

## **GSK**

### **Accelerating our oncology pipeline:**

#### **belantamab mafoditin (GSK'916) DREAMM-2 data**

**Tuesday, 17 December 2019**

**Sarah Elton-Farr (Head of Global Investor Relations):** Good afternoon. Thank you for joining us here today on our call to discuss the data from the DREAMM-2 study, which was published yesterday in the *Lancet Oncology*.

#### **Agenda**

Our speakers today are: Dr Hal Barron, Chief Scientific Officer and President of R&D; Dr Peter Voorhees, Member of the Plasma Cell Disorders Division from the Levine Cancer Institute; Dr Axel Hoos, Head of Oncology R&D; and Luke Miels, President of Global Pharmaceuticals.

We also have Christine Roth, Global Oncology Therapy Area Head, and Ira Gupta, Medicine Development Lead for belantamab on the line for Q&A.

#### **Cautionary statement regarding forward-looking statements**

Before we begin, I would refer you to our cautionary statements on slide two, and with that I will hand over to Hal.

#### **Science x Technology x Culture**

**Hal Barron:** Thanks, Sarah.

In July of 2018 we unveiled our overall R&D approach, which is based on the multiplier effect of Science x Technology x Culture to strengthen our pipeline to a focus on science related to the immune system, the use of human genetics, and advanced technologies, and this continues to guide our investments in R&D to strengthen our pipeline and improve the drug development timelines and success rates.

We also highlighted our increased focus and investment in oncology, and during this call we will focus on the substantial progress we have made over the past year.

#### **Accelerating our oncology pipeline**

As you can see from this slide, we have made substantial progress in advancing the oncology portfolio, actually doubling the number of potential medicines in the pipeline over

the last 18 months, and, in fact, the pipeline had been at its most advanced stage in phase 1 about 18 months ago and now, in fact, we will have three potential launches in 2020.

We have strengthened the pipeline through business development deals such as the Tesaro acquisition, which brought us *Zejula* into the pipeline, and that's a terrific medicine. We are very pleased with the outcome of the PRIMA study in the frontline ovarian cancer maintenance setting, and the impact that these data will have on patients' lives.

We are on track to file these data as well as the GARNET data for dostarlimab by the end of the year.

In addition this year we also announced the strategic alliance with Merck KGaA of bintrafusp alfa. This is an asset that is progressing very well and is actually in a pivotal study for biliary tract cancer, as well as in a lung cancer study currently.

We are also making very good progress with our in-house assets, including, as we will talk about at length today, belantamab mafoditin, as well as other medicines, such as our ICOS agonist, which we recently presented the first efficacy data on at ESMO, and for which we have started a phase 2/3 study in combination with pembrolizumab in head and neck cancers. We have, as you can see on the slide, several epigenetic modifying drugs as well as several other IO agents, such as a STING agonist, a TIM-3 antibody, etc., as well as, actually, a deep focus on T-cell therapies, with our most advanced being NY-ESO for a number of different cancers, including sarcoma.

As I mentioned, we have nearly doubled the number of potential oncology drugs in the pipeline, and with the success in the data we now have three potential filings in 2020.

**Belantamab mafoditin (GSK'916): accelerated development plan advancing rapidly in multiple myeloma (MM)**

As I mentioned, one of the first assets that I highlighted to you back in July of 2018 was belantamab mafoditin, our BCMA/ADC, and just to remind you, this is a very unique and powerful molecule, whose activity is actually driven by four specific modes of action, if you will. The first being the fact that it is an antibody-blocking BCMA, which is a B-cell survival factor, and possibly even more importantly, this is an antibody drug conjugate. When the BCMA receptor and the ADC is internalised the antibody drug conjugate is released and the cell killing is induced by a very, very powerful MMAF conjugate.

In addition, we have consolidated this antibody so that it has enhanced ADCC activity, allowing effector NK cells and effector cells to bind the FC portion and cause a T-cell mediated destruction of the plasma cells, giving it further enhanced activity, and we also have shown pre-clinically and believe that a very important fourth mechanism by which this drug works is to potentiate, if you will, immunogenic cell death, and if there are questions we

can get into that, but we think that will allow it to be having a very interesting effect, not only as monotherapy, but in combination trials as it advances.

Based on a relatively small phase 1 programme, as you can see less than 85 patients originally, we decided to aggressively accelerate its development and, essentially, 18 months after deciding that and starting our pivotal trial, which I should say also included an additional dose based on FDA feedback, we have now positive data, and are filing that data. We actually have a series of studies, some of which are pivotal called the DREAMM-3 through 10 studies, which we can get into again if there are questions, and have a combined dataset now of 478 patients, and what this demonstrates is that when we find data from assets very encouraging and warrant aggressive approaches we now have the means and culture to, I think, develop transformational medicines to get them to patients in a very, very expedited manner.

That's just a brief overview.

