For joining this is Yale.

Highlights of ASH 2021 presented by Yale Hematology and today's seminar is presented by the program for multiple myeloma and Gammopathy’s, and we have really fantastic set of speaker presentations. Today.

Our program presented by Doctor Gore, our expert clinical expert in hematology doctor Terry Parker, who's the clinical leader of our program with extensive experience and expertise in clinical trials.
Doctor no far bar.

Who's our expert in cellular?

Therapies and transplantation in myeloma and doctor Sabrina Browning,

who has expertise in preclinical studies and alloyed doses.

And I just like to share this structure of today's seminar.

First, Doctor Gore Shine will present updates in smoldering multiple myeloma and newly diagnosed myeloma.

This will be followed by Doctor Terry Parker with updates in relapse and refractory myeloma.

Later, 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 consistently preceded by precursor.

states of monoclonal gammopathy of undetermined significance and smoldering multiple myeloma.

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

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

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 and 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
00:05:53.763 --> 00:05:56.599 treatment naive patient population,
NOTE Confidence: 0.674787556
00:05:56.600 --> 00:05:57.653 but there are.
NOTE Confidence: 0.674787556
00:05:57.653 --> 00:05:59.057 There are unanswered questions
NOTE Confidence: 0.674787556
00:05:59.057 --> 00:06:01.229 and we need more information.
NOTE Confidence: 0.674787556
00:06:01.230 --> 00:06:03.900 How does this regimen impact the
NOTE Confidence: 0.674787556
00:06:03.900 --> 00:06:05.680 high risk patient population?
NOTE Confidence: 0.674787556
00:06:05.680 --> 00:06:08.403 What about those that are stem cell
NOTE Confidence: 0.674787556
00:06:08.403 --> 00:06:10.330 transplant eligible versus ineligible?
NOTE Confidence: 0.674787556
00:06:10.330 --> 00:06:13.130 And clearly we need more long term
NOTE Confidence: 0.674787556
00:06:13.130 --> 00:06:16.162 results that we currently have for VRD,
NOTE Confidence: 0.674787556
00:06:16.162 --> 00:06:18.198 but you know it is not quite
NOTE Confidence: 0.674787556
00:06:18.198 --> 00:06:19.250 not quite there yet.
NOTE Confidence: 0.674787556
00:06:19.250 --> 00:06:22.438 For the quadruple therapy.
NOTE Confidence: 0.674787556
00:06:22.440 --> 00:06:24.924 So moving onto the updated Griffin
NOTE Confidence: 0.674787556
00:06:24.924 --> 00:06:27.940 analysis so this was published in Ash.
NOTE Confidence: 0.674787556
00:06:27.940 --> 00:06:30.440 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 regimen 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 was added to 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 they were randomized to either the quadruple it or the triplet with RV. They subsequently underwent stem cell transplant,
followed by two cycles of consolidation

continued by two cycles of consolidation

Maintenance for up to two years.

The primary endpoint here was a stringent CR.

Secondary endpoints included various response rates, MRD, negativity, progression, free survival,

You note that the patient characteristics were 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 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.
And then revised higher,
so genetic risk profile.
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
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
a 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 MRD 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 these results were actually originally published.
00:11:55.006 --> 00:11:57.030 last summer at the FAP meeting,
00:11:57.030 --> 00:11:59.864 but I’m gonna review it here also,
00:11:59.864 --> 00:12:02.655 within the context of this
00:12:02.655 --> 00:12:07.065 presentation by Doctor Usmania at MSK.
00:12:07.070 --> 00:12:09.350 Who essentially wanted to determine
00:12:09.350 --> 00:12:12.532 the effects of the Maya on patients
00:12:12.532 --> 00:12:14.344 with impaired renal function,
00:12:14.350 --> 00:12:15.910 which is relevant here?
00:12:15.910 --> 00:12:18.250 Because really up to up to
00:12:18.336 --> 00:12:20.530 50% of patients can have some
00:12:20.530 --> 00:12:22.490 baseline renal compromise that can
00:12:22.562 --> 00:12:24.587 impact our choice of treatment.
00:12:24.590 --> 00:12:26.630 So the the Maya the mitral.
00:12:26.630 --> 00:12:27.970 As you may know,
00:12:27.970 --> 00:12:30.528 evaluated the addition of Dara to Rev
00:12:30.534 --> 00:12:33.833
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, and this was despite the fact that almost half the patients in the Rev Dex population received subsequent therapy, including a dare to Matt based regimen.

