.316 tolerated dose was not reached with CRS
NOTE Confidence: 0.626279934444444
00:28:33.316 --> 00:28:35.938 being reported in only 38% of patients,
NOTE Confidence: 0.626279934444444
00:28:35.938 --> 00:28:37.768 the majority events were grade
NOTE Confidence: 0.626279934444444
00:28:37.768 --> 00:28:39.903 one occurred within the first two
NOTE Confidence: 0.626279934444444
00:28:39.903 --> 00:28:41.913 weeks and resolved within one day.
NOTE Confidence: 0.626279934444444
00:28:41.920 --> 00:28:44.554 The phase two portion of the
NOTE Confidence: 0.626279934444444
00:28:44.554 --> 00:28:46.310 study is currently recruiting.
NOTE Confidence: 0.626279934444444
00:28:46.310 --> 00:28:47.846 And moving away from a BCM,
NOTE Confidence: 0.626279934444444
00:28:47.850 --> 00:28:49.092 a target doctor,
NOTE Confidence: 0.626279934444444
00:28:49.092 --> 00:28:50.748 Krishnan presented updated Phase
NOTE Confidence: 0.626279934444444
00:28:50.748 --> 00:28:53.067 one results from monumental one at
NOTE Confidence: 0.626279934444444
00:28:53.067 --> 00:28:55.095 first in human study of Calcutta
NOTE Confidence: 0.626279934444444
00:28:55.095 --> 00:28:57.869 Mad so till catnip is a G protein
NOTE Confidence: 0.626279934444444
00:28:57.869 --> 00:28:58.883 coupled receptor family.
NOTE Confidence: 0.626279934444444
00:28:58.890 --> 00:29:02.272 See Group 5D Member D as also
NOTE Confidence: 0.626279934444444
00:29:02.272 --> 00:29:04.127 known as GPRC 5D CD.
A bispecific antibody she presented updated data at the first recommended phase. Two dose and initial results for patients treated as second recommended phase. Two dose of 800 micrograms per kilogram Q 2 weeks. Patients had to be relapsed refractory or intolerant to all established my limit therapies and have measurable disease previously. A recommended phase. Two dose of 405 micrograms per kilogram weekly subcutaneously was identified. Step up testing was utilized and premedication was given before all step up.
dusting and the first full dose.

The primary end point was to identify the recommended phase.

Two dose is 30 patients received weekly dosing and 25 at the key.

Two weekly schedule.

Three patients in.

Each cohort had high risk genetics.

The meeting number of pirate therapies was six and five, and eight and four patients, had prior be CMA directed therapy.

And looking at the hematological treatment emergent adverse events, the most common was neutropenia and...
and 44% of patients followed by anemia and lymphopenia. The most common nonhematologic treatment emergent adverse event was cytokine release syndrome seen in 77 and 72%. It should be noted that 75% of patients did have skin and or nail related findings. In the study, the most common being skin exfoliation in 37 and 36% of patients. And taking a closer look at the CRS again, it was 77 and 72%. The median onset was two days, with the median duration of two days. 63.3% and 60% of patients in the
two cohorts did require Tuscaloosa.

And looking at overall response data at the median follow-up was nine and 4.8 months.

They shouldn’t overall response rate of 70% and 67.7% for the Q2 week dosing.

With Fiji, Fiji PR rates of 53.3 and 52.4.

The trial also showed that the overall response rate held in patients who were triple class refractory at 65.2 and 66.7% and in patients who are penta directory factory at 83.3%.

Although the numbers are low.

Five out of 6 patients.

The median time to response was
zero point 9 and 1.2 months, and the median duration of response was not reached. So in conclusion, the until catnip 800 microgram per KQ, two week dosing appeared to have comparable efficacy and safety compared to the weekly dosing at 405 micrograms per kilogram. No new safety signals were reported. Overall response rates range from 67 to 70% across triple class and pencil drug refractory patients and a phase two expansion study of both of these recommended.
00:31:50.090 --> 00:31:53.260 Ways to Jesse is ongoing.
NOTE Confidence: 0.565365134
00:31:53.260 --> 00:31:56.080 And moving away from the bispecific
NOTE Confidence: 0.565365134
00:31:56.080 --> 00:31:58.230 antibodies and a presentation
NOTE Confidence: 0.565365134
00:31:58.230 --> 00:32:00.470 was done on loaded,
NOTE Confidence: 0.565365134
00:32:00.470 --> 00:32:03.508 loaded excuse me alpha which is immuno
NOTE Confidence: 0.565365134
00:32:03.508 --> 00:32:05.520 cytokine shows clinical activity.
NOTE Confidence: 0.565365134
00:32:05.520 --> 00:32:07.160 Updated results from my first
NOTE Confidence: 0.565365134
00:32:07.160 --> 00:32:08.800 in human phase one study.
NOTE Confidence: 0.565365134
00:32:08.800 --> 00:32:10.893 So Mataka Alpha is a first in
NOTE Confidence: 0.565365134
00:32:10.893 --> 00:32:13.223 class in unison in you know
NOTE Confidence: 0.565365134
00:32:13.223 --> 00:32:15.035 cytokine designed to deliver
NOTE Confidence: 0.565365134
00:32:15.035 --> 00:32:16.860 attenuated interferon alpha to CD.
NOTE Confidence: 0.565365134
00:32:16.860 --> 00:32:18.450 38 positive cells patients were
NOTE Confidence: 0.565365134
00:32:18.450 --> 00:32:20.425 eligible if they had three or
NOTE Confidence: 0.565365134
00:32:20.425 --> 00:32:22.399 more prior lines of therapy were
NOTE Confidence: 0.565365134
00:32:22.399 --> 00:32:24.099 refractory or intolerant to at least.
One P&M and could have prior daratumumab exposure within a washout period of 90 days. For patients who had received more than five months of therapy in the escalation portion, the primary objective was to determine the maximum tolerated dose and the dose escalation phase at 3 + 3 design was used. Looking at four different schedules in the expansion phase, they looked at a dose of 0.4 and makes per cake every three weeks, with or without dexamethasone. Data was presented in 29 patients.
Five patients were that had cytogenetic data were considered to be high risk.

