GLAXOSMITHKLINE
ESMO INVESTOR CALL:
ACCELERATING OUR ONCOLOGY PIPELINE

Monday, 30 September 2019

Sarah Elton-Farr (Global Head, Investor Relations): Good evening and good afternoon. Thank you for joining our ESMO investor call. You can view our slides on the Investor section of the GSK website. Our speakers today are: Dr Hal Barron, Chief Scientific Officer & President of R&D; Dr Antonio Gonzàlez Martin, Primary Investigator on the PRIMA study and Head of Medical Oncology at the University Clinic of Navarra; Dr Axel Hoos, SVP of Oncology R&D, and Luke Miels, President of Global Pharmaceuticals. We have a broader team on the line for Q&A.

Cautionary statement regarding forward-looking statements

Before we start, I draw your attention to our cautionary statements on slide 2 and with that, I shall hand over to Hal.

Science x Technology x Culture

Dr Hal Barron: Last June, we outlined our new approach to R&D with a focus on Science x Technology x Culture. In addition to deciding to invest heavily in Oncology, we also stated that we were going to focus on the science related to the immune system, use of human genetics and advanced technologies.

One of the technologies that we highlighted back in June of last year was the use of functional genomics because of its importance in identifying new targets, particularly those targets that we believe have the characteristics that we describe as "synthetic lethality". This now plays an important role in the discussion today given that the focus will be, at least in part, on the exciting data from PRIMA.

GSK Oncology: building on a strong foundation and investing for future performance

Today, the call will focus on our growing Oncology pipeline. We have made substantial progress over the last 12 to 16 months or so. In about last June, we had eight molecules in the Oncology portfolio, with the most advanced really being in Phase I, and 16 months later we have 17 assets in our Oncology pipeline in the clinic. In addition, we have three Oncology filings expected by the end of the year, one of which will be for the PRIMA

data that you will hear about in a minute. We have 16 abstracts in nine different tumour types this ESMO and a lot more great science will be emerging over the next few months.

The success that we believe we have experienced, and will continue to experience, is driven by a continued focus on three different components: smart business development, where we believe that science will come both from internal as well as from external places, and we are very committed to ensuring that we make smart decisions there and I shall talk about that in a second.

The other area of clear strength that is increasing over time is in Oncology R&D where we have very high calibre scientists both within the research organisation as well as in the clinical teams. We now have a very diverse portfolio of potentially transformative medicines and Axel Hoos, our Head of Oncology, will be discussing more with you later on the strategy and a couple of the assets about which we are very excited.

The third pillar is, of course, strengthening our in-market operations and Luke Miels will be focusing on that.

Before turning it over to discuss PRIMA, I thought I would take a moment to talk to you about the business development focus. BD has really allowed us to augment our Oncology pipeline and strengthen it quite substantially over the last 18 months. We have signed a recent agreement with Merck KGaA for the alliance on bintrafusp alfa, which is a very promising molecule. Of course, we have also made a lot of progress through the acquisition of Tesaro by both gaining access to early stage molecules, as well as *Zejula* which is a marketed drug. The dostarlimab data that have recently been presented will be filed by the end of this year giving us another opportunity to develop combination therapies.

As we told you when we described the rationale for the acquisition, we believe strongly in a few principles that I hope will become clear over the next 20 or 30 minutes. First, the PARP class was a very much under-appreciated class of medicines. We based that on both preclinical and clinical data, suggesting that we thought there would be the opportunity to help patients beyond the classic indications of BRCA mutation as you will hear and the PRIMA data and other data presented at this meeting did confirm that.

We also believe that *Zejula* is a very unique molecule within the class and it has some features that differentiate it from other molecules, and we shall go through the attributes of *Zejula* and providing insight as to why the effects not only in the HRD positive patients but the fact was also observed in the HRD negative giving us the opportunity to see benefit in all of the different marker sub-groups. You will be hearing from Dr Antonio González-Martin next, who will take us through the results of PRIMA.

Results of PRIMA

Dr Antonio González-Martin: Hello. Thank you very much for having me here. I am going to show the results of a trial that has already changed the landscape of ovarian cancer, and should change how we treat ovarian cancer.

Niraparib is effective in recurrent ovarian cancer - (BRCAmut and BRCAwt)

For the first time we have positive data of PARP inhibitors in first-line ovarian cancer, not only for the BRCA-mutative patients, but also for the BRCA wild type. In this introductory slide I would like to highlight three specific points:

The first is that advanced ovarian cancer is a leading cause of cancer deaths in women, because, unfortunately, up to 85% of our patients will recur after a standard first-line platinum-based chemotherapy.

Currently, we have some options for maintenance after chemotherapy. However, there is still a high unmet need for many patients. We have the approval of olaparib, but only for the BRCA-mutated patients.