So so important 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
I told 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 here 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, which is another CD 38 monoclonal antibody and hear the IT evolved 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% 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.
00:17:00.680 --> 00:17:02.776 and transplant ineligible patients.
NOTE Confidence: 0.911890994
00:17:05.500 --> 00:17:08.074 And finally, I think it’s also
NOTE Confidence: 0.911890994
00:17:08.074 --> 00:17:10.500 important to discuss the master
NOTE Confidence: 0.911890994
00:17:10.500 --> 00:17:13.000 trial which involved daratumumab,
NOTE Confidence: 0.911890994
00:17:13.000 --> 00:17:14.426 carfilzomib, Lenalidomide,
NOTE Confidence: 0.911890994
00:17:14.426 --> 00:17:16.565 and dexamethasone togus
NOTE Confidence: 0.911890994
00:17:16.565 --> 00:17:19.417 transplant and MRD response.
NOTE Confidence: 0.911890994
00:17:19.420 --> 00:17:22.650 Adaptive consolidation.
NOTE Confidence: 0.911890994
00:17:22.650 --> 00:17:24.939 We know that there are two have
NOTE Confidence: 0.911890994
00:17:24.939 --> 00:17:26.415 improves outcomes when combined
NOTE Confidence: 0.911890994
00:17:26.415 --> 00:17:28.540 with a proteasome inhibitor and
NOTE Confidence: 0.911890994
00:17:28.540 --> 00:17:30.240 or an immunomodulator agents.
NOTE Confidence: 0.911890994
00:17:30.240 --> 00:17:33.648 We also know that MRD negativity
NOTE Confidence: 0.911890994
00:17:33.648 --> 00:17:35.352 has prognostic implications.
NOTE Confidence: 0.911890994
00:17:35.360 --> 00:17:38.275 Now, this study incorporated a
NOTE Confidence: 0.911890994
00:17:38.275 --> 00:17:41.190 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 shirt 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 and genetic abnormalities 2 or more.

00:18:28.850 --> 00:18:32.000 Observation and surveillance.

NOTE Confidence: 0.800925246875

00:18:32.000 --> 00:18:34.856 Those patients who did not achieve MRD

NOTE Confidence: 0.800925246875

00:18:34.856 --> 00:18:37.215 shirt continued to receive Lenalidomide

NOTE Confidence: 0.800925246875

00:18:37.215 --> 00:18:40.383 maintenance as their standard of care.

NOTE Confidence: 0.800925246875

00:18:40.390 --> 00:18:41.550 And here are the results.

NOTE Confidence: 0.800925246875

00:18:41.550 --> 00:18:43.310 You can appreciate that.

NOTE Confidence: 0.800925246875

00:18:43.310 --> 00:18:46.150 Overall, the majority of patients at

NOTE Confidence: 0.800925246875

00:18:46.150 --> 00:18:49.660 80% achieved MRD negativity and the

NOTE Confidence: 0.800925246875

00:18:49.660 --> 00:18:53.545 depth of response and MRD negativity

NOTE Confidence: 0.800925246875

00:18:53.545 --> 00:18:57.265 improved at each therapy phase.

NOTE Confidence: 0.800925246875

00:18:57.270 --> 00:19:00.108 As you can appreciate with these

NOTE Confidence: 0.800925246875

00:19:00.108 --> 00:19:02.000 blocks and became comparable

NOTE Confidence: 0.800925246875

00:19:02.078 --> 00:19:04.746 among the groups with no high risk,

NOTE Confidence: 0.800925246875

00:19:04.746 --> 00:19:06.836 cytogenetic anomalies 1 high risk

NOTE Confidence: 0.800925246875

00:19:06.836 --> 00:19:09.455 genetic anality or two or more

NOTE Confidence: 0.800925246875

00:19:09.455 --> 00:19:11.179 high risk genetic abnormalities.
When we assess when they assessed MRD to at level of $1 \times 10^{-6}$, 666% 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, 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
00:19:54.818 --> 00:19:57.630 about 14 months and the risk of MRD,
NOTE Confidence: 0.56494648
00:19:57.630 --> 00:20:01.710 resurgence or clinical progression was
NOTE Confidence: 0.56494648
00:20:01.710 --> 00:20:06.198 40 and 27% among the standard high risk
NOTE Confidence: 0.56494648
00:20:06.198 --> 00:20:10.110 and ultra high risk patient groups,
NOTE Confidence: 0.56494648
00:20:10.110 --> 00:20:12.570 respectively. And importantly,
NOTE Confidence: 0.56494648
00:20:12.570 --> 00:20:14.796 none of the patients who entered this
NOTE Confidence: 0.56494648
00:20:14.796 --> 00:20:17.089 phase of MRD sure ultimately died
NOTE Confidence: 0.56494648
00:20:17.090 --> 00:20:20.658 from multiple myeloma progression.
NOTE Confidence: 0.56494648
00:20:20.660 --> 00:20:21.839 So, in conclusion,
NOTE Confidence: 0.56494648
00:20:21.839 --> 00:20:23.018 next generation sequencing,
NOTE Confidence: 0.56494648
00:20:23.020 --> 00:20:23.850 MRD response,
NOTE Confidence: 0.56494648
00:20:23.850 --> 00:20:26.340 adaptive therapy is feasible in the
NOTE Confidence: 0.56494648
00:20:26.340 --> 00:20:28.238 overwhelming majority of patients in
NOTE Confidence: 0.56494648
00:20:28.238 --> 00:20:30.762 multicenter settings with 70 to 72% of
NOTE Confidence: 0.56494648
00:20:30.762 --> 00:20:33.288 patients or she reaching MRD shore.
NOTE Confidence: 0.56494648
00:20:33.290 --> 00:20:36.209 Patients who have standard and high risk,
newly diagnosed myeloma had similar depth of response and low risk of MRD, 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.