The meeting number of prior lines with therapy was 728 patients had prior CD 38 monoclonal antibody treatment. 26 of those patients were considered to be monoclonal antibody refractory and 15 patients had prior PC and major active therapy. The maximum tolerated dose was exceeded at six weeks per kid Q4 due to disciplining toxicities of a Grade 3 infusion reaction and prolonged grade. 4 thrombocytopenia and neutropenia.
As a 1.5 mix per KQ, four week dosing, one patient did have a great treat bleeding event but was able to remain on treatment and three patients had grade 3 infections. The most commonly seen treatment emergent adverse events at the 1.5 MB per kid Q4 week dosing, hematologic with thrombocytopenia and current 76% of patients and neutropenia and 69% all grades. Infusion related reactions did occur in 31% of patients. Most of these were grade one and two.
The median follow-up was 4.2 months and the overall response rate was 38% of note. The overall response rate held at 38% in patients who were CD38 monoclonal antibody factory. The median time to response was one month. In those patients who achieved a PR or better with a median duration of response not being reached, the median progression free survival was 5.7 months. So in conclusion, Modaco Alpha showed promising single agent activity and patients who were heavily pretreated, including patients who...
NOTE Confidence: 0.7402168875
00:34:31.209 --> 00:34:32.628 were refractory toasty.
NOTE Confidence: 0.7402168875
00:34:32.630 --> 00:34:34.538 38 monoclonal antibody had
NOTE Confidence: 0.7402168875
00:34:34.538 --> 00:34:36.446 a manageable safety profile.
NOTE Confidence: 0.7402168875
00:34:36.450 --> 00:34:38.886 Q For Weeks was identified as the
NOTE Confidence: 0.7402168875
00:34:38.886 --> 00:34:40.838 optimal dosing interval and further
NOTE Confidence: 0.7402168875
00:34:40.838 --> 00:34:42.522 enrollment identified the maximum
NOTE Confidence: 0.7402168875
00:34:42.522 --> 00:34:45.070 tolerated dose as three mics per keg.
NOTE Confidence: 0.7402168875
00:34:45.070 --> 00:34:47.296 A randomized phase two trial is
NOTE Confidence: 0.7402168875
00:34:47.296 --> 00:34:49.363 planned in order to determine
NOTE Confidence: 0.7402168875
00:34:49.363 --> 00:34:51.908 the optimal single agent dosing.
NOTE Confidence: 0.7402168875
00:34:51.910 --> 00:34:54.225 Lastly, Dr Lonial presented herbicide
NOTE Confidence: 0.7402168875
00:34:54.225 --> 00:34:56.540 in combination with dexamethasone in
NOTE Confidence: 0.7402168875
00:34:56.602 --> 00:34:59.227 patients with relapsed refractory myeloma.
NOTE Confidence: 0.7402168875
00:34:59.230 --> 00:35:00.819 Results from the district expansion of the
NOTE Confidence: 0.703098704545455
00:35:03.050 --> 00:35:03.860 CC-220MM-001 trial.
NOTE Confidence: 0.703098704545455
Roberta Mine is a novel

Cereblon E3 leg is modulator, also known as the cell Mod.

This was a phase one two study that, evaluated at EBR with different combinations of treatment.

Previously, the recommended phase two dose was identified as 1.6 milligrams days,

When given in combination with dexamethasone here,

She reported safety and efficacy and the dose expansion cohorts.

Cohort D, which is Eber plus tax

And cohort I which was Eber plus tax in patients who had prior BC
made treatments for both cohorts.

Patients had to have three or more lines of prior therapy and again for cohort I.

All patients had treatment with her prior PC may targeted Agent 107.

In patients were treated in cohort D and 26 in poker I 32 patients and six.

Patients respectively, had high risk cytogenetics in the two cohorts.

The median number of pirate therapies was six and seven in Cohort I6.

Patients had prior card T 18 and antibody drug conjugate, and eight bispecific T cell engager.
The most common adverse events occurring in 59 point, working in cohort D and 42.3% in cohort I. Infections were common at 57.9% AL grading Health, Part D and 50% in cohort I. I'm looking at the response data. The overall response was 26.24, cohort D and 25% in cohort I. Again this year they post be CMA treated patients. Additional data was presented for Cohort D with a median duration of response of seven months and median time to respond to 4.21
weeks and a median progression free survival of three months. The authors concluded that in heavily pretreated patients, again 97% were Triple Classic factory. The combination of ever, ever, and Dex demonstrated clinically meaningful and durable responses. The treatment was well tolerated with adverse events that were deemed manageable with dish reductions and interruptions and treatment. Authority of grade three or four treatment emergent adverse events were primarily hematological and this
supported the future development.

Iber based regimens including combination studies with PRISM inhibitors and CD.

monoclonal antibodies.

As previously stated, all questions will be answered at the end of the program.

Please encourage you to submit this in the Q&A portion and now I will turn it over to Doctor Barr.

Thank you Terry so. Let’s get started.

I’m focusing on car T cell therapy in the relapsed refractory myeloma patients.