We also have the possibility of using bevacizumab, but not for all the patients for two main reasons: first, safety concerns in some patients; and second, because we do not have very solid or robust data in patients that require neoadjuvant chemotherapy, so for many patients after chemotherapy we only do surveillance.

The third important background point, and you probably know very well is that niraparib was the first PARP inhibitor approved as maintenance in recurrent ovarian cancer for all patients, and that was based on the NOVA/ENGOT-OV16 trial that showed the benefit after chemotherapy in all the patients independently of the BRCA status and the homologous recombination studies.

PRIMA was designed to address the unmet need in 1 L advanced ovarian cancer

What we did in the PRIMA study that was an ENGOT model C trial, a good example of cooperation between the pharmaceutical industry and academy is to test the efficacy and safety of niraparib therapy after response to platinum-based chemotherapy in patients with newly diagnosed advanced volume cancer at high risk of relapse.

Patients who were included in this trial needed to have high grade serous or endometrial pathology; a stage III disease with macroscopic residual disease after primary debulking surger; or a stage III disease treated with neoadjuvant chemotherapy, regardless of the residual disease at interval debulking surgery; or any stage IV.

Importantly, all patients included in PRIMA were platinum-responders. It was a must to have a complete or partial response to front-line chemotherapy.

We also took tissue from the beginning during the screening in order to test the homologous recombination status according to the Myriad myChoice test that I will review later.

PRIMA trial design

In this slide you can see the trial design. Patients were randomised to 2:1 to receive niraparib or placebo for 36 months or active progression. We started all the patients on 300mg dose once daily.

Later the study was amended to give 200 or 300mg dose based on baseline platelets and body weight. The impact of the doses will be a matter of future analysis and presentations.

Patients were stratified according to three factors: receipt of neoadjuvant chemotherapy, yes or no; best response to chemo, complete response or partial; and homologous recombination test status – deficient or proficient. The primary endpoint of this study was the progression-free survival determined by a blinded independent central review, and it was tested hierarchically.

First, in patients who have a homologous recombination deficient tumours and if that was positive, then we tested the overall population. Overall survivor was a pre-specified key secondary endpoint, and other secondary endpoints were patient reported outcomes, safety, progression free survival 2, and time to first subsequent therapy.

PRIMA tissue test for homologous recombination

In this slide, you can see the homologous recombination testing. As I said before, all the tumours, samples underwent testing for homologous recombination status according to the Myriad myChoice Test. This could be a little complicated, but I will try to make it as simple as possible.

This is the same test that we have used in the NOVA trial, and this test provides a scoring based on three genomic scoring that are called LOH, TAI or LST. According to the testing, the patients are classified in three groups; homologous recombination deficient tumours are those that have a BRCA mutation or a scoring equal or superior to 42. Homologous recombination proficient tumours are those patients that do have in the tumour, BRCA wild type and scoring below 42.

In some circumstances it was not possible to determine the homologous recombination status. The majority of the cases lead to a small amount of tissue and those were classified as not determined.

PRIMA enrolment and outcomes

Now let's have a look at the patient's position in this slide. You can see 733 patients were randomised. The main reason for discontinuation in the trial was disease progression, 45% in the niraparib arm, and 66% in the placebo arm. In the database log made this year, 37% of the patients were still receiving niraparib and 28% of the patients were still receiving placebo. The median duration of follow-up of our study was 13.8 months.

PRIMA patient characteristics and baseline demographics

In this slide, you can see that the patient characteristics and demographics were well balanced across each arm. As I said before, patients included in PRIMA trial were patients with high risk of early relapse as you can see and was defined by the following characteristics; 35% of the patients had stage 4, 67% of the patients received neoadjuvant chemotherapy and 31% of the patients achieved a partial response, a best response from chemotherapy.

Regarding the biomarkers status, half of the patients had homologous recombination deficient tumours, and 30% of patients had BRCA mutation.

PRIMA primary endpoint, PFS benefit in the HR-deficient

Now let me show you the result of the hierarchical analysis of the primary endpoint that already has changed how the landscape is in ovarian cancer.

The addition of niraparib after chemotherapy reduced the risk of progression in homologous recombination deficient population by 57%. You can see the median progression free survival was significantly increased from 10.4 to 21.9. In addition, at 18 months after randomisation, which means two years after the initiation of chemotherapy, almost 60% of the patients treated with niraparib remain alive and progression free.

PRIMA primary endpoint, PFS benefit in the overall population

Now the results of the overall population; niraparib reduced the risk of progression by 38% and improved the median of progression survival from 8.2 to 13.8 months. As you can see at 18 months after randomisation, and again I would like to highlight that this means two years after initiation of chemotherapy, 42% of patients with niraparib remain alive and progression free.

PRIMA exploratory analysis, PFS benefit in pre-specified groups

On this slide you can see the furthest block that shows the consistent benefit of niraparib in all the specified sub-groups. I would like to notice major attention to a couple of sub-groups of particular high risk of a relapse as those that do have partial response as the best response to chemotherapy with a hazard ratio of 0.6 and those patients that need to receive new adjuvant chemotherapy would have the ratio of 0.59.