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 is at BCM a CD3 bispecific antibody here. 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.
receive stubborn.

Testing at 0.06 and 0.3 makes per

kig subcutaneously followed by weekly

Treatment of 1.5 mix perchik subcutaneously.

The primary endpoint for the trial was

overall response rates 40 patients

were accrued in phase one on 125.

In phase two.

The median treatment duration was 5.9 months.

38 patients had high rossetto genetics,

38 with ISS three disease,

and this is a heavily pretreated

patient population.

With five medium prior lines of therapy,

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.
00:24:23.708 --> 00:24:25.628 with a progression free survival
00:24:25.628 --> 00:24:27.729 rate at nine months of 58.
00:24:27.730 --> 00:24:30.060 Lakeside percent in patients who
00:24:30.060 --> 00:24:32.810 did achieve a CR better MRD.
00:24:32.810 --> 00:24:36.618 Negativity rate was 41.9%.
00:24:36.620 --> 00:24:38.060 I’m looking at the safety data.
00:24:38.060 --> 00:24:40.010 The most common hematologic treatment.
00:24:40.010 --> 00:24:42.860 Emergent adverse event was neutropenia
00:24:42.860 --> 00:24:45.520 occurring in 65.5% of patients with the
00:24:45.520 --> 00:24:47.670 most common non unity logic treatment.
00:24:47.670 --> 00:24:50.185 Emergent Adverse bank was cytokine
00:24:50.185 --> 00:24:52.854 release syndrome occurring in 71.5% of
00:24:52.854 --> 00:24:55.470 patients and taking a closer look at CRS.
00:24:55.470 --> 00:24:57.528 The meeting time to onset was two
00:24:57.528 --> 00:24:59.747 days with the meeting duration of
today’s 60 patients did require supportive care with tocilizumab. The conclusions from this presentation was that the overall response rate with 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. If they occurred,
were all grade one and two and resolved,

moving on to another PC MA targeted fights.

And doctors and represented early,

depth and durable.

Response to this with low rates

of cytokine release syndrome.

With Regina on 5458.

Regenerx on 5458 again as ABC made.

CD3 bispecific antibody.

This is a phase one,

two first in human study with key

eligibility criteria including three

or more lines of prior therapy,

and these patients had to be

triple class refractory.
Part One was a dose escalation utilizing a modified 4 + 3 design with dose ranges from 3 to 800 milligrams. Part 2 will be an 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 lenses 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 question in the presentation. 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.

22% they showed an acceptable and manageable safety profile as the maximum
 tolerated dose was not reached with CRS

being reported in only 38% of patients,

the majority events were grade

one occurred within the first two

weeks and resolved within one day.

The phase two portion of the

study is currently recruiting.

And moving away from a BCM,

Krishnan presented updated Phase

one results from monumental one at

first in human study of Calcutta

Mad so till catnip is a G protein

coupled receptor family.

See Group 5D Member D as also

known as GPRC 5D CD.
NOTE Confidence: 0.626279934444444
00:29:04.130 --> 00:29:06.422 3 bispecific antibody she presented updated
NOTE Confidence: 0.626279934444444
00:29:06.422 --> 00:29:09.149 data at the first recommended phase.
NOTE Confidence: 0.626279934444444
00:29:09.150 --> 00:29:11.096 Two dose and initial results for patients
NOTE Confidence: 0.626279934444444
00:29:11.096 --> 00:29:12.829 treated as second recommended phase.
NOTE Confidence: 0.626279934444444
00:29:12.830 --> 00:29:14.885 Two dose of 800 micrograms
NOTE Confidence: 0.626279934444444
00:29:14.885 --> 00:29:16.940 per kilogram Q 2 weeks.
NOTE Confidence: 0.626279934444444
00:29:16.940 --> 00:29:18.670 Patients had to be relapsed
NOTE Confidence: 0.626279934444444
00:29:18.670 --> 00:29:20.400 refractory or intolerant to all
NOTE Confidence: 0.626279934444444
00:29:20.459 --> 00:29:22.584 established my limit therapies and
NOTE Confidence: 0.626279934444444
00:29:22.584 --> 00:29:24.257 have measurable disease previously.
NOTE Confidence: 0.626279934444444
00:29:24.257 --> 00:29:25.448 A recommended phase.
NOTE Confidence: 0.626279934444444
00:29:25.448 --> 00:29:28.820 Two dose of 405 micrograms per kilogram
NOTE Confidence: 0.626279934444444
00:29:28.820 --> 00:29:31.000 weekly subcutaneously was identified.
NOTE Confidence: 0.626279934444444
00:29:31.000 --> 00:29:32.836 Step up testing was utilized and
NOTE Confidence: 0.626279934444444
00:29:32.836 --> 00:29:34.698 premedication was given before all step up,
NOTE Confidence: 0.626279934444444
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, respectively.

had prior be CMA directed therapy.