I want to highlight that patients who are refractory to image produce...
them inhibitors and anti CD 38 antibodies have a poor prognosis. These are triple class refractory patients and when these patients if they get another line of treatment, the chance that they will respond to another agent is roughly 30%. If they respond, the median progression free survival is often less than six months, with median overall survival often less than one year. Now I want to show you how this is no longer the case, as most of you already know that in
2021 the FDA approved the first car T cell product in myeloma this is. Called either sell formerly known as BB 2121 and now the train name is a Beckman. This is a car T cell product that has four one BB costimulatory domain and it binds to BCMA on the cell surface of the tumor cell. It’s approved for patients who are refractory to image PRISM inhibitor and anti CD 38 antibody’s. 76% of the patients responded about a third of the patients achieve deep responses. CR and stringent complete response. Most of those patients were emordi negative potential negative 5th
00:39:15.746 --> 00:39:17.650 using next generation sequencing.
00:39:17.650 --> 00:39:18.104 Now,
00:39:18.104 --> 00:39:20.828 these patients had initially dose escalation,
00:39:20.830 --> 00:39:24.268 so not all of them received the same dose.
00:39:24.270 --> 00:39:25.845 If you look at the total population,
00:39:25.850 --> 00:39:27.830 the median progression free survival,
00:39:27.830 --> 00:39:30.380 survival was 8.8 months,
00:39:30.380 --> 00:39:32.310 but if you hone in on the target dose,
00:39:32.310 --> 00:39:34.866 the patients that received
00:39:33.446 --> 00:39:34.866 the target FDA approved dose.
00:39:34.870 --> 00:39:36.490 It is about one year.
00:39:36.490 --> 00:39:39.740 All the population median overall
00:39:39.740 --> 00:39:41.690 survival 24 months.
00:39:41.690 --> 00:39:43.524 Now we also know that deep responses
00:39:43.524 --> 00:39:45.448 lead to longer duration of response,
and here I show you a graph where patients who have a CR complete response or higher exemplified by the light blue line compared to very good partial response by the Purple line and the partial response by the dotted purple line. Clearly you see that these curves spread out and the meaning of two years of follow up. Those patients who have a CR or higher had a median duration of response 21 months. So that’s almost two years now. I’ve showed you before that only about a third of the patients got into this deep responses,
so it’s interesting to to figure out who the patients that went into these deep responses. Perhaps? Who are those that don’t respond as well to have that mind, and this was presented by Nina Shaw. This year is ash and she looked at disease characteristics at baseline and correlated it with patients who had the CR or not. What they found is that patients who did not have a CR tended to have a higher soluble BCMA knob. May is a receptor on the cell surface of tumor cells,
but it can be cleaved and then circulates in the bloodstream as soluble. BCMA is often seen with higher burden of disease and the conservative sink, so if you’re giving the targeted car T right instead of going to the tumor, it’s going to this soluble BCMA, so you can imagine how this would prevent its efficacy. The other thing they noted is that patients not achieving CR tended to have a high an increase of inflammatory markers by having higher fare to know D dimer. Now these could be patients who are sicker and more burden of disease,
and you might think maybe perhaps this, in you know, inflammatory microenvironment can impede T cell functionality, but again, these needs. This needs to be further dissected. These are just. The start of trying to understand biomarkers for response need to be tested in larger cohorts. They did find that having a higher vector copy number in the drug product was more associated with patients who had a CR. Now we know that number of
car T is not the full picture.

We also understand that quality of T cells are important and this is a diagram showing you the T cell differentiation from the naive T cell all the way to the T effector cell. These earlier T cell, the memory like phenotypes have some key qualities that make it quite attractive for car two products example though long lived. They have ability to self renew and they have a T cell plasticity. Furthermore, these memory, like T cells,
were correlated with peak expansion and sustain response in karty studies. So this brings me to the next abstract, which was presented by Doctor Raj and it looked at using API 3 kinase inhibitor, maybe 007, which is known to enrich memory like T cells and combine it with Ida cell. It in vitro and this product was now termed BB 2121 seven and the hypothesis is that higher memory like T cell in the cell product will improve duration of response. The patient characteristics here were similar to other karty studies. I want to highlight a few things. This was a dose escalation study.
46 patients out of the 72 received the target dose. High risk.

Better genetics were found in 39% of the patients. This is slightly higher.

That was than what was reported with the back comma, which was around 27% and extramedullary disease was 22.

Safety profile with BB 2121 seven with similar to Avec mom.

Not going to go into the details but briefly CR S 75% mostly grade one and two I cans which is the neurotoxicity that we see with car and T cells with 15% very comparable.
00:43:48.122 --> 00:43:50.306 Said opinions are very common in
general with all CAR T cells filling
NOTE Confidence: 0.970727627142857
00:43:50.306 --> 00:43:52.735 to the lymphodepletion that they
NOTE Confidence: 0.970727627142857
00:43:52.735 --> 00:43:54.432 get before and the Grade 3 and
NOTE Confidence: 0.970727627142857
00:43:54.432 --> 00:43:57.170 above infections which is clinically
NOTE Confidence: 0.970727627142857
00:43:57.170 --> 00:43:59.310 very meaningful is about 30%.
NOTE Confidence: 0.970727627142857
00:44:03.530 --> 00:44:06.218 In terms of efficacy.
NOTE Confidence: 0.970727627142857
00:44:06.220 --> 00:44:09.377 We’re all response rate was 74 percent,
NOTE Confidence: 0.970727627142857
00:44:09.380 --> 00:44:11.172 39% with a CR and most of
NOTE Confidence: 0.970727627142857
00:44:11.172 --> 00:44:12.520 them being emerging negative.
NOTE Confidence: 0.970727627142857
00:44:12.520 --> 00:44:14.350 But this doesn’t look very
NOTE Confidence: 0.970727627142857
00:44:14.350 --> 00:44:15.814 different than Beckman information,
NOTE Confidence: 0.970727627142857
00:44:15.820 --> 00:44:16.330 but really,
NOTE Confidence: 0.970727627142857
00:44:16.330 --> 00:44:17.860 what this study is looking at
NOTE Confidence: 0.970727627142857
00:44:17.860 --> 00:44:19.000 is duration of response,
which I’ll show you in this slide.

So in median follow up of about two years, the median progression of meaning, progression of free survival for patients getting the target dose with 18 months and in the back MACI put in Gray.

Here was 12 months and this is not a head-to-head comparison. Any means, but I want to give you this as a framework to kind of digest the the results here.

Now in patients who achieve deeper responses, CR and above the median duration of response was 30-4 months and in the back of my disk was 21 months.
They did see that memory like T cells in both the car T product and peak expansion in the patient was associated with better response and duration of response. So this is a good example of how you can build on an already established party product. The next topic will be focused on information updated information on the car T cell product that will be approved next and this is self sell. Sell to sell is also an anti BCMA CAR T. It also has a four one.
The difference is it has two binding domains here extracellularly, so this was a two year follow-up of the Phase 1B2.

Patient characteristics are represented here. They had almost 100 patients, heavily pretreated similar to other party studies. Perhaps the percentage of triple refractory right.

This is triple class refractory. They do comment on penta refractory that’s refractory to two image 2 and one and CD 30 antibody. So this is 42% they had 23% high risk.
energetics, mostly deletion 17 P.