I am now going to turn over to Dr Voorhees to share with you the very exciting data that I mentioned we generated in the pivotal DREAMM-2 study. Dr Voorhees –

## **Results of DREAMM-2**

**Dr Peter Voorhees**

**Director of Clinical Operations and Outreach for the Department of Hematologic  
Oncology and Blood Disorders**

**Member, Plasma Cell Disorders Division  
Levine Cancer Institute, Atrium Health**

Thank you very much. Just for those of you on the line, I was a Principal Investigator prior to being at Levine Cancer Institute at the University of North Carolina, where we participated in the first in-human DREAMM-1 trial, and then when I moved to Levine Cancer Institute back in the fall of 2016 I quickly became involved in the DREAMM programme here, played a role in participating and enrolling patients in the DREAMM-2 study, and we also are involved in other DREAMM protocols as well, so lots of familiarity with treating myeloma patients with belantamab mafoditin.

### **Trial design**

DREAMM-2 was a randomised phase 2 study. It was a randomised phase 2 study to better characterise optimal dosing moving forward, so patients were assigned to either 2.5 mg/kg intravenously once every three weeks, or 3.4 mg/kg once every three weeks. There was also an additional third cohort utilising the lyophilised product. The primary outcome for

the study, as in many relapsed refractory multiple myeloma studies was overall response rate utilising the standard International Myeloma Working Group guidelines.

Key secondary outcomes included other clinical efficacy perimeters such as progression-free and overall survival, duration of response, and, certainly and importantly, safety.

As far as eligibility criteria for this study are concerned, patients could have up to an ECOG performance status of 2. Patients had to have received at least three prior lines of multiple myeloma therapy, and, very importantly, patients had to be refractory to a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody, and just to provide you with some context, there was a retrospective study called the MAMMOTH trial that was published earlier this year, a retrospective analysis looking at close to 300 patients who had CD38 monoclonal antibody refractory disease, and for those patients who had what we call triple refractory disease, so that's refractoriness to a CD-38 antibody and a proteasome inhibitor and an IMiD, the median overall survival, not progression-free, but overall survival was anywhere from 5.6 to 9.2 months depending on specifically what you were looking at. So this is certainly a patient with an unmet medical need, and a lot of the patients that were enrolled on this trial when the investigators were discussing the options for those patients hospice care would have been one of those options for these patients, so a very heavily pre-treated group of patients.

Under the eligibility criteria we are fairly flexible with regards to renal function and patients with underlying low white blood cell count, low platelets were allowed, and, in fact, patients were allowed to be transfused to get on study, so this is a very heavily pre-treated group of patients.

### **Baseline demographic and disease characteristics**

Moving onto the next slide, as far as baseline patient characteristics are concerned, median age was in the mid-60s. There was an appropriate proportion of men and women based on the fact that myeloma is somewhat more predominant in men than women.

I do want to highlight that a very large percentage of patients on the study had ISS stage III disease, which is fairly unusual for a relapsed refractory multiple myeloma study, and I think that that's just a testimony to the fact that these patients were fairly sick going into treatment, and, in fact, only about 20% of patients had ISS stage I disease.

Then, the other thing I want to highlight is the fact that patients had – there's a high percentage of patients who had high-risk cytogenetic disease – 42 and 47% in the 2.5 versus 3.4 mg/kg cohort.

Median number prior lines of therapy was seven and six, so patients had had a lot of prior therapy, and 100% of patients were refractory to both an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, as stipulated in the protocol.

### **Primary endpoint, meaningful ORR with deep responses in both dose groups**

When we move to the next slide, again, the primary endpoint was overall response, and it was 31% in the 2.5 mg/kg arm, and 34% in the 3.4 mg/kg arm, and, not surprisingly, that's not significantly different.

I do want to point out that a lot of the responses were deep responses, so more than half of the responses in both arms of the trial were very good partial responses or better, and what that basically means is at least a 90% reduction in disease burden or better.

### **Primary endpoint, meaningful ORR with deep responses in both dose groups**

When we look at clinical benefit rate, so these are patients who not only had at least a 50% reduction in disease burden, but 25 or more, 34 and 39% respectively, and just to provide you with some context as far as the overall response rate is concerned, when daratumumab or Darzalex, the CD38 antibody first came onto the scene in 2015 and made a splash the overall response rate in that particular trial in which the majority of patients had proteasome inhibitor and IMiD-refractory disease was 30%, and then when we look at the recent data from the selinexor-dexamethasone study, selinexor being a novel myeloma drug in a similar space, an exportin-1 inhibitor in that two-drug combination the overall response rate was 26%, and we will talk more about that study in a moment.

### **Response rates in high-risk patient cohorts were comparable to the overall patient population**

Moving onto the next slide, responses were seen in a large number of different patients, so regardless of the ISS stage responses were seen, regardless of level of renal impairment, whether they had had three or four prior lines of therapy, or more than four, and, importantly, we saw responses that were very similar from those patients who had high-risk cytogenetics versus standard-risk cytogenetics.

### **Median DoR and OS were not reached for responders in either cohort**

Moving onto the next slide, as far as duration of response and progression-free survival are concerned, so median progression-free survival in the 2.5 mg/kg arm was 2.9 months, and it was 4.9 months for those patients that received 3.4 mg/kg, and this is not a statistically significant difference.