And looking at the hematological treatment emergent adverse events, the most common was neutropenia and
67 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
two cohorts did require Tuscaloosa
Mab for supportive care.
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 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 kilogram, 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.
Ways to Jesse is ongoing.

And moving away from the bispecific antibodies and a presentation was done on loaded, excuse me alpha which is immune cytokine shows clinical activity. Updated results from my first in human phase one study. So Mataka Alpha is a first in class in unison in you know cytokine designed to deliver attenuated interferon alpha to CD. 38 positive cells patients were eligible if they had three or more prior lines of therapy were 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.
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, where 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...
were refractory toasty.

38 monoclonal antibody had a manageable safety profile.

Q For Weeks was identified as the optimal dosing interval and further enrollment identified the maximum tolerated dose as three mics per keg.

A randomized phase two trial is planned in order to determine the optimal single agent dosing.

Lastly, Dr Lonial presented herbicide in combination with dexamethasone in patients with relapsed refractory myeloma.

Results from the district expansion of the CC-220MM-001 trial.
Robert 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,

One through 21 every 28 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.
NOTE Confidence: 0.703098704545455
00:35:34.660 --> 00:35:36.390 made treatments for both cohorts.
NOTE Confidence: 0.703098704545455
00:35:36.390 --> 00:35:38.847 Patients had to have three or more lines
NOTE Confidence: 0.703098704545455
00:35:38.847 --> 00:35:41.207 of prior therapy and again for cohort I.
NOTE Confidence: 0.703098704545455
00:35:41.210 --> 00:35:43.778 All patients had treatment with her
NOTE Confidence: 0.703098704545455
00:35:43.778 --> 00:35:46.318 prior PC may targeted Agent 107.
NOTE Confidence: 0.703098704545455
00:35:46.318 --> 00:35:48.964 In patients were treated in cohort D
NOTE Confidence: 0.703098704545455
00:35:48.964 --> 00:35:52.090 and 26 in poker I 32 patients and six.
NOTE Confidence: 0.703098704545455
00:35:52.090 --> 00:35:52.840 Patients respectively,
NOTE Confidence: 0.703098704545455
00:35:52.840 --> 00:35:54.540 had high risk cytogenetics in
NOTE Confidence: 0.703098704545455
00:35:54.540 --> 00:35:55.560 the two cohorts.
NOTE Confidence: 0.703098704545455
00:35:55.560 --> 00:35:57.396 The median number of pirate therapies
NOTE Confidence: 0.703098704545455
00:35:57.396 --> 00:35:59.601 was six and seven in Cohort I6.
NOTE Confidence: 0.703098704545455
00:35:59.601 --> 00:36:01.563 Patients had prior card T 18
NOTE Confidence: 0.703098704545455
00:36:01.563 --> 00:36:03.680 and antibody drug conjugate,
NOTE Confidence: 0.703098704545455
00:36:03.680 --> 00:36:05.768 and eight bispecific T cell engager.
NOTE Confidence: 0.832980580769231
The most common adverse events occurring in 59 point, 8% in cohort D and 42.3% in cohort I.
Infections were common at 57.9% AL grading Health, Part D and 50% in Coker 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.
00:37:12.432 --> 00:37:13.576 supported the future development.
NOTE Confidence: 0.832980580769231
00:37:13.580 --> 00:37:15.855 Iber based regimens including combination
NOTE Confidence: 0.832980580769231
00:37:15.855 --> 00:37:18.380 studies with PRISM inhibitors and CD.
NOTE Confidence: 0.832980580769231
00:37:18.380 --> 00:37:21.650 38 monoclonal antibodies.
NOTE Confidence: 0.832980580769231
00:37:21.650 --> 00:37:23.010 I will stop there.
NOTE Confidence: 0.832980580769231
00:37:23.010 --> 00:37:24.030 As previously stated,
NOTE Confidence: 0.832980580769231
00:37:24.030 --> 00:37:25.620 all questions will be answered
NOTE Confidence: 0.832980580769231
00:37:25.620 --> 00:37:27.810 at the end of the program.
NOTE Confidence: 0.832980580769231
00:37:27.810 --> 00:37:32.319 Please encourage you to submit
NOTE Confidence: 0.832980580769231
00:37:32.319 --> 00:37:34.314 this in the Q&A portion and now I
NOTE Confidence: 0.832980580769231
00:37:34.314 --> 00:37:37.069 will turn it over to Doctor Barr.
NOTE Confidence: 0.9398939
00:37:37.069 --> 00:37:37.612 Thank you Terry so. Let’s get started.
NOTE Confidence: 0.9398939
00:37:37.612 --> 00:37:40.269 I’m focusing on car T cell therapy in
NOTE Confidence: 0.9398939
00:37:40.269 --> 00:37:41.215 the relapsed refractory myeloma patients.
NOTE Confidence: 0.9398939
00:37:41.215 --> 00:37:43.248 I want to highlight that patients
NOTE Confidence: 0.9398939
00:37:43.248 --> 00:38:02.968 who are refractory to image produce