And they did have 19 patients with extramedullary disease, 13 patients had extramedullary disease plasmacytomas outside of the bone, which is a higher risk feature. So efficacy I showed you part of this last year, but there are some updates. Overall response rate 89. Sorry 98% which is great. So literally two patients here did not respond. However, one of those patients wasn’t invaluable because were they?
They couldn’t really assess response because he’s not measurable disease, but they did clinically response. Really only one patient did not respond to this and deep responses as you see here. 92% stringent complete response. Is really unprecedented. The median time to first response was one month, and the median time to best response was about 2 1/2 months. Response was not met. They further looked at MRD at
00:47:11.599 --> 00:47:14.868 10 to negative 50 based on next Gen sequencing in 61 patients.

00:47:14.868 --> 00:47:17.198 92 I'm really negative 30 patients had sustained.

00:47:19.540 --> 00:47:20.320 From our deep at six months and above and 18 had sustained MRD at 12 months and above.

00:47:22.708 --> 00:47:25.317 and above and 18 had sustained.

00:47:25.317 --> 00:47:28.095 Now looking at progression free survival based on depth of response.

00:47:28.100 --> 00:47:30.320 So patients who had a CR stringent CR as exemplified by the Green Line here,

00:47:30.320 --> 00:47:32.460 had a two year progression free survival of 71% compared to 60 for the total population.

00:47:32.460 --> 00:47:35.764 Now going deeper,
sustained MRD responses at six months and 12 months had a progression free survival of 91 and 100% at 2 year follow up. So this is really fantastic. You might be wondering what is driving that the blue curve down. You know a lot of these patients did the cheap, really great responses and they did do a subgroup analysis trying to understand this, and they found that the two year progression first level was lower for patients who had baseline plasmacytomas, high risk cytogenetics and high tumor burden.
So this is important to keep in mind. Certainly these patients benefit, but they might not benefit as well as others.

Safety. CRS was extremely common and most everyone had it mostly grade one followed by grade two.

They did have a good amount of use totals map at 70%, which is higher than what’s reported with the beckmeyer. Around 50% that Icams neurotoxicity was comparable.

17% infections grade 3 or above 20%. There was six deaths related to cell to cell. Predominantly driven by infections and
it followed by CRS and art existing,
NOTE Confidence: 0.77864265
they saw 15 events,
NOTE Confidence: 0.77864265
secondary primary malignancy and 11
NOTE Confidence: 0.77864265
patients which were felt unrelated
NOTE Confidence: 0.77864265
to me from cell to cell.
NOTE Confidence: 0.77864265
And the thought is that this is
NOTE Confidence: 0.77864265
not out of the usual for this.
NOTE Confidence: 0.77864265
Multiply relapsed heavily pretreated
myeloma patient population.
NOTE Confidence: 0.77864265
One thing to note that it’s
different with silty cells opposed
NOTE Confidence: 0.77864265
to either sell or Beckman is that
the CRS it has a later onset.
NOTE Confidence: 0.77864265
The median of seven days after infusion
compared to two days after a back comma.
NOTE Confidence: 0.77864265
So it is a great possibility to give it
00:49:35.381 --> 00:49:38.123 in alkylation setting and it is being tested in clinical trials like that.

00:49:38.123 --> 00:49:40.449

00:49:40.450 --> 00:49:42.080 Last thing to comment about Silver cell is this movement and neurocognitive adverse effects.

00:49:44.287 --> 00:49:45.817

00:49:44.287 --> 00:49:47.948 When the cell to cell was first given to patients, they saw the incidence of.

00:49:47.948 --> 00:49:49.730 He’s at 12% and actually was concerning the risk factors that they found to develop.

00:49:49.730 --> 00:49:53.943 This was high tumor burden.

00:49:53.943 --> 00:49:57.170

00:49:58.510 --> 00:49:59.304 High car,

00:49:59.304 --> 00:50:01.289 T cell expansion and persistence,

00:50:01.290 --> 00:50:03.495 development of AI camps and CRS grade two or above.

00:50:03.495 --> 00:50:07.702 So Jameson and Team decided that they
need to do something about this and develop patient management strategies, including enhancing bridging therapy to reduce tumor burden before they get Kartik and early and aggressive treatment. For CRS and I cans and probably is with driving, the higher use of toasting in this agent. With this there have been no further toxicities in the current incidents in over 200 patients treated on several clinical trials at 0.05, and this is important because this is what held up after your approval of this drug last year and now seems to be much better in much better shape
and will likely be approved next week.

I do want to highlight that solar cells being used.

Earlier in the treatment course for myeloma and we will have a study open here using cell to cell as part of upfront treatment myeloma.

The last topic I will talk about is another car T product that is targeting the GPRC 5D protein.

GPRC 5D is expressing my luma cells as well as skin and hair follicles. It’s a receptor that actually

This is called mcar H 109.

GPCR 5D is expressing my luma cells as well as skin and hair follicles. It’s a receptor that actually

no one really understands what it does.
This is a small study. At Memorial Sloan Kettering 16 patients. But what is unique is that these are really heavily pretreated patients. Very high risk population, so everyone was panda exposed. Almost everyone was triple class refractory. About half had plasmacytoma months and. About 20% had non secretary Malama, which is really a patient population not
NOTE Confidence: 0.717015916428571
00:51:57.309 --> 00:51:59.600 represented in the clinical studies.
NOTE Confidence: 0.717015916428571
00:51:59.600 --> 00:52:02.296 So this is a swim plot of swimmers
NOTE Confidence: 0.717015916428571
00:52:02.296 --> 00:52:04.200 plot of responsive follow-up
NOTE Confidence: 0.717015916428571
00:52:04.200 --> 00:52:07.065 of 18 months dose escalation.
NOTE Confidence: 0.717015916428571
00:52:07.070 --> 00:52:08.904 You see here the doses go up
NOTE Confidence: 0.717015916428571
00:52:08.904 --> 00:52:09.690 with higher doses.
NOTE Confidence: 0.717015916428571
00:52:09.690 --> 00:52:11.650 It does seem that there are deeper
NOTE Confidence: 0.717015916428571
00:52:11.650 --> 00:52:13.730 responses you can see by the green bars.
NOTE Confidence: 0.717015916428571
00:52:13.730 --> 00:52:15.505 The follow up is relatively
NOTE Confidence: 0.717015916428571
00:52:15.505 --> 00:52:16.925 short for these patients.
NOTE Confidence: 0.717015916428571
00:52:16.930 --> 00:52:19.980 Overall response rate about 70%.
NOTE Confidence: 0.717015916428571
00:52:19.980 --> 00:52:22.308 About 1/4 achieved a complete response.
NOTE Confidence: 0.717015916428571
00:52:22.310 --> 00:52:23.196 All populations,
NOTE Confidence: 0.717015916428571
00:52:23.196 --> 00:52:25.854 so more to follow on that
NOTE Confidence: 0.717015916428571
00:52:25.854 --> 00:52:27.750 safety was manageable.
NOTE Confidence: 0.717015916428571
Sierras 93% similar to cell to cell.