I do want to highlight the duration of response. It is not unusual for these studies in very heavily pre-treated refractory patients – again, the overall response rate is 30%, so there are some patients that are not responding to therapy, and those patients that are not

responding to therapy could have driven that median PFS down. But when you look at those patients that are actually responding to therapy, median duration of response is really quite impressive. If you look at the bottom left of this particular slide in the 2.5 mg/kg cohort, at six months you are looking at 74% of patients still in response, and then when you look at the 3.4 mg/kg arm it's 65%, and we can talk a little bit more later about why there might be some slight differences there, but these are very durable responses. Just to provide you with a little bit more context, going back to the selinexor-dexamethasone study where I said the overall response rate was 26%, in that particular trial the median progression-free survival was 3.7 months, somewhat similar to what we are seeing here, but the median duration of response was only 4.4 months. When you go back to the original single arm studies of daratumumab monotherapy when it first came to fruition in 2015 the median duration of response was 7.6 months. I do want to highlight that this is patients that are not only refractory to proteasome inhibitors and IMiDs, but refractory to CD38 antibodies as well. Therefore, those patients that are responding are responding very well.

### **Median PFS was not reached for responders in either cohort**

If we go onto the next slide, this gets at basically the same point I was just trying to make on the previous slide.

If you break down progression-free survival based on response, those patients that are achieving at least a partial response or better, or what we call a minimal response or better, that's the clinical benefit rate, those patients are having durable responses and, clearly, quite durable when you think about other competing therapeutics in this space.

### **Safety overview**

Going onto the next slide, as far as safety overview is concerned, and we will talk more about this, corneal toxicity is the most common side effect of this agent and has been seen with other MMAF-based antibody drug conjugates. Not a significant difference between the overall incidence of corneal side effects between the two arms of the trial. However, as far as clinically symptomatic corneal side effects such as blurred vision or dry eyes, there was a smaller proportion of patients on the 2.5 mg/kg arm that experienced actual symptoms of these corneal findings.

You will also note that when we look at hematologic toxicities, specifically low platelets and low neutrophils, you had less of that in the 2.5 mg/kg arm in contrast to the 3.4 mg/kg arm, and then when you look at some of the constitutional side effects such as fatigue, or if you look at gastrointestinal side effects like nausea, that also favoured the 2.5 mg/kg arm.

### **Adverse event-related dose reductions and delays were less frequent in 2.5 mg/kg vs 3.4 mg/kg group**

Moving onto the next slide, and this gets to what I was just hinting at just on the last slide. Although the adverse events rates were the same in both arms, if you look at adverse events leading to permanent treatment discontinuation, only 8 and 10%, which is very good in a multiple myeloma study.

Also, when you look at adverse events leading to dose reduction, that favoured the lower dose, the 2.5 mg/kg – specifically 29% versus 41%. Adverse events leading to dose delay favoured the lower dose as opposed to the 3.4 mg/kg dose, and there was also a trend towards fewer serious adverse events in the 2.5 mg/kg arm compared to 3.4 mg/kg arm, and that may be in part why we are seeing a somewhat better median duration of response at the six-month mark in the 2.5 mg/kg arm in contrast to the 3.4 mg/kg arm.

### **Keratopathy through common, led to few discontinuations**

Moving onto the next slide. Again, there was not a significant difference in the overall incidence of corneal findings between the two doses, but keratopathy or corneal effects did lead to dose reduction in 23 and 27% of patients in the two arms, and dose delays in 47 and 48% of the patients in the two arms respectively.

However, only four patients – one in the 2.5 mg/kg arm, and three in the 3.4 mg/kg arm actually had to permanently discontinue therapy due to corneal side effects.

As far as the patients with keratopathy or corneal side effects worse at the end of treatment compared to baseline, median time to resolution was 71 days and 96 days in the two arms of the study, and just based from personal experience both of the DREAMM-1 and DREAMM-2 study I will say that it is 100% reversible, and talking with other investigators who have worked with this agent they would say the same thing.

There were only three patients that had significant worsening of vision while they were on the study, but I am happy to report that their visual acuity returned to baseline with follow-up.

We see these findings on ophthalmologic exam, but not everybody has symptoms. The most common patient-reported corneal symptoms included blurry vision, which occurred in 22 and 30%, most of which was grade 1 and grade 2, so present but manageable, and then dry eyes was a common reported event as well, occurring in 14 and 23% of patients with only 1% of patients reporting a grade 3 dry eye.

### **Corneal event management protocol**

Moving onto the next slide, as far as corneal event management – again, as I alluded to before, the corneal events that were seen here are not uncommon for immunoconjugates

that use MMAF as the warhead. The exact mechanism of action remains unknown and definitely needs to be studied further, but it might be related to non-specific uptake of the antibody drug conjugate into dividing in epithelial cells in the basal epithelial layer of the cornea.

The keratopathy that was seen ophthalmologic exam was largely restricted to the corneal epithelium and not other structures of the eye.