60
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
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 BB costimulatory domains and it binds to BCMA on the cell surface of the tumor cell. It's approved for patients who are refractory to image PRISM and anti CD 38 antibody's. 76% of the patients responded, and about a third of the patients achieved deep responses, CR and stringent complete response. Most of those patients were emordi. 62
using next generation sequencing. Now, these patients had initially dose escalation, so not all of them received the same dose. If you look at the total population, the median progression free survival was 8.8 months, but if you hone in on the target dose, the patients that received the target FDA approved dose. It is about one year. All the population median overall survival 24 months. Now we also know that deep responses lead to longer duration of response,
00:39:45.450 --> 00:39:47.490 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 thePurple 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 figure out who are 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 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

67
00:41:55.804 --> 00:41:57.660 car T is not the full picture.
NOTE Confidence: 0.890803468823529

00:41:57.660 --> 00:41:59.934 We also understand that quality of
NOTE Confidence: 0.890803468823529

00:41:59.934 --> 00:42:02.418 T cells are important and this is
NOTE Confidence: 0.890803468823529

00:42:02.418 --> 00:42:04.504 a diagram showing you the T cell
NOTE Confidence: 0.890803468823529

00:42:04.575 --> 00:42:06.335 differentiation from the naive T
NOTE Confidence: 0.890803468823529

00:42:06.335 --> 00:42:10.360 these earlier T cell, the memory like phenotypes have
NOTE Confidence: 0.890803468823529

00:42:10.360 --> 00:42:11.656 some key qualities that make it
NOTE Confidence: 0.890803468823529

00:42:11.656 --> 00:42:13.276 quite attractive for car two
NOTE Confidence: 0.890803468823529

00:42:13.276 --> 00:42:15.195 products example though long lived
NOTE Confidence: 0.890803468823529

00:42:15.195 --> 00:42:16.730 they last longer.
NOTE Confidence: 0.890803468823529

00:42:16.793 --> 00:42:18.660 They have ability to self renew
NOTE Confidence: 0.890803468823529

00:42:20.080 --> 00:42:22.252 and they have a T cell plasticity.
NOTE Confidence: 0.890803468823529

00:42:25.170 --> 00:42:26.190 Furthermore, these memory,
NOTE Confidence: 0.890803468823529

00:42:26.190 --> 00:42:27.210 like T cells,
00:42:27.210 --> 00:42:29.095 were correlated with peak expansion and sustain response in karty studies.

00:42:33.910 --> 00:42:37.470 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 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 T 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,
so 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 T cells with 15% very comparable.
Said opinions are very common in general with all CAR T cells filling to the lymphodepletion that they get before and the Grade 3 and above infections which is clinically very meaningful is about 30%. In terms of efficacy, we’re all response rate was 74 percent, 39% with a CR and most of them being emerging negative. But this doesn’t look very different than Beckman information, what this study is looking at 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 results here.

Now in patients who achieve deeper responses, 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 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. peas 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. and then at 2 year follow up the median progression free survival, overall survival and duration of 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
00:47:14.868 --> 00:47:17.198 Gen sequencing in 61 patients.
00:47:17.200 --> 00:47:19.540 92 I’m really negative 30 patients
00:47:19.540 --> 00:47:20.320 had sustained.
00:47:20.320 --> 00:47:22.708 From our deep at six months
00:47:22.708 --> 00:47:25.317 and above and 18 had sustained
00:47:25.317 --> 00:47:28.095 MRD at 12 months and above.
00:47:28.100 --> 00:47:29.955 Now looking at progression free
00:47:29.955 --> 00:47:32.460 survival based on depth of response.
00:47:32.460 --> 00:47:35.764 So patients who had a CR stringent CR
00:47:35.764 --> 00:47:38.497 as exemplified by the Green Line here,
00:47:38.500 --> 00:47:40.750 had a two year progression free
00:47:40.750 --> 00:47:42.976 survival of 71% compared to
00:47:42.976 --> 00:47:45.436 60 for the total population.
00:47:45.440 --> 00:47:46.610 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 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 I came 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, they saw 15 events, secondary primary malignancy and 11 patients which were felt unrelated to me from cell to cell. And the thought is that this is not out of the usual for this. Multiply relapsed heavily pretreated myeloma patient population. One thing to note that it’s different with silty cells opposed to either sell or Beckman is that the CRS it has a later onset. The median of seven days after infusion compared to two days after a back comma. So it is a great possibility to give it
in alkylation setting and it is being tested in clinical trials like that. Last thing to comment about Silver cell is this movement and neurocognitive adverse effects. When the cell to cell was first given to patients, they saw the incidence of. He’s at 12% and actually was concerning the risk factors that they found to develop. This was high tumor burden. High car, T cell expansion and persistence, development of AI camps and CRS grade two or above. So Jameson and Team decided that they
00:50:07.702 --> 00:50:10.499 need to do something about this and
NOTE Confidence: 0.77864265
00:50:10.499 --> 00:50:12.375 develop patient management strategies,
NOTE Confidence: 0.77864265
00:50:12.380 --> 00:50:14.725 including enhancing bridging therapy to
NOTE Confidence: 0.77864265
00:50:14.725 --> 00:50:17.760 reduce tumor burden before they get the
NOTE Confidence: 0.77864265
NOTE Confidence: 0.77864265
00:50:20.020 --> 00:50:21.772 For CRS and I cans and
NOTE Confidence: 0.77864265
00:50:21.772 --> 00:50:22.940 probably is with driving,
NOTE Confidence: 0.77864265
00:50:22.940 --> 00:50:25.740 the higher use of toasting in this agent.
NOTE Confidence: 0.77864265
00:50:25.740 --> 00:50:28.484 With this there have been no further
NOTE Confidence: 0.77864265
00:50:28.484 --> 00:50:30.658 toxicities in the current incidents
NOTE Confidence: 0.77864265
00:50:30.658 --> 00:50:33.424 in over 200 patients treated on
NOTE Confidence: 0.77864265
00:50:33.424 --> 00:50:35.986 several clinical trials at 0.05,
NOTE Confidence: 0.77864265
00:50:35.986 --> 00:50:38.128 and this is important because this is
NOTE Confidence: 0.77864265
00:50:38.128 --> 00:50:40.222 what held up after your approval of
NOTE Confidence: 0.77864265
00:50:40.222 --> 00:50:42.353 this drug last year and now seems to
NOTE Confidence: 0.77864265
00:50:42.353 --> 00:50:44.640 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. This is called mcar H 109.