There was one patient that had a grade 3IN neurotoxicity in terms of off tumor on target side effects, nail changes, rash taste changes.

We're seeing all grade one all transient. So this is a great product is furthering it. It goes into.

Further development with the multicenter study. So with that I will end my part of the talk.

And move on to doctor Browning.
So with the remaining time I will review a few abstracts highlighting basic and preclinical work in multiple myeloma and then provide an update on the management of patients with light chain or ALE amyloidosis. And I have no disclosures to report, so this slide outlines the abstracts I will review with you today. I’d note that there were many exciting preclinical updates in myeloma with a focus really on immunology in the myeloma immune microenvironment, as well as advances in genomics and myeloma pathogenesis.
And I will highlight abstract 159, which provides us with an updated analysis from a practice changing study in AL Amyloidosis. So to begin, obesity is closely linked to my Loma pathogenesis and has also been associated with increased mortality in multiple myeloma. It is thought that obesity increases the production of proinflammatory cytokines and adipokines and leads to ectopic accumulation of adipocytes in the bone marrow which can change the bone marrow microenvironment.
00:54:24.378 --> 00:54:26.977 by Doctor Hsu from the Sun Yat
Sen Cancer Center in China,
00:54:26.977 --> 00:54:28.512 the authors aim to investigate
00:54:28.520 --> 00:54:29.675 the role of bone marrow.
00:54:29.675 --> 00:54:30.830 Adipocytes in myeloma Genesis and explore
00:54:30.830 --> 00:54:33.932 potential novel therapeutic agents
00:54:33.932 --> 00:54:36.053 targeting the bone marrow microenvironment.
00:54:36.053 --> 00:54:38.868 They evaluated patients with newly diagnosed
00:54:38.870 --> 00:54:41.582 multiple myeloma and healthy controls.
00:54:41.582 --> 00:54:44.010 The myeloma patients were separated
00:54:44.010 --> 00:54:45.775 into two groups based on BMI and
00:54:45.775 --> 00:54:48.312 underwent testing from bone marrow
00:54:48.312 --> 00:54:50.077 that included RNA sequencing,
00:54:50.077 --> 00:54:51.850 metabolomics and flow cytometry analysis.
00:54:57.130 --> 00:54:59.314 And there was an increase in bone marrow
89
adipocytes in patients with myeloma and metabolomic analysis revealed that several metabolites work very closely, associated with BMI with glycerolipid metabolism enriched in myeloma patients with obesity RNA sequencing data from the bone marrow. Adipocytes showed that patients with myeloma had an increased expression of fatty acid binding protein or FAP four, and this is seen in figures A&B with FA PB having an important role in linking lipid. Metabolism with immunity and inflammation further enhanced the expression of FA BP4 in these studies to further evaluate the potential role.
00:55:37.740 --> 00:55:40.020 of fabp 4IN pathogenesis in myeloma,

00:55:40.020 --> 00:55:42.610 the authors studied of fabp 4 knockout

00:55:42.610 --> 00:55:45.499 and wild type mice who were fed a high

00:55:45.499 --> 00:55:48.315 fat diet for 12 weeks and you can see

00:55:48.315 --> 00:55:50.550 here in figure see that the knockout

00:55:50.550 --> 00:55:52.755 mountain mice had less tumor burden by

00:55:52.755 --> 00:55:55.134 PET scan and as displayed in figured D,

00:55:55.140 --> 00:55:57.666 they also had improved overall survival.

00:56:02.498 --> 00:56:05.044 The authors then applied and FAP

00:56:02.498 --> 00:56:05.044 4 inhibitor known as BMS 309403,

00:56:05.044 --> 00:56:06.592 which resulted in significant

00:56:06.592 --> 00:56:08.580 attenuation of the tumor burden

00:56:08.580 --> 00:56:10.455 and improved survival and obesity

00:56:10.455 --> 00:56:12.331 induced myeloma mice as outlined

00:56:12.331 --> 00:56:14.487 in the two figures on this slide.
So, in summary, these data suggest that bone marrow adipocytes, which are increased in obesity, may shape metabolism and immunity in the bone marrow microenvironment and play a role in promoting myeloma pathogenesis. This certainly requires further investigation, though it does raise an important question regarding whether modification of obesity and other such associated risk factors can serve as a preventative strategy in multiple myeloma.
at Fred Hutchinson Cancer Center, the combination of immunomodulatory, the immunomodulatory drug, Lenalidomide, and an antigen antibody was studied in mice. After undergoing autologous stem cell transplantation. As many of you know, high dose chemotherapy and autologous stem cell rescue has been shown to provide progression free survival benefit in multiple myeloma. Though in myeloma disease, relapses are expected, and there is definitely a
need to enhance the antitumor efficacy of stem cell transplant.

As you can see in the figure here, autologous stem cell transplant via lymphodepletion and immune reconstitution is thought to establish a myeloma immune equilibrium with an inflammatory microenvironment. However, tumor escape is inevitable, and exhaustion of CD8 positive T cells is thought to play a major role in disease relapse. TIGIT, which is an inhibitory receptor, is upregulated on exhausted T cells and is thought to play a
major role in disease of relapse, with studies showing a strong association between myeloma burden and expression of TIGIT on CD 8 positive T cells and mice status post stem cell transplant there for you guys. As you can imagine, TIGIT has emerged as an attractive target for immunotherapy in multiple myeloma. So in this study, myeloma mice underwent high dose Miy ablative radiation and then received bone marrow grafts, followed by the administration of a antigen monoclonal antibody,
twice weekly for five weeks, starting on the day of transplant or day zero and then Lenalidomide administered daily for three weeks beginning on day, plus 14 and synergistic anti myeloma activity was observed with this combination. As you can see in figure B, there was a significant reduction in the rate of tumor growth and also improved median. Overall survival in the mice who received this combination post transplant and the authors also found, through flow cytometry and flow, some clustering, that this combination increased T
cell memory and reduced exhaustion as displayed in the representative heat map on the bottom right in Figure C and lastly, the combination of an anti-TIGIT monoclonal antibody and the 4th generation image or cell mod Iberity mid which was discussed by Doctor Parker earlier. In our discussion is now entering human trials shortly.