There was a very clever sub-study that was done in DREAMM-2 where a subset of the sites had patients instil corticosteroid eye drops in one eye and no corticosteroid eye drops in the other eye and there was really no difference in the ophthalmologic findings in the two eyes of the patients, suggesting that the corticosteroid eye drops are not effective, so management is best dealt with with dose reductions and dose delays, as well as preservative-free artificial tears, particularly for those patients that are having dry eyes.

Therefore, for those patients experiencing corneal adverse reactions or changes in visual acuity of grade 2 or higher it is advised that these patients seek a consultation with an ophthalmologist.

For grade 2 events a dose reduction by 25% and continuation of treatment, and for those patients, the few patients that developed grade 3 or 4 events, withhold treatment until they improved to grade 2 or better, and then resume with the dose reduction.

### **DREAMM-2 data published in the *Lancet Oncology***

Then, on the last slide here, and as was alluded to at the beginning of the call, the study was actually just published in *Lancet Oncology* yesterday, which is a terrific kudos to the GSK team, and I think recognition of the importance of this agent in relapsed refractory multiple myeloma. I do want to highlight the fact that this is really an agent that has been studied in patients with an unmet medical need, and if you think again back to 2015, drawing the analogy with daratumumab or Darzalex, again, there an agent with single-agent activity with an overall response rate of 30%, a median progression-free survival between three and four months, and a median duration of response of about seven-and-a-half months. Daratumumab has since gone onto early relapse myeloma, it has gone onto newly diagnosed myeloma, and it's completely changed the landscape of myeloma therapy, and I think that belantamab mafoditin is poised to do the same thing.

With that, I will stop.

## **Putting DREAMM-2 in context**

### **Dr Axel Hoos, SVP Oncology R&D**

Good afternoon, this is Axel Hoos. I will now take the data from DREAMM-2 and provide some context information around it.

#### **Belantamab mafoditin: critical features**

As a quick snapshot, belantamab mafoditin has certain critical features that we believe are relevant to place it in the right context, including in the treatment landscape in the expansion of the development programme.

First, it is the most advanced BCMA-targeting agent currently investigated in multiple myeloma.

The DREAMM-2 data, as you have just heard, has demonstrated deep and durable responses in the very last line of therapy in patients that are very heavily pre-treated and have also been refractory to CD38-targeting antibodies.

The unique side-effect profile, particularly treatment-related corneal events were very manageable with the use of artificial tear drops and recommended dose modifications as Dr Voorhees has just explained, so we believe this is quite manageable and requires patient and physician education mostly to keep it controlled.

A critical feature is the easy administration of the agent. It can be given in as a 30-minute infusion every three weeks. It makes it relatively easy for the patient to handle.

We have a scalable manufacturing. Similar to other antibodies it is a relatively straightforward process to produce belantamab mafoditin and provide it to a large number of patients, both in expanding clinical trials as much as in a commercial setting.

Finally, we believe similar to what Darzalex has shown, once you go into earlier lines of treatment combinability is a critical feature, so we believe that synergy for combinations in earlier lines, either when combined with standards of care, or when you look at novel/novel combinations, and investigations that are testing that in the clinical programme are either already underway or are about to start.

Overall, this is the first agent that for monotherapy has filed at BLA as a BCMA-targeting agent just a few days ago, this December.

#### **DREAMM-2 results in line with expectations based on DREAMM-1 subpopulation**

With that said, I would like to give a bit of context between the DREAMM-1 study and the DREAMM-2 study.

These two studies had different objectives. DREAMM-1 was the first in-human trial, including dose escalation with a slightly more mixed population of patients, and DREAMM-2 was a highly focused last line of therapy registrational trial that involved patients that were refractory to an IMiD, to a proteasome inhibitor, and to a CD38-targeting antibody.

On average, we had about seven prior lines of therapy in the 2.5 mg/kg group, which is the chosen group that we will go forward with.

If you look at DREAMM-1 for a moment, this study began before Darzalex was approved, so not all patients had actually access to that compound and it wasn't relevant for the first in-human investigation, so we saw in the majority of patients no use of Darzalex, so these patients are one line earlier than what we are now looking at in DREAMM-2.

The response rate here was about 60%. If we now look at the sub-group of patients in the same study that actually did receive Darzalex there were 13 patients in total. It is a small number. Here we saw about the 38.5% response rate. This group is closer to what we then later studied in DREAMM-2.

You already can see that the later line of therapy does impact the response rate and indicates something about the potency of the agents and I will come back to that in a moment.

Then, if you now compare that to the much larger patient population in DREAMM-2 we do see a response rate that is slightly below what we had seen in the small cohort of 13 patients in DREAMM-1, which is a regression to the mean now that we are studying a more well-defined and larger patient cohort in the last line of treatment.

Therefore, we believe that DREAM-2 very much is in line with the expectations that one could have derived from DREAM-1 and confirms the potency of this agent in the last line of therapy in multiple myeloma.

#### **Dose selection based on benefit/risk**

A critical decision was to be made from DREAMM-2 about the dose for further investigation in other lines of therapy, but also for the filing with regulatory authorities.