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

So this is a swim plot of swimmers plot of responsive follow-up of 18 months dose escalation.

You see here the doses go up with higher doses.

It does seem that there are deeper responses you can see by the green bars.

The follow up is relatively short for these patients.

Overall response rate about 70%.

About 1/4 achieved a complete response.

All populations, so more to follow on that safety was manageable.
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.

OK great so thank you again and those who may be able to stay on a little bit past the 1:00 o’clock hour.
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. And in this abstract presented
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.
00:54:51.850 --> 00:54:53.414 And there was an increase in bone marrow
00:54:53.414 --> 00:54:55.077
adipocytes in patients with myeloma and
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
NOTE Confidence: 0.915951835
00:55:37.740 --> 00:55:40.020 of fabp 4IN pathogenesis in myeloma,
NOTE Confidence: 0.915951835
00:55:40.020 --> 00:55:42.610 the authors studied of fabp 4 knockout
NOTE Confidence: 0.915951835
00:55:42.610 --> 00:55:45.499 and wild type mice who were fed a high
NOTE Confidence: 0.915951835
00:55:45.499 --> 00:55:48.315 fat diet for 12 weeks and you can see
NOTE Confidence: 0.915951835
00:55:48.315 --> 00:55:50.550 here in figure see that the knockout
NOTE Confidence: 0.915951835
00:55:50.550 --> 00:55:52.755 mountain mice had less tumor burden by
NOTE Confidence: 0.915951835
00:55:52.755 --> 00:55:55.134 PET scan and as displayed in figured D,
NOTE Confidence: 0.915951835
00:55:55.140 --> 00:56:02.498 The authors then applied a FAP
NOTE Confidence: 0.7780690435
00:56:02.498 --> 00:56:05.044 4 inhibitor known as BMS 309403,
NOTE Confidence: 0.7780690435
00:56:05.044 --> 00:56:06.592 which resulted in significant
NOTE Confidence: 0.7780690435
00:56:06.592 --> 00:56:08.580 attenuation of the tumor burden
NOTE Confidence: 0.7780690435
00:56:08.580 --> 00:56:10.455 and improved survival and obesity
NOTE Confidence: 0.7780690435
00:56:10.455 --> 00:56:12.331 induced myeloma mice as outlined
NOTE Confidence: 0.7780690435
00:56:12.331 --> 00:56:14.487 in the two figures on this slide.
NOTE Confidence: 0.7780690435
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.

In this next abstract that was presented by Doctor Simone Mini...
00:56:46.035 --> 00:56:47.825 at Fred Hutchinson Cancer Center,

00:56:47.830 --> 00:56:49.678 the combination of immunomodulatory,

00:56:49.678 --> 00:56:51.064 the immunomodulatory drug,

00:56:51.070 --> 00:56:52.750 Lenalidomide, and an antigen

00:56:52.750 --> 00:56:54.850 antibody was studied in mice.

00:56:54.850 --> 00:56:56.539 After undergoing autologous

00:56:56.539 --> 00:56:58.228 stem cell transplantation.

00:56:58.230 --> 00:56:59.210 As many of you know,

00:56:59.210 --> 00:57:00.955 high dose chemotherapy and autologous

00:57:00.955 --> 00:57:03.542 stem cell rescue has been shown to

00:57:03.542 --> 00:57:05.114 provide progression free survival

00:57:05.114 --> 00:57:06.686 benefit in multiple myeloma.