So to move, move along light chain or a lymphoid ossis is a rare systemic disorder of clonal plasma cells that generate aberrant or abnormal
00:59:19.099 --> 00:59:21.147 immunoglobulin light chains which
NOTE Confidence: 0.82114971
00:59:21.147 --> 00:59:23.752 misfolded form insoluble amyloid fibrils.
NOTE Confidence: 0.82114971
00:59:23.752 --> 00:59:26.367 These fibrils then deposit into
NOTE Confidence: 0.82114971
00:59:26.367 --> 00:59:28.763 extracellular tissues and organs resulting
NOTE Confidence: 0.82114971
00:59:28.763 --> 00:59:31.457 in impairment of vital organ function
NOTE Confidence: 0.82114971
00:59:31.525 --> 00:59:33.705 and sometimes or often death with
NOTE Confidence: 0.82114971
00:59:33.705 --> 00:59:35.080 the introduction of novel therapies,
NOTE Confidence: 0.82114971
00:59:35.080 --> 00:59:36.815 there has been improvement in
NOTE Confidence: 0.82114971
00:59:36.815 --> 00:59:38.203 overall outcomes and prognosis
NOTE Confidence: 0.82114971
00:59:38.203 --> 00:59:40.070 for ALE amyloidosis which were.
NOTE Confidence: 0.82114971
00:59:40.070 --> 00:59:42.178 Historically, very, very grim.
NOTE Confidence: 0.82114971
00:59:42.178 --> 00:59:44.080 In an abstract 155,
NOTE Confidence: 0.82114971
00:59:44.080 --> 00:59:46.320 which was presented by Doctor Starin from
NOTE Confidence: 0.82114971
00:59:46.320 --> 00:59:48.699 the Boston University Amyloidosis Center,
NOTE Confidence: 0.82114971
00:59:48.700 --> 00:59:50.506 there was a 40 year Natural History
NOTE Confidence: 0.82114971
00:59:50.506 --> 00:59:52.224 study that was reviewed on outcomes
00:59:52.224 --> 00:59:53.994 for patients with a lambdoid seen

00:59:53.994 --> 00:59:55.919 at their center and what they found

00:59:55.919 --> 00:59:57.596 is displayed on on the slide.

00:59:57.596 --> 00:59:59.752 Here was that in a cohort of

01:00:01.924 --> 01:00:04.336 a slightly over 2300 patients,

01:00:04.336 --> 01:00:07.982 the five year overall survival improved

01:00:07.982 --> 01:00:10.238 from 15% between 1980 and 1989 to 48%

01:00:10.240 --> 01:00:13.170 in the most recent decade that was studied,

01:00:13.170 --> 01:00:15.470 Median overall survival improved from

01:00:15.470 --> 01:00:18.174 1.4 to 4.6 years and the six month

01:00:18.174 --> 01:00:21.085 mortality rate dropped from 23% to 13%.

01:00:21.085 --> 01:00:22.865 When comparing between these

01:00:22.865 --> 01:00:24.575 two time periods, however,

01:00:24.575 --> 01:00:26.450 amyloid remains a challenging disease,
both due to delays in diagnosis

and challenges with treatment,

notably, in patients with cardiac involvement

and further advances in therapy

are really crucial.

So the Andromeda study is a phase three randomized open label controlled trial

that compares our prior standard of care for amyloid which was Bortezomib,

cyclophosphamide and dexamethasone.

Ortved versus VCT,

plus the anti CD 38 monoclonal antibody daratumumab which was administered subcutaneously in
patients with newly diagnosed tail.

Amyloid and cardiac stage one through 3/8 disease were recruited for the study.

And both arms received for six cycles with the study, the protocol or daratumumab arm getting VCD Times 6 studies 6 cycles and then monotherapy with their two mab every four weeks for a maximum of 24 total cycles. Prior analysis at 6 and 12 months revealed that the addition of subcutaneous there are two in map to VCD resulted in deeper and more rapid hematologic response
01:01:30.589 --> 01:01:32.344 is also improved organ,
NOTE Confidence: 0.82114971
01:01:32.344 --> 01:01:34.854 responses and prolongation of major
NOTE Confidence: 0.82114971
01:01:34.854 --> 01:01:37.210 major organ deterioration progression.
NOTE Confidence: 0.82114971
01:01:37.210 --> 01:01:40.290 Free survival and this data led to
NOTE Confidence: 0.82114971
01:01:40.290 --> 01:01:42.650 Derived being the first approved
NOTE Confidence: 0.82114971
01:01:42.650 --> 01:01:45.968 therapy for a limoy dose in nine
NOTE Confidence: 0.82114971
01:01:45.968 --> 01:01:48.117 countries with FDA accelerated
NOTE Confidence: 0.82114971
01:01:48.117 --> 01:01:51.191 approval granted in January of 2021,
NOTE Confidence: 0.82114971
01:01:51.191 --> 01:01:56.361 and so the current abstract presented
NOTE Confidence: 0.82114971
01:01:56.361 --> 01:01:58.536 by Doctor Raymond Comenzo from Tufts
NOTE Confidence: 0.82114971
01:01:58.536 --> 01:02:01.030 a median follow-up of 25.8 months.
NOTE Confidence: 0.945517786470588
01:02:03.120 --> 01:02:05.412 So these tables outline the demographics
NOTE Confidence: 0.945517786470588
01:02:05.412 --> 01:02:07.346 and baseline characteristics of patients
NOTE Confidence: 0.945517786470588
01:02:07.346 --> 01:02:09.440 that have been enrolled in Andromeda,
NOTE Confidence: 0.945517786470588
01:02:09.440 --> 01:02:10.990 and they were well balanced
between the two treatment arms.