PRIMA PFS benefit in biomarker subgroups

In the next slide, I will review in detail the benefit across the biomarker status because this analysis has already generated a lot of discussion in this ESMO, that has significantly changed our view on this molecule on how to treat our patients.

What we have seen is that niraparib provides similar clinical benefits in the two homologous recombination deficient sub-groups, with a hazard ratio of 0.4 in the BRCA mutated group of patients and 0.5 in the BRCA wild type. What does this mean? This means that the benefit in the homologous recombination deficient group was not driven only by the BRCA mutated patients.

Importantly, we have observed in this sub-group that we call homologous recombination proficient tumour group, a reduction of 32% in the risk of progression.

PRIMA key secondary endpoint, overall survival (11% data maturity)

According to our statistical analysis plan, we integrated a pre-planned interim analysis of the overall survival that have to be measured at the time of the progression-free survival analysis, and that is what we are showing here. The data are very immature because we have only 11% of the events, but it is enough to say that we do not have any evidence of a negative impact, and on the contrary, the data are, at this moment, numerically in favour of niraparib.

PRIMA safety overview

In this slide I can show you the safety overview of this study. Most of the patients enrolled in the trial have some treatment emergent adverse event. The majority of the side effects were manageable, with dose interruption or with dose reduction, and that is in some way confirmed because the discontinuation rate was 12% - that is exactly the same that we know with niraparib in the prior trials that we have run, and only 4% was due to thrombocytopenia, and importantly no deaths related with niraparib were observed in our trial.

PRIMA Conclusions

In my final slide I would like to summarise all the things that I have presented to you. First, I would like to remind you that many patients with newly-diagnosed advanced ovarian cancer still have a high unmet need because they have a high risk of relapse after frontline platinum-based chemotherapy. What we have demonstrated is that the treatment with niraparib after response to first line platinum-based chemotherapy significantly improved progression-free survival in all the patients with advanced ovarian cancer, with a hazard ratio of 0.62 in the overall population, 0.43 in the homologous recombination deficient group of patients, and 0.68 in the homologous recombination proficient group.

This means that niraparib is the first PARP inhibitor which has demonstrated benefit in monotherapy after frontline platinum-based chemotherapy across all the biomarkers, and these data are consistent with the data that we have from the recurrent setting with the NOVA study.

I would like to highlight that a couple of sub-group populations with high risk of early disease progression to have a great benefit with niraparib are those patients that receive neoadjuvant chemotherapy, or that do achieve only partial response after frontline chemotherapy. Importantly, no new safety signals were observed, and quality of life was kept during the trial with niraparib.

What does this mean for our patients and our practice? We think that based on these results niraparib monotherapy after surgery and platinum-based chemotherapy could be an important new treatment option for our patients.

Thank you for your attention. I would also like to add that these data have already been published in the *New England Journal of Medicine* and are available online.

Thank you very much.

Hal Barron: Thank you very much, Dr González-Martín. Congratulations on announcing the study.

Putting PRIMA in Context

What I would like to do for the next 5-6 minutes is to take you through why we were very excited about the PRIMA study and Tesaro and *Zejula*.

Why was Tesaro a smart risk?

Just to summarise briefly, the questions that you heard were asking whether *Zejula* would offer benefit to women with ovarian cancer with an HR deficiency, the so-called HRD positive, in the frontline maintenance setting.

We had said that we were encouraged by both the pre-clinical data and some clinical data that this would be the case offering the potential to benefit as many as three times the number of women that were previously indicated for with the data from SOLO 1. We also had a hypothesis that *Zejula* would benefit all-comers in the trial, and this was based on the belief that in addition to helping the women who had a homologous recombination defect beyond that seen with BRCA, that we saw in the HR proficient tumours, there is the possibility for a number of different things to be happening.

There were several different hypotheses, one of which was that there may be alternate mechanisms of action that could be complementary or distinct from some of the homologous recombination theory that included immune activation through either the distinct pathway where there is some preclinical data showing that PARP inhibitors can activate the distinct pathway, or actually through other mechanisms such as PDL-1 upregulation which has also been shown.

We were intrigued by the unique features that had been observed preclinically with *Zejula* that I'll go into in a minute, from a pharmacokinetic perspective, that we thought we'd set *Zejula* up to be a uniquely suitable PARP to demonstrate these characteristics. As you heard, the conclusion from the study is that if that is the case, then it works in all-comers.

Caution needs to be taken when making cross trial comparisons, especially when patient populations vary

This next slide is a slide that was shown by Dr Mirza in the panellist discussion at the end of all the three PARP inhibitor studies, both PRIMA, PAOLA and VELIA. Of course, it's very challenging to draw any firm conclusions when making cross-trial comparisons and of course we all say we shouldn't do that and we go ahead and do that, and that's of course because we need to understand how to think about the patients given the data we have.