The FDA had requested that GSK would look at at least two different doses in DREAMM-2. We have followed that and investigated the two highest doses from the first in-human study, 2.5 mg/kg and 3.4 mg/kg, and in this summary here you see the two dose cohorts side-by-side on some critical features. Dr Voorhees has given you some colour on this already, so I am not going to go through all the numbers again, but what I can say here is that we believe the activity profiles, the clinical activity is quite similar between the two doses, but the safety profile is slightly improved for the lower dose, the 2.5 mg/kg, so we

have a lower rate of either low-grade or high-grade keratopathies, hematologic adverse events, or then also dose delays or dose reductions as a consequence of these adverse events.

Therefore, we feel we are doing better for patients if we go forward with the 2.5 mg/kg dose because the drug presents similar activity, a favourable safety profile, and, therefore, a favourable benefit/risk ratio. So for the submission that just occurred to FDA, we have chosen the 2.5mg/kg dose as the proposed label dose.

Now one important thing to consider, as the treatment landscape in multiple myeloma has unfolded, and more agents that are introduced usually in the last line of treatment at each respective point in time, we have seen that the response rates for those agents have been relatively consistent, anywhere between 24 and 31%. Importantly, the patient population has got increasingly more refractory and increasingly harder to treat, so with the introduction of belantamab mafodotin, since we have data in the first in human trials, in the prior line, before Darzalex, and now in DREAMM-2 we have data post-Darzalex, the response rate was 60% in the pre-Darzalex population. Now we have 31% in the post-Darzalex population, that already indicates that these patients are increasingly harder to treat; and if you compare Darzalex response rate from its first in human trial with ours, it's about half, so 60% versus 30% is about the comparison that we would need to make. This suggests to us that belantamab mafodotin is a very potent agent, that even in the worst patient population it still maintains a strong response rate, with strong durability, so the duration of response has not yet been reached, with a median follow-up of six to seven months, so we expect that the median response rate will have to be above that median follow-up.

As we follow those patients further we will get more data and we will report on that at another point in time. So overall we think that belantamab mafodotin is a very potent agent that, introduced into early lines of therapy, should provide more benefit than the agents that have been there before.

#### **Four upcoming pivotal study starts across 3L, 2L and 1L multiple myeloma (MM)**

Here I would like to put the DREAMM-2 data in the context of the overall development programme: we have after the first in human trial and now this registrational trial planned eight more studies in this programme to date; of those eight there are four that are registrational in nature, and several others that are exploratory, to give us access to more innovative and novel approaches to change the treatment landscape.

As you see here in the red circles, DREAMM-3, 7, 8 and 9 allow us to go into earlier lines of therapy, so third-line, second-line and first-line. These four studies will either start

within the next month or so – that’s two of those – or then over the course of the next six to nine months for the other two, and we expect that those will give us the opportunity to understand how belantamab mafodotin can be tested in the context of existing standards of care, and then reach all earlier lines of therapy, similar to what Darzalex has done before us.

Important to note is that the studies DREAMM-4 and DREAMM-5, which are exploratory studies that test belantamab mafodotin either in combination with an immune modulatory agent like PD1 or with a variety of different combination agents on a platform, which is DREAMM-5, the one agent to draw attention to is a combination with a gamma secretase inhibitor that we gained access to through a collaboration with SpringWorks, that was announced earlier this year.

The gamma secretase inhibitor is a blocker of an enzyme that clips off BCMA receptor from the surface of cells, and therefore reduces the target on the target cell, and therefore provides a possibility that the antibody-drug conjugate can reach the killer cell, and might actually be diverted to a detailer mechanism when BCMA appears in the serum; so we believe there’s a chance that combining a gamma secretase inhibitor with our BCMA antibody-drug conjugate might increase the response rate and potentially the durability of response to the agent.

Important to note is that at this year’s ASH just a few days back, there was a CAR T targeting BCMA, combined with a gamma secretase inhibitor and there are two noteworthy observations from that dataset: first, the BCMA expression on target cells is substantially increased in the presence of a gamma secretase inhibitor; and second, even though this is a small dataset and still in dose escalation, all patients had a response, so this suggests to us this is a very worthwhile combination to test for our compound.

### **Unique features of different BCMA targeting modalities**

With that, I’d like to make one other comparison that’s important, given that there’s a lot happening in the BCMA space, and there are at least three different modalities targeting BCMA: antibody-drug conjugates, or immuno-conjugates, CAR T-cells, and bispecific antibodies. We aimed to put them side-by-side here to just provide some contrast.

So, we believe that in terms of scalability the antibody-drug conjugate is the easiest to use. In terms of dosing and administration, 30 minutes of infusion is easy, and very tolerable for patients, and then we have the combinability question as we get into earlier lines, the current standards of care require combinations, and certainly an antibody has proven to be combinable, as we have seen with Darzalex.

In terms of the safety profile, the corneal events are manageable, as you have heard from Dr Voorhees, and all these features on the ADC side compare somewhat favourably

with the CAR Ts, that have a very high response rate, but otherwise it's a more complex safety profile, difficulties in manufacturing or scalability, and there's still the need for a bit more data.