The median age of in the dairy

VCD arm was 62 years and both arms

had a slate mail predominance.

I would like to point out that

only three to 4% of patients on

both arms in this study identified

as black or African American,

which is important in considering the

generalizability of these results,

and was a a discussion when

this abstract was presented at.

Gosh, I think really highlighting the

importance of improving improving

diversity in our clinical trials,
and that includes in trials of plasma cell disorders.

66% of patients had involvement of two or more organs with cardiac and renal involvement being the most common,

36% of the patients in the dairy VCD arm had stage 3A cardiac disease at the median follow-up of 25.8 months.

77.2% of patients in the dairy VCD arm had received daratumumab monotherapy.

After six cycles of Derrived and 36% of patients and either in both groups had discontinued study treatment. So over two years of follow up, more patients achieved a hematologic
01:03:18.595 --> 01:03:21.190 complete response in the Derived arm at
01:03:21.190 --> 01:03:24.850 60% compared to only 19% on the VCD arm.
01:03:24.850 --> 01:03:26.770 And you can see this hematologic
01:03:26.839 --> 01:03:28.627 complete response response is
01:03:31.310 --> 01:03:33.626 Patients achieving a very good partial
01:03:33.626 --> 01:03:35.820 response or better improved from 77%
01:03:35.820 --> 01:03:38.270 of the time of primary analysis to
01:03:38.270 --> 01:03:41.630 79% in this updated analysis analysis.
01:03:41.630 --> 01:03:42.087 Importantly,
01:03:42.087 --> 01:03:44.372 hematologic complete response was higher
01:03:44.372 --> 01:03:47.346 with therapy CD and all prespecified
01:03:47.346 --> 01:03:49.694 subgroups and those included groups
01:03:49.694 --> 01:03:51.949 with cardiac involvement at baseline.
01:03:51.950 --> 01:03:54.232 Those who had cardiac stage three disease

and those with translocation 11;4, which makes up about 50 to 60% of our 
our population.

And as you can see in these graphs, the cardiac and renal response rates 
significantly higher at both 6 and 18 months when compared to the VCD arm at 
the 18 month mark presented at this ash, both cardiac and renal response 
rates were more than twice as high as the organ responses that 
were achieved with just VCD alone, and it’s important to remember that 
organ response and Dale amyloidosis can be delayed or lagged behind.
Hematologic response in that organ responses. Are thought to really improve quality of life in this complex patient population. There were a greater number of deaths related to disease progression in the VCD arm, though with a longer time on therapy, the absolute number of deaths while on treatment was higher in the Derrived arm? Serious treatment, emergent adverse events occurred in 47% of patients on the Derrived arm. And 36% of patients receiving VCD alone with pneumonia being the most common serious adverse event.
that was observed in both groups.

The rate of discontinuation due to treatment emergent events was similar in both groups and the most common adverse events observed in the study are outlined, and the tables at the bottom of this slide. So in summary, after more than two years of follow-up hematologic and Oregon response has continued to increase with their trauma BCD when compared with VCD alone. Fortunately, there were no new safety concerns that were identified with this longer follow-up, and overall survival will be analyzed and major organ deterioration progression.
Free survival will be updated after approximately 200 events, though at the median follow-up presented here of 25.8 months, there were fewer deaths that were observed in the derived. And so this updated analysis really confirms the treatment benefit of this regimen out to 18 months, and supports derived as a new standard of care for our patients with newly diagnosed ALE amyloidosis? So the final abstract that I will touch upon was presented by Doctor.
Jason Valent from the Cleveland Clinic, and it reviewed the safety and tolerability of Cal 101 in combination with anti plasma cell therapy for patients with a lamb.

Lloyd Ossis and this was from a one year results from an open label phase two trial.

So, as we previously discussed, amyloid fibril deposition and organs results in organ dysfunction with significant morbidity and mortality for patients with a lamb.

Lloyd and our standard of care anti plasma cell therapy is just discussed.

Really decreases the production of amyloidogenic like chains by targeting abnormal bone marrow plasma.
cells but doesn’t address the amyloid fibrils already present in and organs.

So Cal 101 is a chimeric monoclonal antibody and it binds annio appetite. That’s present on both Kappa and Lambda light chain fibrils, resulting in proteolysis and removal of the amyloid fibrils from tissues and organs in a phase.

One study of this agent Cal 101 was well tolerated up to 500 milligrams per meter squared in patients who had relapsed or refractory ale, in the phase two component. It was tolerated up to 1000 milligrams.
per meter squared when administered in combination with standard of care and I plasma cell therapy, and this was the patients recruited had cardiac stage one through three a disease.

So 25 patients are included in the analysis that was presented at ASH and all had a confirmed diagnosis at amyloid at least a six month minimum life expectancy.

And there were the patients recruited were not planned for autologous stem cell transplant in the first six months of the study. Patients were excluded if they had concomitant multiple myeloma or

01:07:55.330 --> 01:07:56.850 And subjects received four weekly doses of Cal.

01:07:58.370 --> 01:08:00.605 101 and then biweekly dosing until clinical deterioration,

01:08:02.793 --> 01:08:05.121 and as you can see in the schema

01:08:05.121 --> 01:08:07.186 Part B of the study added daratumumab to the standard of care therapy

01:08:09.353 --> 01:08:11.327 based on the Andromeda trial.

01:08:11.327 --> 01:08:12.967 The mean age of the study group was 65.2 years,

01:08:14.699 --> 01:08:16.086 80% of the patients had cardiac
amyloid involvement in 92% of these individuals had cardiac stage two or three a disease. 96% of patients had treatment emergent adverse events with the most common ones being listed in the table at the bottom right. The only 24% of those were felt to be related to treatment and most adverse events were low grade with the thought that the cardiac safety of this agent was really more warm or well tolerated than expected overall. So though there was a limited
number of patients, 18 of the 20 patients with cardiac involvement showed stability or improvement based on the NT Pro BNP values, with some of the 35% of those who responded, reportedly showing dramatic improvement and similarly eight of nine patients with renal involvement at baseline achieved renal responses with more than 30% reduction in their proteinuria and some patients having very rapid and deep responses. So to summarize, Cal 101 appears to be very well tolerated. And safe in combination with
our standard of care anti plasma

NOTE Confidence: 0.909779082380952

cell therapy which is now.