I say that just to highlight the fact that what the challenge is in making cross-trial comparisons is that in studies such as PRIMA, SOLO, PAOLA and VELIA – and we put in there the GOG-218 and ICON 7 on this slide – was to highlight that the characteristics of the patients, the enrolment criteria and the baseline co-variant is different quite significantly by trial, giving you a lot of baseline risk differentiations, and therefore we will observe a difference in the median if that is across all these trials.

We know that from trying to interpret many different trials that, comparing PFS medians is really fraught with complications because, to a large extent, they reflect the baseline risk and the heterogeneity in the trials. Therefore, I think most of you on the call are aware of this and agree with this, but what was pointed out at the discussion was that hazard ratios are not ideal but clearly the best way to assess biologic activity and give you much more insight into what we are seeing.

Comparing PARPi and bevacizumab in 1L ovarian cancer

Dr Mirza put this slide together which I thought we would describe both what he said and how we made four specific points from this summary slide, which again includes the PRIMA trial that he's just told us, the SOLO 1 trial with olaparib in the HR deficiency patient population which was previously studied, so was PAOLO, VELIA and the two Avastin studies.

First conclusion

The first point I'd like to make and was made by Dr Mirza, is that when you look at PRIMA and you look at SOLO-1, PAOLA-1 and VELIA, it is extremely clear that patients with homologous recombination defects, or so-called HR-deficient patients, benefit from a PARP inhibitor and whether that PARP inhibitor is given as monotherapy or in combination, it is very clear that these patients experience a benefit, again providing the opportunity for a significantly larger number of patients to benefit from this previously under-appreciated class. I think that was reasonably well understood and agreed to.

Second conclusion

The next point that Dr Mirza made which is interesting, is that he looked at the subgroup analysis of GOG-218, which is published data, and showed that the overall population had a hazard of 0.73 but it differed by subgroup, in that the HR-deficient BRCAwt patients had a very small benefit of 0.95 with the hazard. You can see below that that the hazard in the HR-proficient BRCAwt patients was much more profound, in fact it was statistically significant at 0.71.

The fact that Avastin in this trial wasn't really contributing significantly, raises the possibility and the question mark that came up for discussion of how much benefit is Avastin adding in the PAOLA-1 trial? Unfortunately, the PAOLA-1 trial did not have the third arm that would allow you to set independent contribution of Avastin and just called into question not the addition of PARP and its value there, which is clear, but how much incremental value was Avastin having now that we have PARP as a potential standard for care in this population.

Third conclusion

The third point that was made was regarding the HR-proficient BRCAwt patients and, as you can see and as I just mentioned, with Avastin you do see a significant benefit with a hazard of 0.71. However, interestingly and uniquely, the PRIMA data showed, as you have just heard, a benefit in this HR-proficient subgroup with a hazard of 0.68 and statistically significant. This was different than what you saw in other trials.

Comparing PARPi & bevacizumab in 1L ovarian cancer

In summary, the findings of PRIMA, putting them in context, demonstrate that only *Zejula* demonstrated efficacy in all of the patient subgroups by HR status and provides us with the data that suggest that niraparib is in fact a very unique PARP inhibitor.

Could Zejula's unique PK profile explain the benefit in HRD patients?

The question is what are the potential reasons for that? One possibility is *Zejula's* unique PK profile, which we believe could explain the benefit that we see in the HRD negative population. I won't go into too much detail but have provided this reference as something to read through.

This article makes two points that are very important. First, when you look at the plasma PK and the tumour PK and you compare both niraparib and olaparib in preclinical models, you find that at steady state there is a 3.3 times greater than plasma exposure in the tumour xenograft mouse models. In other words, the exposure in the tumour xenograft is 3.3 times higher than the PK in the plasma. That is in comparison to the tumour exposure to olaparib which is less than what we've seen in the plasma, so a unique differentiator there.

Where that might manifest if you look preclinically, the BRCA mutant TNBC model, which you see on the bottom left here, the two drugs look very similar in terms of their efficacy and are both profound. When you look at a BRCAwt ovarian model, and this is the A2780 model, you can see that while olaparib has a statistically significant benefit in terms of tumour growth, tumour volume over time, that isn't observed with olaparib and that may be related to the concentration of the drug in the tumour.

Clinical confirmation of higher exposure to niraparib in tumour versus plasma in patients with breast cancer

Finally, this is an abstract that was presented at this meeting, and I don't want to go into in any detail other than to say that the data that were generated from preclinical studies have now been validated for the first time in the intra-tumour concentrations of niraparib in the clinical study. What we found was that the concentration of niraparib was 36-fold greater in tumour tissue than it was in the plasma, consistent with the data that were just described

to you in providing rationale for the fact that *Zejula* not only works in all patients as we described, but the rationale for why that might be the case in the HRD subgroup.