The same is true for bispecifics. The safety profile there still needs to be better understood, and we just need to generate more data to understand durability of effect and then other practical aspects around administration. Overall we think, having just filed for first registration with our ADC, that we are ahead of the curve, and that we should be able to access all lines of therapy in multiple myeloma in a reasonable timeframe, with expected launches in the earlier lines anywhere between 2022 and 24.

### **Belantamab mafodotin: critical features**

Here is the last slide, that basically repeats what I said at the beginning: these are the critical features of the asset that we think will drive its behaviour as we do further investigation.

### **Commercial ambitions in multiple myeloma**

**Luke Miels:** Thanks, Axel, and I'll try and cover my part a little faster, to give us enough time for questions.

### **Multiple myeloma (MM) is the 2<sup>nd</sup> most common haematological malignancy with high unmet need, despite new treatments**

Thinking of the opportunity to help patients, on Slide 28 you can see the scale of the unmet need in multiple myeloma, which is the second most common haem malignancy, and continues to have high relapse and low survival rates.

On the bar chart on the right, you can see the numbers of patients on treatment across the various lines of therapy, and DREAMM-2 will initially see belantamab mafodotin approved for later lines, but as Axel has mentioned, we are starting pivotal studies soon to move into earlier lines of treatment.

### **Growing market with opportunity for more durable, innovative agents**

From a value perspective, the market is large and growing: it's expected to grow around 7% annually, reaching \$24 billion by 2023. This is driven by a variety of factors, including the overall ageing populations, as well as longer duration of treatment due to the introduction of new and innovative medicines.

The pie chart on the right shows the current estimated split across the different mechanisms used to treat multiple myeloma, with the IMiDs holding the majority of the global market share, followed by CD-38s and then the PIs.

Uptake and acceptance of new agents is driven by demonstrating an efficacy improvement over existing options, and belantamab has shown impressive efficacy through DREAMM-2, as we get the data from the future studies we believe that it can take a material amount of market share.

### **Building our oncology commercial capability**

Finally on Slide 30, as Hal said, 2019 has been a very important year for GSK oncology, and I think it's very fair to say we've made a great deal of progress on both the R&D and commercial sides. In 2020 we plan to continue this progress, and hope to have three oncology launches: belantamab, of course, for multiple myeloma, Zejula with the PRIMA data in ovarian, and dostarlimab in recurrent endometrial.

Pleasingly, we continue to make strong progress hiring the right people, and building the right capabilities, and we expect to be ready for launch.

With that, I will now open to Q&A. If we could have the first question please, operator.

## Question & Answer Session

**Peter Wellford:** Hi, thanks for taking my question – I have a couple, but hopefully they're very quick. Firstly, did you measure minimal residual disease at all in this study, and if so, can you comment on that at all for any of these preliminary results that you have? Secondly, then, I wonder if you could just comment on the lyophilised form – did that conclude that there is indeed the opportunity to have this available as lyophilised, or will the final form be a frozen drug?

Then just finally on the duration of treatment, you commented on the median duration of response, I wonder if you could give us an idea as to how long typically patients stayed on drug, to give us an idea of that, because it looks like most patients were off drug by the time the results were presented. Thank you.

**Hal Barron:** Thank you Peter, for your question. Dr Voorhees, if you don't mind taking the MRD question and Axel, maybe you could take the lyophilised question, and maybe Dr Voorhees maybe you could also take the duration question, all based on the DREAMM-2 data – so the first and third, and Axel, you can take the lyophilised.

**Peter Voorhees:** Sure, not a problem. With regard to MRD testing, I do not believe that MRD testing was required on this particular trial. At the end of the day this is a relapsed refractory patient population, heavily pre-treated, and the fact that we saw any good deep responses was really quite remarkable. The majority of patients in a study like this would be considered to have - I would say that the majority of patients who responded probably still had, MRD positivity. Ira might be able to comment a bit more in depth on this particular point, but I would think, again, just given the nature of the patient population, that the majority of the patients on the study probably had minimal residual disease detectable at the end, but I certainly would not view that as a down side.

**Ira Gupta:** I just wanted to say yes, we have collected MRD negativity data in this patient population. As Pete mentioned, given the limited follow-up at this time, the analysis is still ongoing, and we hope to present the data in a future conference or presentation.

**Hal Barron:** Dr Voorhees, do you want to take the duration question as well, just from the clinical trials experience?

**Peter Voorhees:** I think as far as median duration of therapy, a lot of that is going to be impacted by those patients who ultimately stop therapy due to lack of response, in this heavily pre-treated patient population. At the end of the day, only 10% of patients

actually stopped therapy because of toxicities, so I would say in general, although dose holds and dose reductions did occur relatively frequently, largely due to cornea side effects, the vast majority of patients who responded to therapy were able to stay on therapy, and toxicities were manageable.