00:57:06.690 --> 00:57:08.026 Though in myeloma disease,

00:57:08.026 --> 00:57:09.028 relapses are expected,

00:57:09.030 --> 00:57:10.670 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...
00:57:43.246 --> 00:57:45.209 major role in disease of relapse,
00:57:45.210 --> 00:57:47.295 with studies showing a strong
00:57:47.295 --> 00:57:49.380 association between myeloma burden and
00:57:49.448 --> 00:57:51.506 expression of TIGIT on CD 8 positive
00:57:51.506 --> 00:57:53.969 T cells and mice status post stem
00:57:53.969 --> 00:57:55.510 cell transplant there for you guys.
00:57:55.510 --> 00:57:56.290 As you can imagine,
00:57:56.290 --> 00:58:01.639 TIGIT has emerged as an attractive target
00:58:01.640 --> 00:58:02.808 for immunotherapy in multiple myeloma.
00:58:02.808 --> 00:58:04.268 So in this study,
00:58:04.268 --> 00:58:06.108 myeloma mice underwent high dose
00:58:06.108 --> 00:58:07.596 received bone marrow grafts,
00:58:07.600 --> 00:58:09.652 followed by the administration
00:58:09.652 --> 00:58:12.217 of a antigen monoclonal antibody,
twice weekly for five weeks,
starting on the day of transplant or day
Lenalidomide administered daily for three weeks beginning on day,
plus 14 and synergistic anti myeloma activity was observed with this combination.
there was a significant reduction in the rate of tumor growth and also improved median.
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 anti-TIGIT monoclonal antibody and the 4th generation image or cell mod. I liberty 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...
immunoglobulin light chains which misfolded form insoluble amyloid fibrils. These fibrils then deposit into extracellular tissues and organs resulting in impairment of vital organ function and sometimes or often death with the introduction of novel therapies, there has been improvement in overall outcomes and prognosis for ALE amyloidosis which were. Historically, very, very grim. In an abstract 155, which was presented by Doctor Starin from the Boston University Amyloidosis Center, there was a 40 year Natural History study that was reviewed on outcomes.
for patients with a lambdoid seen at their center and what they found is displayed on the slide. Here was that in a cohort of a slightly over 2300 patients, the five year overall survival improved from 15% between 1980 and 1989 to 48% in the most recent decade that was studied, which was 2010 to 2019. Median overall survival improved from 1.4 to 4.6 years and the six month mortality rate dropped from 23% to 13%. When comparing between these two time periods, however, 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, VCD, plus the anti CD 38 monoclonal antibody daratumumab which was administered subcutaneously in
NOTE Confidence: 0.82114971
01:00:59.256 --> 01:01:00.786 patients with newly diagnosed tail.
NOTE Confidence: 0.82114971
01:01:00.790 --> 01:01:03.989 Amyloid and cardiac stage one through 3/8
NOTE Confidence: 0.82114971
01:01:03.989 --> 01:01:06.438 disease were recruited for the study.
NOTE Confidence: 0.82114971
01:01:06.440 --> 01:01:08.575 And both arms received for
NOTE Confidence: 0.82114971
01:01:08.575 --> 01:01:10.710 six cycles with the study,
NOTE Confidence: 0.82114971
01:01:10.710 --> 01:01:12.675 the protocol or daratumumab arm
NOTE Confidence: 0.82114971
01:01:12.675 --> 01:01:15.065 getting VCD Times 6 studies 6
NOTE Confidence: 0.82114971
01:01:15.065 --> 01:01:19.019 their two mab every four weeks
NOTE Confidence: 0.82114971
01:01:19.019 --> 01:01:21.294 for a maximum of 24 total cycles.
NOTE Confidence: 0.82114971
01:01:21.300 --> 01:01:23.442 Prior analysis at 6 and 12 months
NOTE Confidence: 0.82114971
01:01:23.442 --> 01:01:25.050 revealed that the addition of
NOTE Confidence: 0.82114971
01:01:25.050 --> 01:01:26.610 subcutaneous there are two in
NOTE Confidence: 0.82114971
01:01:26.610 --> 01:01:29.101 map to VCD resulted in deeper and
NOTE Confidence: 0.82114971
01:01:29.101 --> 01:01:30.589 more rapid hematologic response
NOTE Confidence: 0.82114971
is also improved organ,

responses and prolongation of major

major organ deterioration progression.

Free survival and this data led to

Derived being the first approved

therapy for a limoy dose in nine

countries with FDA accelerated

approval granted in January of 2021,

and so the current abstract presented

by Doctor Raymond Comenzo from Tufts

University provided an update after

a median follow-up of 25.8 months.

So these tables outline the demographics

and baseline characteristics of patients

that have been enrolled in Andromeda,

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, and importantly, 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 Derrived arm at 60% compared to only 19% on the VCD arm.

01:03:24.850 --> 01:03:26.770 And you can see this hematologic complete response response is deepened overtime in the dairy group.

01:03:31.310 --> 01:03:33.626 Patients achieving a very good partial response or better improved from 77% at time of primary analysis to 79% in this updated analysis.