With that, let me turn it over to our Head of Oncology, Axel Hoos, to go through the oncology overview and the ICOS results from the INDUCE-1.

GSK Oncology: data at ESMO ICOS: results from INDUCE-1

Dr Axel Hoos: Thank you, Hal, and good evening everyone. While PRIMA is certainly the highlight for us at ESMO, I would like to provide a little bit of context around what else GSK has been doing at ESMO.

GSK oncology: building on a strong foundation & investing for future performance

As you know, we have been building our oncology pipeline as it currently exists over the course of the last eight years and there has been a distinct strategy behind it. Over the last two years, we have been significantly accelerating our progress, moving more assets into the clinic, that included also a build in terms of bringing more high calibre scientists and clinical teams, diversification of the portfolio and prioritisation of high profile assets such as our BCMA antibody drug conjugate, the ICOS agonist antibody and, of course, *Zejula*.

Oncology R&D: Strategy and scientific focus

With that said, the focus area is supporting our mission of maximising patient survival through transformational medicine. The focus areas are on four different areas of science. The first, beginning with immuno-oncology where our intent has been to build a diversified immuno-oncology portfolio that is not duplicating forms that other companies have already created and focus on new mechanisms that enable either add-ons to PD-1 or can stand alone, and potentially create new backbones.

In addition, with cancer epigenetics, we believe we have created an industry-leading precision in terms of compounds either in discovery or in the clinic, and we have shown some data on PRMT5 in the context of ESMO.

For the oncology cell and gene therapy, an area we aimed for establishing our presence in solid tumours, and proved that oncology cell therapy, particularly TCR-T can provide value to patients in solid tumours.

Then, finally, the synthetic lethality area is something that came to us through the Tesaro acquisition, and we are now building out around the success of *Zejula* and in other areas that deal with DNA damage repair and other related mechanisms.

The totality of that has brought us a portfolio that was mostly organically built and recently expanded through acquisitions and partnerships.

Data at ESMO: oncology clinical pipeline

There are 17 assets in the clinic. As you can see here, of the 17 we have reported on eight at ESMO, and that led us to 16 abstracts of presentations and three oral presentations or discussions, including the plenary presentation on *Zejula.*

GSK'609 ICOS receptor agonist

Now, a word about the second aspect that we feel has some noteworthy detail here at ESMO beyond *Zejula* is our ICOS agonist, antibodies that we have carefully engineered and a programme that has been built over the last six years based on biomarker data that resulted from the first checkpoint inhibitor programme in the industry, the ipilimumab programme that originated from Bristol-Myers Squibb.

The ICOS agonist is an antibody that binds an agonist receptor on a T-cell after it has been activated. It can be activated through natural mechanisms, but also through pre-treatment, either PD-1 blocking or CTLA-4 blocking antibodies.

Once the T-cell is activated and ICOS is expressed, the further agonism of that receptor can grow the army of T-cells and potentially expand the benefit that these T-cells can provide.

Our hypothesis here has been adding on ICOS to either one of the two existing successful mechanisms of CTLA-4 or PD-1, or creating a set-up in which activated T-cells can express ICOS, can be further stimulated and might lead us to clinical success.

ICOS: checkpoint modulation beyond PD-1

Here is more background on what to expect from an ICOS agonist programme. There are basically two classes of agonist receptors. The first one is the B7-CD28 class, and ICOS belongs into that class. If we look at that more closely, both PD-1 and CTLA-4 are sitting in that class, and we know that they have already been successful clinically, so we believe that alone, since we are talking about stimulating a cell, the same cell that CTLA-4 and PD-1 are already targeting, we might actually be on a good path for adding further value.

The second class is the TNFR category receptor, which is less clinically proven. What we expect from the ICOS agonist is similar to what we have seen with CTLA-4 and PD-1. Response rates, they are relatively low in monotherapy and a greater impact on overall survival and durability of response.

I am showing two examples here, the ipilimumab activity in metastatic melanoma, and pembrolizumab activity in head and neck cancer, which is the indication which we have shown some data at ESMO.

GSK'609: first time monotherapy activity has been seen with an ICOS agonist in multiple tumour types

Here is a waterfall plot for the monotherapy data from the first in-human trial with the ICOS agonist. This is a study that has actually enrolled more than 500 patients, has treated patients with monotherapy in a series of different indications, and then switched to combination therapy with PD-1, and subsequently other agents.

We have seen about a 6% response rate – one responder out of 16 here in this first data that is part of the dose escalation programme, so this is Phase 1 data, but it shows monotherapy activity, and we have seen this not only in head and neck cancer, but across a spectrum of different indications across this trial.

GSK'609: early data point to ORR of 24% in combination with pembrolizumab with durable response

Further, we have seen signals of combination therapy activity in combination with pembrolizumab that has exceeded the pembrolizumab monotherapy activity. We consider this a signal that is promising and would need to be further investigated, and in light of the assumption that survival might actually be the real readout for these kinds of agent, we would need randomised data to really fully understand it.