**Hal Barron:** Thank you. Axel, do you want to comment on the question about the ability to use lyophilised drug?

**Axel Hoos:** In very simple terms, we started out in the clinical testing of belantamab mafodotin with a frozen formulation because it was faster and easier for physicians to use in the context of a clinical trial. When it comes to shipping drug around the globe, and storing it at clinical sites in a commercial setting, a lyophilised formulation is easier, and as such, bridging from frozen to a lyophilised formulation, this is all in line with FDA support. We generated comparability data, with the lyophilised cohort that was mentioned in Dr Voorhees's presentation at the very beginning, which shows comparability between lyophilised and frozen material, and that will be part of the file that we have submitted with FDA, to ensure that we can supply the drug in the best way possible to sites, once it goes commercial.

**Hal Barron:** Okay, thank you – next question.

**Andrew Baum (Citi):** Many thanks – a couple of questions. Firstly, the subject of quality of life, particularly as this drug moves upstream. Could you comment on the impairment of driving ability, given the corneal event rate. Then second question, which has two parts, relates to the emergent future competitive environment with bispecific and CAR Ts. It seems that this agent has a very good durability of response, but the response rate is obviously lower, from what we have seen with the other modalities in earlier stage trials, so in terms of the GSI combination, there's a problem of thrombocytopenia with both agents, so I would obviously be worried about the risk of overlapping tox. How is that manageable within this setting?

Then second, you have an ongoing open label combination trial with your PD1, or with a PD1, I think it's pembrolizumab. I understand you had ten or so patients enrolled, they're very refractory patients. I realise it's a very small number, but given how refractory the patient population is, perhaps you might like to share the response rate that you're seeing at this still early stage. Thank you.

**Hal Barron:** Thanks, Andrew. Let me just comment on the DREAMM-4 study, just because at this point we're not going to be commenting on the data, it's inappropriate to do so at this early stage, but we remain, as you do, very interested and excited by potential.

Why don't I ask Dr Voorhees, if you wouldn't mind talking about from a clinical perspective the clinical significance of the ocular toxicity, particularly as it relates to things like driving; and then Axel, maybe you could follow up with the potential for the GSI thrombocytopenia interaction and how we're thinking about that.

**Peter Voorhees:** With regard to quality of life issues, from the corneal toxicity, I think it's important to note that what's found on ophthalmologic exam is far more prevalent than the incidence of the symptoms, of the findings. But certainly again, there were patients with blurry vision, there were patients with dry eyes, so for those folks who had Grade 1, 2 dry eye, that's nothing - while it might be an irritation, if you will, it's a manageable one with artificial tears, and certainly won't impair someone's ability to drive.

If someone has, say, a Grade 2 or higher blurred vision, that would be a scenario where we would seek help from the ophthalmologists to try and correct the problem, with corrective lenses, and if we're not able to completely do that, that is the patient that could potentially have a negative impact on quality of life. Thankfully, that was a minority of patients.

Similarly, the photosensitivity that we saw sometimes from the corneal toxicity, again if it's high enough grade it can have an impact, but for those with Grade 1 toxicity, which is what was seen in the majority of circumstances, a manageable problem. Certainly, a lot of the quality of life metrics that are used in multiple myeloma don't specifically get at that eye toxicity issue, and we probably need to think about a better way to capture that moving forward in other studies.

**Hal Barron:** Thank you, and Axel, do you want to take the GSI thrombocytopenia question?

**Axel Hoos:** What I recall was, there was the GSI question and then the overall response rate for combinations. Clearly, we have not yet started the study to test the gamma secretase inhibitor with our compound, so it's really impossible to take a position on safety in the absence of data. At the moment, we don't anticipate a major challenge with toxicity, we have not seen one in any of the combination studies we have started, but of course, you cannot know this until you really have data, so I would defer this answer until we have started the trial and have generated some data.

The question about overall response rate: remember, in the treatment landscape when you go to earlier lines, everything is combination therapy. We have seen Darzalex start out in the third-line with about 30% response rate, and reach up to 90% response rate in triple or quadruple combinations. Our agent is likely more potent than Darzalex, and we expect that we will reach very high response rates as this gets combined and goes into

earlier lines, and then the real question is, not just the rate of response, it's also the depth of response, impact on MRD, and then ultimately durability.

We are hopeful that there is going to be a significant addition to the effect that Darzalex has already provided, so we continue to improve the treatment landscape, and we will aim of course to do that through standard of care combinations and through these novel combinations like the PD1 combo or others that are coming up.

**Peter Voorhees:** If I could, I would like to comment on the comparison to CAR T-cell therapy. I think it's important to recognise that candidacy for a CAR T-cell study is very different than candidacy for a study like DREAMM-2. With CAR T-cell therapy, the patient has to undergo apheresis for collection of T cells, and then there's a manufacturing process that lasts weeks, and during that period of time you are only allowed to use bridging therapy with agents that the patient has received before, and is supposedly refractory to, so for those of us investigators that have also participated in CAR T-cell studies, you have to pick your patients very carefully. These are patients who have heavily pre-treated disease, and increasingly refractory disease, but their disease is progressing relatively slowly, and you can afford that waiting period during the manufacturing process before the patient actually gets the agent.