01:03:35.820 --> 01:03:38.270 Importantly, hematologic complete response was higher with therapy CD and all prespecified subgroups and those included groups with cardiac involvement at baseline.

01:03:41.950 --> 01:03:54.232 Those who had cardiac stage three disease
and those with translocation 1114, which makes up about 50 to 60% of our ale amyloid population.

And as you can see in these graphs, the cardiac and renal response rates in patients receiving derived were 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 Derived arm? Serious treatment, the most common serious adverse event was pneumonia being the
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 amyloid oh genic 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 to amyloid 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 amyloid and in the phase two component. It was tolerated up to 1000 milligrams.
per meter squared when administered

in combination with standard of care and 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 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...

And subjects received four weekly doses of Cal.

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

01:07:56.850 --> 01:08:00.605 and then biweekly dosing until clinical deterioration,

01:08:00.605 --> 01:08:01.946 until clinical deterioration,

01:08:01.950 --> 01:08:02.793 toxicity or death,

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

01:08:07.190 --> 01:08:09.353 Part B of the study added daratumumab

01:08:09.353 --> 01:08:11.327 to the standard of care therapy based on the Andromeda trial.

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

01:08:12.970 --> 01:08:14.692 The mean age of the study group was 65.2 years,

01:08:18.130 --> 01:08:20.140 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. Here, 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
01:08:54.198 --> 01:08:55.137 number of patients,

01:08:55.140 --> 01:08:57.996 18 of the 20 patients with cardiac

01:08:57.996 --> 01:08:59.625 involvement showed stability or

01:08:59.625 --> 01:09:02.273 improvement based on the NT Pro BNP values,

01:09:02.280 --> 01:09:05.944 with some of the 35% of those who responded,

01:09:05.944 --> 01:09:07.297 reportedly showing dramatic

01:09:07.297 --> 01:09:09.489 improvement and similarly eight of

01:09:09.489 --> 01:09:11.424 nine patients with renal involvement

01:09:11.424 --> 01:09:13.310 at baseline achieved renal responses

01:09:13.310 --> 01:09:15.556 with more than 30% reduction in

01:09:15.556 --> 01:09:17.846 their proteinuria and some patients


01:09:20.620 --> 01:09:21.457 So to summarize,

01:09:21.457 --> 01:09:24.050 Cal 101 appears to be very well tolerated.

01:09:24.050 --> 01:09:25.615 And safe in combination with
our standard of care anti plasma
cell therapy which is now.
There are two memorable plus V CD
and it has yielded cardiac and renal
responses in a majority of patients.
Cal 101 is now being studied in phase three trials.
For patients with Mayo stage 3/8 and also stage 3B disease.
Cardiac disease which was previously
excluded from this and from a patients
that were previously excluded from
this and from the Andromeda trial.
So I will stop there and.
We will move to questions and answers.
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 unbelieviable 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 any subjects included with them? 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
01:11:24.600 --> 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 question because of the role that autologous stem cell transplant has played in amyloid.
01:11:28.915 --> 01:11:30.590 In terms of, you know, improvement in progression, free and overall survival,
01:11:32.440 --> 01:11:33.700 in Andromeda with their VCD are really impressive,
01:11:35.188 --> 01:11:36.676 but I think now you know the the hematologic and organ response rates in Andromeda with their 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 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. And I think what we and other centers have adopted is in patients who have achieved a hematologic complete response. 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 competing environment of therapies for relapsed refractory myeloma. Where do you position trials are still in early phase, 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.

I can’t hematological toxicity.

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

especially 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 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 of the clinical trial context, when would you use Dara? RVD in clinical setting? General standard of care.
01:14:00.290 --> 01:14:01.984 He said, is that meant to be Dara, RVD, or this is our VP.
NOTE Confidence: 0.742161594
01:14:05.470 --> 01:14:08.340 Well I guess spread needs Prednisone,
NOTE Confidence: 0.742161594
01:14:08.340 --> 01:14:12.340 Prednisone or dexamethasone platinum.
NOTE Confidence: 0.949571865
NOTE Confidence: 0.949571865
01:14:14.720 --> 01:14:16.600 Obviously we have a couple of options here.
NOTE Confidence: 0.949571865
01:14:16.600 --> 01:14:18.497 You know, like we discuss VRD backbone.
NOTE Confidence: 0.949571865
NOTE Confidence: 0.949571865
01:14:19.661 --> 01:14:22.839 You know if you’re if you’re a little more concerned about high risk,
NOTE Confidence: 0.949571865
01:14:22.839 --> 01:14:28.794 there are some centers that would go KRD,
NOTE Confidence: 0.949571865
01:14:28.800 --> 01:14:33.967 but to me I think that the quadruple it we see the durable improvement in response is,
NOTE Confidence: 0.949571865
01:14:33.967 --> 01:14:39.800 you know, approaching the 24 month of maintenance therapy.
NOTE Confidence: 0.949571865
01:14:39.800 --> 01:14:43.180 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 and with more and more data accumulating and data maturing to show. So far it’s the murded 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.
Thank you everyone. Thank you.