Therefore, we took the decision to move this into a randomised trial. We have a randomised study running in Phase 2, and we just decided to open a randomised Phase 3 study in a very specific population of patients with head and neck cancer.

GSK'609: responses not correlated to PD-L1 expression suggesting ICOS against activity

Another important feature is that since most patients that have received PD-1 blocking antibodies have the majority of their responses in PDL-1 high patient subgroups, we looked at PDL-1 status in the first in-human studies, and the patients that did have a response on ICOS and PD-1 were predominantly below the 20% threshold, which gives us a bit more confidence that these responses are not just purely driven by PD-1 blockade, but potentially by the addition of ICOS.

GSK'609: safety and tolerability consistent with results previously reported

A word about safety from this programme. In both the monotherapy and in a combination therapy cohort we have seen a very familiar safety profile of checkpoint

modulating anti-bodies which have some immune related adverse events related to diarrhoea, nausea and rash and then other less specific adverse events. Overall, we did not see any surprises and considered this a manageable safety profile.

GSK'609: progressing to advanced trails and novel combinations

In terms of expansion of this programme, INDUCE-1 study as stated, has treated more than 500 patients. You will see a lot more data from this coming as we show information beyond head and neck cancer over the coming months. As it comes to head and neck cancer itself, we have randomised studies ongoing, a randomised Phase 2 study in combinations with a CTLA-4 blocking antibody and now announced a pivotal study in first-line head and neck cancer in PD-L1 high expressing patients, in combination with pembrolizumab. We expect the study to start around the end of this year.

With that, I give the word to Luke Miels, President of Global Pharmaceuticals.

Building our Oncology Commercial Capabilities

Luke Miels: Thanks. So Hal has covered how I hope you can see we have improving governance around business development and also the capabilities in R&D. My part is going to cover about how we aim to make oncology core to our identity within the countries.

Oncology: building on a strong foundation and investing for future performance

Of course, you do this by starting with differentiated products like *Zejula* and belantamab and then building the right gene pool and on this front we are making rapid, material progress, assembling people who are great people in the countries with a track record in oncology.

The acquisition of Tesaro catalysed this process and creates a critical mass of people who think in a certain way. Separately, we changed the policy for HCP engagement and the salesforce in the countries.

Building our oncology commercial capability

These changes with appropriate controls are designed to ensure that we are in the right position to communicate the science behind our products. Placing oncology at the core of who we are as a company will ensure strong execution of the three potential launches next year.

Expect increase in use of PARPs following ESMO data with 1L monotherapy taking leading share

In this next slide we have the three key points; the first is that the PARP group as a class are under-utilised, and if you look at the orange bars on the chart, overall, and this continues to surprise me, only 31% of patients get a PARP. Even in the BRCAm, the use is below 50% and this is in the US, and the data at ESMO I am quite confident will change this.

The second point is that Avastin use in maintenance is limited and this is shown in the red bar on the chart, which is around 15%. Post ESMO, we now know that adding a PARP to Avastin only helps half the patients in first-line maintenance with the concomitant burden of infusions, costs and toxicity challenges. Furthermore, GOG-218 has shown there is no overall survival benefit for Avastin. On top of this, the decision to employ Avastin in the first-line maintenance limited use is an option in second-line.

This leads to the third point, which is that *Zejula* is uniquely positioned to help patients in first-line maintenance. We have demonstrated a PFS benefit in all-comers, including the HRD proficient population, and we anticipate doctors will be able to start patients without any need for testing, which is around 2% for HRD in the US and about 54% for BRCA.

The pre-planned interim, which it must be stressed is early, favours overall survival on *Zejula* versus placebo, and with the commercial lens, we expect physicians in the community will seek a hypothesis here. Early data which got our attention in due diligence, as Hal outlined, suggested *Zejula* has unique PK properties which means it has a greater tumour or brain penetration which could account for these effects.

Finally, these women will be treated, fortunately in many cases, for an extended period, as an oral once daily monotherapy, it represents a convenient and cost effective way to treat patients in a maintenance setting. So with that, we will now switch to Q&A to answer your questions, so operator Mark, over to you.

Question & Answer Session

Tim Anderson (Wolfe Research): Thank you. I'm wondering if you can just talk about the tolerability and toxicity of *Zejula* – in the battle with Astra they're certainly going to go after unique toxicities that your product has on the cytopenia front, so thrombocytopenia for example, I think you showed 29% they showed 2%. I'm wondering

what the defence will be against this counter-detailing, because it does kind of complicate the treatment of patients relative to a PARP that doesn't have those toxicities.