NOTE Confidence: 0.909779082380952

There are two memorable plus V CD

NOTE Confidence: 0.909779082380952

and it has yielded cardiac and renal

NOTE Confidence: 0.909779082380952

responses in a majority of patients.

NOTE Confidence: 0.909779082380952

Cal 101 is now being studied

NOTE Confidence: 0.909779082380952

in phase three trials.

NOTE Confidence: 0.909779082380952

For patients with Mayo stage

NOTE Confidence: 0.909779082380952

3/8 and also stage 3B disease.

NOTE Confidence: 0.909779082380952

Cardiac disease which was previously

NOTE Confidence: 0.909779082380952

excluded from this and from a patients

NOTE Confidence: 0.909779082380952

that were previously excluded from

NOTE Confidence: 0.909779082380952

this and from the Andromeda trial.

NOTE Confidence: 0.909779082380952

So I will stop there and.

NOTE Confidence: 0.909779082380952

We will move to questions and answers.

NOTE Confidence: 0.825972825714286

OK, thank you everyone
01:10:03.714 --> 01:10:05.547 for great presentations.
01:10:05.550 --> 01:10:06.982 I will start by asking know
01:10:06.982 --> 01:10:08.620 far could you tell us your
01:10:08.682 --> 01:10:10.367 perspective on how would you
01:10:10.367 --> 01:10:12.445 envision CAR T cell therapies in
01:10:12.445 --> 01:10:14.431 the coming years in the future
01:10:14.431 --> 01:10:15.880 for transplant eligible patients?
01:10:16.850 --> 01:10:18.327 I think it’s a very good question.
01:10:18.330 --> 01:10:20.074 I mean, many studies are looking at that.
01:10:20.080 --> 01:10:22.378 I think moving clearly you see
01:10:22.378 --> 01:10:24.354 unbelievable responses in patients who
01:10:24.354 --> 01:10:26.269 typically didn’t respond like this.
01:10:26.270 --> 01:10:28.406 So one could imagine even better
01:10:28.406 --> 01:10:30.210 responses and longer duration of
01:10:30.210 --> 01:10:32.422 responses and more fit patients with a
better immune system and given up front.

So then I think this is what?

The future is going to be.

It’s going to be evaluated upfront in transplant eligible and ineligible patients.

Right, and can you comment either?

Either the M car or the cell to cell.

Were there any subjects included with them? CNS involvement.

No CNS involvement. These are excluded.

I think within our practice we have had patients who had a CNS enrollment and they’ve been treated.

These are anecdotal,

but I’m sure it’s evolving.

I also wanted to ask a question of
01:11:17.320 --> 01:11:19.617 doctor Browning Sobrino how how do
01:11:24.600 --> 01:11:25.280 Yeah, I think you know.
01:11:25.280 --> 01:11:27.224 I think that’s that’s an important
01:11:27.224 --> 01:11:28.915 question because of the role
01:11:28.915 --> 01:11:30.590 that autologous stem cell
01:11:30.590 --> 01:11:32.440 transplant has played in amyloid.
01:11:32.440 --> 01:11:33.700 In terms of, you know,
01:11:33.700 --> 01:11:35.188 improve improvement in progression,
01:11:35.188 --> 01:11:36.676 free and overall survival,
01:11:36.680 --> 01:11:39.192 but I think now you know the the
01:11:39.192 --> 01:11:40.661 hematologic and organ response
01:11:40.661 --> 01:11:42.591 rates in Andromeda with their
01:11:42.591 --> 01:11:44.540 VCD are really impressive,
and I think importantly, the responses occur rapidly, which is an important in terms of subsequent organ responses. So I would say that you know, I think in. Most of our patients we should use Darragh VCD and then the question becomes of those patients who should go on to get autologous stem cell transplant. The thought is that there may...
not be additional benefit to auto transplant and that those patients have transplant available available to them if they were to relapse subsequently.

Great and a question for Terry with this in this competing environment of therapies for relapsed refractory myeloma. Where do you position by tone? Approach.

Yeah, and that’s a good question. So it’s you know, a lot of these trials are still in early phase, and they’re still in really
heavily treated patients.

So I think we don’t know which ones gonna win, right?

All the bispecific seem to have very similar toxicity profiles as far as CRS minimal.

can’t hematological toxicity.

do see the by specifics being moved into that one to three lines of therapy,

epecially if we can improve upon the duration of response.

Similar to kind of what never was saying with the car.

T and then I believe the question of car T versus advice specifics really gonna come up and the vice specifics.

Maybe for those individuals who really can’t.
Wait for the treatment sooner rather than later, as a majority of their responses were seen within a month of therapy. And so I think it’s going to depend on how extensive the disease is, how quickly a patient needs therapy, and how fit they are overall. But I think we have a question in the chat if you see it for Doctor Gore shot. So the question asks outside the clinical trial context, when would you use Dara? RVD in clinical setting? General standard of care.
He said, is that meant to be Dara, RVD, or this is our VP.

Well I guess spread needs Prednisone, Prednisone or dexamethasone platinum. So I think that I mean look. Obviously we have a couple of options here. You know, like we discuss VRD backbone. Well established, efficacious. You know if you’re if you’re a little more concerned about high risk, there are some centers that would go KRD, but to me I think that the quadruple it we see the durable improvement in response is, you know, approaching the 24 month of maintenance therapy. So if a patient has.
If a patient can tolerate a quadruplet, you know whether they're standard risk or high risk. I would strongly consider that. Yeah, I agree, I think the quadruplet therapies for monoclonal antibody backbone are entering the frontline care and with more and more data accumulating and data maturing to show. So far it's the murdered superiority. But we know from separate trials that MRD negativity is associated translates into much improved progression, free survival and overall survival. So I think the field is really evolving and...
which one will emerge as the next favorite.

Therapy is a big question.

I think one has to consider that high risk patients.

You know situation may still not be optimal, so further work needs to be done for the high risk population.

Say I think it’s hour and 15 minutes, which is the time we provisioned for this seminar.

I don’t see any other questions.

Any other discussion from the panelists here?

If not, we will conclude and thank you very much for participation. Everyone, thanks.