So it's a very different scenario, and the initial CAR T-cell studies are typically - and this is the case with the bispecific studies as well which we also participate in - restricting patients with ECOG performance status of 0 and 1, and at the end of the day, if you have an FDA-approved CAR T-cell product directed against BCMA, and a BCMA ADC, is a community oncologist going to treat their own patient with the GSK ADC, or are they going to send their patient to an institution that's able to do CAR T-cell therapy and have them treat them, and lose their patient?

I think you will see a much greater penetration in the market with belantamab mafodotin than the CAR T-cells, especially since we're not seeing any tail on the curve with regard to progression-free survival. These are powerful, the overall response rate is good, we are seeing MRD negativity there, but there was a press release during ASH on the KarMMa 2 trial, bb2121 and the median progression-free survival is 8.6 months. That's good, but again, everybody's relapsing, and are payers going to be interested in forking out \$4 or 500,000 for an agent like that?

**Hal Barron:** Thank you, Dr Voorhees. Andrew, I just would add one more thing about the gamma secretase. As Axel said, we have no data and it's a very intriguing concept, and of course overlapping tox has to be considered and we would do so, given the importance of patient safety to us. But the other point that Axel made earlier, that I think is

an intriguing one, that we will obviously get data to assess, is that the clipped BCMA from the protease acts as a sink, not only for lack of efficacy, but the MMAF complex will now be floating around in the blood, so it's possible by keeping the BCMA bound to the plasma cell that, at least in theory, it might have a differential tox profile by doing so as well, so it's an interesting concept we'll be exploring.

Can we have the next question?

**Louise Pearson (Redburn):** Hi, thanks for taking my question. I have two, please: firstly, could you confirm if your application with the FDA might be considered for an expedited review, whether that's a priority review, or through the FDA's real-time oncology review programme? Then secondly, when might we expect the next analysis of survival or response data from DREAMM-2 to take place? Thank you.

**Hal Barron:** Axel, do you want to take both those?

**Axel Hoos:** I'm not going to comment on the review process with FDA at this point in time. Obviously, the FDA will tell us very shortly how this is going to work. If you could just please repeat the second question, because I had a disturbance here, I couldn't hear it.

**Louise Pearson:** When might we expect the next analysis of survival or response data from DREAMM-2 to take place?

**Axel Hoos:** Over the course of the middle of next year we should have more data to report, it's just a matter of follow-up, and given the durability we have seen previously in DREAMM-1, if we really want to report something meaningful it will take at least six more months before that's the case.

**Hal Barron:** Okay, thanks – I think we have time for one more question.

**Steve McGarry (HSBC):** Hi there, thanks for taking the question. A couple of things: firstly, just on the keratopathy, first of all when did patients develop the side effect, was it early, and was it cumulative? And in terms of delaying discontinuations, was this due to patient reporting, or were the clinicians looking for it proactively? Lastly on that, just practically, is that likely to reflect what happens in clinical practice, especially if the drug moves earlier in the treatment paradigm?

Then secondly, just on the gamma secretase inhibitor, if it's validated clinically, what's the royalty rate that you would need to pay on nirogacestat Thanks.

**Hal Barron:** Why don't I take the GSI question. We're not going to be commenting on the royalty at this time, but why don't I turn it over to Dr Voorhees, so he can talk about the clinical significance of the keratopathy and discontinuation rate.

**Peter Voorhees:** As far as time to onset, it was typically after the second to third dose, where if patients were going to have clinical symptoms that they would start to experience them. As far as discontinuing therapy because of corneal side effects, again, it was only one patient in the 2.5mg/kg arm, and just three patients in the 3.5mg/kg arm that actually had to stop therapy because of corneal toxicity, and whether those patients had clinically symptomatic corneal findings or just findings at ophthalmologic exam, I would have to defer to Ira on that specific point.

As far as moving it in earlier lines of therapy, I do think that the ophthalmologic toxicity is going to need to be addressed, I think GSK has plans in place to better understand the mechanism of action, and looking at potential strategies to mitigate the side effects for patients as we move it to earlier lines of therapy – exploring alternate dosing schedules, etc.

At the end of the day, given the potency of this agent in relapsed refractory myeloma patients, it's conceivable that patients may only need a defined course of therapy with a belantamab mafodotin-containing treatment, and be able to come off therapy and be free of all symptoms of the drugs, which is certainly not the paradigm in multiple myeloma now.

**Hal Barron:** Thank you, and GSK has put in a fair amount of infrastructure to help manage this. Luke, do you want to comment on that?

**Luke Miels:** Yes, sure. I think firstly we want to clearly characterise what is occurring here for physicians, and to acclimatise them with that. Then it's really particularly in the community to provide a framework for patients and physicians using the drug, so that's education of ophthalmologists and optometrists, and making it very easy for patients to pass through that process, and I think if we can get that right in the first six months of launch, then this is going to be something that treating physicians in the community are going to become comfortable with managing.

**Hal Barron:** Okay, I think we have to end now, but I just want to thank everybody on the phone for taking the time for this call. Obviously we're very, very excited about the molecule and the DREAMM-2 data, and look forward to hopefully continued good news, and the ability to get this to patients as fast as possible. Thanks again for your time.

[Ends]