Then the second question I have is specific on your ICOS programme: slide 41, you show that it's advanced into lung, into the platform setting called ENTRÉE and that started earlier this year. I'm guessing you have lung data in hand from INDUCE-1 that informed the decision to start this lung trial, but we haven't seen that data, if you have it, either ESMO before, I don't believe, we've only see data on head and neck, so I'm wondering if you can clarify what data you have on lung at this point on ICOS that hasn't been published, and will we see that at some point?

Hal Barron: Thanks Tim, for your question. Why don't we go over to you, Dr González-Martín and you can talk to us about the tox and tolerability profile, and then we'll go over to Axel to follow up on the ICOS lung question.

Dr González-Martín: Regarding tolerability, the most frequent side effect with niraparib is the myelosuppression, that's the reason why during the trial we amended the trial to allow the possibility to give 200mg instead of 300mg. That decision was based on what we call the "Radar analysis" that was an analysis performed on the data of the recurrent setting in the ENGOT-OV16/NOVA trial.

What we have demonstrated in this trial, those data were not shown in the plenary session but you can see those data in the supplement of the manuscript of the *New England Journal of Medicine*, is that the introduction of this individualised dose of 200mg for patients with baseline platelets less than 150,000 platelets, or body weight less than 77kgs, reduced significantly the rate of grade 3 and 4 myelotoxicity.

I would like to say two additional important things from the practical point of view. The first is that the myelosuppression with niraparib is reversible, and that is very important; and the second is that the team of Tesaro did a great job training doctors for the use of niraparib in the recurrent setting, so I think that, at least in my country and I think in other countries across Europe and probably in the States also, the doctors are very aware of how to manage this drug.

I think that it's very important that we haven't seen any significant new signal of toxicity, that is something that has not happened. For instance, in PAOLA, they had a 20% rate of discontinuation, probably the antiangiogenic PARP inhibitor together do have worse tolerability, but that was not the case with niraparib – 12% of discontinuation of therapy is in the range that we see in second line with all the PARP inhibitors, 4% due to thrombocytopenia is really, I think, a good figure if we consider that myelosuppression is frequent, but as I said before, it's reversible.

Hal Barron: Thank you very much. Axel?

Axel Hoos: Thank you. I'd like to clarify what the ENTRÉE lung study actually represents. This is not a Phase 3 trial, it's a randomised Phase 2 study, that operates like a platform, so it is randomising patients to either a control group with a standard of care, in this case docetaxel in a second line plus patient population, and then adds on arms for novel combinations of ICOS plus other agents. So what it is intending to do, is identify biomarker profiles of patient sub-groups that might be more prone to respond, and of course combinations that might be more favourable to develop further.

Since we know, at least believe, that the majority of the benefits for patients treated with ICOS will come on the survival front more than on the response front, as we have seen for CTLA-4 and to some degree with PD-1. We wanted a randomised trial in which we can illustrate what survival impact ICOS combinations can produce, that's why this study is here and it will be very flexible, we will dial in and out arms to learn as much as we can.

It's not a Phase 3 trial, and therefore we didn't necessarily need the same amount of data to justify a Phase 3, but I would like to say that among the 500 patients treated in INDUCE-1 we have a good amount of data in non-small cell lung cancer, it is similar build like what we have shown in head and neck cancer, and the data will be made available soon. I don't want to commit to an exact timeline, but you have to expect it will be both monotherapy and combination with PD-1.

Hal Barron: Thanks, Axel.

Matthew Weston (Credit Suisse): Thank you very much. Two questions please. The first to Dr Martin. Dr Martin, I would be very interested in how you would take all the data that you have seen at ESMO, and how you would treat an HR-proficient patient? Clearly there was positive PFS data from *Zejula* monotherapy, but *Avastin* mono, if we take the control arm in PAOLO-1, look like it demonstrated significantly greater median PFS.

Now, I recognise that there is no overall survival benefit on *Avastin* seen in GOG-218, but also we are unaware of the survival benefit that we're likely to see with *Zejula* over time, so I would be interested in how you would treat that 50% sub-group of patients given what we know now.

Then secondly, if we could just ask a question regarding the dose of *Zejula* in the study. I realise the efficacy by dose will be presented at a later stage, but if you could tell us the average dose, or at least the dose that the majority of patients were on towards the end of the study, that would be very interesting.

Many thanks indeed.

Dr González-Martín: Thank you for your question. I will answer first the topic about homologous recombination proficient

First, I would like to say in that we cannot compare the medians in the trials, PAOLO-1 and PRIMA, for two crucial reasons. First, because the patient population is not the same. Second, because the way we measure progression-free survival of disease with these, performing periodic CT scans, we have a completely different schedule in the PAOLO-1 and in the PRIMA trial.

I will explain this in more detail. In the PRIMA trial we did the CT scans every 12 weeks, but in the PAOLO-1, CT scans were performed every 24 weeks. That has a clear impact in the median progression-free survival because we are measuring how the patients progress with a longer period of time that will not impact the hazard ratio, but can impact the median progression-free survival. Methodologically, it is not possible to compare both trials.

The other point is that the population is completely different. As I mentioned before, the PRIMA study includes patients with highest risk of relapse, so median progression-free survival that is associated with patients with Stage 4 or patients that do receive neoadjuvant chemotherapy are always shorter than the median progression-free survival than those patients that have received preparation and then are treated with chemotherapy followed by maintenance.

I think that this the first thing I would like to clarify. The second thing is how are we going to treat patients after this data? That is a very good question. Honestly, we need to measure this data to think about those, but I see clearly that the PRIMA study has provided the most clear and significant data in a growing population of patients that are those that receive neoadjuvant chemotherapy.

Actually, what we can say is that we do not have good robust data of the role of bevacizumab for patients that receive neoadjuvant chemotherapy. It is something that we have after the interval after surgery, but we do not have randomised data that have provided the benefit of that intervention. However, in the PRIMA study, two-thirds of the patients have received neoadjuvant chemotherapy, so if I am in front of a patient that cannot be operated upon and she received neoadjuvant chemotherapy and the patient is homologous recombination proficient. The patient had a good response and can be operated, I do not have any doubt that *Zejula* or niraparib should be the best option for that patient.

Regarding the dose, unfortunately I cannot provide you with the data for your question, so regarding the median dose that we have, honestly I do not have those data but the data will probably come very soon.

Simon Baker (Redburn): I have two questions please. First, going back to the question of the greater apparent efficacy of *Zejula*, you talk about the PK argument. I wonder what your latest thoughts were on the PARP inhibition versus PARP trapping argument, also referred to in the paper that you highlighted on the slides? Secondly, I wonder if you could update us on any plans for ICOS combination with bintrafusp alfa as well as the pembrolizumab development you are doing?

Hal Barron: Thank you for your questions, Simon. I think your point about PARP trapping versus enzyme inhibition is a good one - they do vary by PARPs. As it relates to olaparib and niraparib, there are hypotheses that could explain a little bit of it, though we believe that the clinical pharmacology data are a little more compelling rationale. There are different PARPs outside of the ones tested in these two trials where the trapping is less and propose to potentially have less impact in certain populations but that is about as much as I would say about that.

Axel, do you want to take the bintrafusp alfa question?

Dr Axel Hoos: It is a logical conclusion that if ICOS will be expanded in development, the logical combination partner for PD-L1 TGF-beta trap bi-specific, so we are evaluating the possibility for that. However, we have not yet initiated the study in that regard. As you know, this is a partner programme, so anything we decide to do would be happening together with Merck Serono.

Peter Welford (Jefferies): I have two quick questions. First, you mentioned the percentage of patients who get testing in the US and I believe you said 2% HRD and 54% BRCA. Do you have any information on the percentage of patients or clinicians who have access to the Myriad myChoice test and any idea of the usage versus patients having access to be able to do the test in the first place?

Secondly, with regard to the HR proficient patient, I wonder if there is any comment at all on how we seem to be seeing a potential early survival benefit in that cohort but not the other two? I appreciate that these are very small numbers and immature data but is there anything that we should read into that at all? The BRCA population seems to be having the most profound benefit on survival earliest? Thank you.

Hal Barron: Luke, why don't you take the first question?

Luke Miels: A great question, thanks Peter. It really depends on the geography. In the US, patients and physicians can access the test, it is not cheap but that infrastructure is in place. The 2% that I quote is from the July Flatiron data so it is there. As far as the PARP testing rate, that really surprised me at 54%. Normally, with EGFR and things like that, you would see rates of 85%-90% or even higher.

One thing about the BRCA testing rate is that, if a physician does order a BRCA test, there is a 90% chance that patient would receive a PARP in the US. With regard to Europe, as you may imagine we looked at this pretty closely, there is no established infrastructure right now for HRD testing in terms of myChoice assay and we would expect that would need to be established if a companion test is required.

Hal Barron: As far as the HRp overall survival data, as you point out and I shall reiterate, it is incredibly early, it is only 11% of events, so there is the potential for over-interpreting this and we have to be careful. Having said that, I probably would not read too much into the fact that the hazard is 0.51 in the HRp and 0.61 in the HRd at this point given that error bars are very big.

The key point is that the trends are pretty strong and the confidence intervals in the HRp are a little narrower in part because there are more events, these are sicker patients, so unfortunately there are more events. You can see that when you look at the number of women alive at two years, you can see in the HRp population, unfortunately, 41% of the women had died and in the niraparib arm in the HRp, that number was down to 19%, so over double the number of women experiencing that. There are encouraging strong trends, very immature, not a really big difference in signal at this point. Next question?

Keyur Parekh (Goldman Sachs): Good evening, I have two questions please if I may. Luke, would you expect the Lynparza label to be updated to reflect the entire PAOLA-1 population from an all-comers perspective based on the hazard ratio of 0.92 that we expect the Lynparza label to only reflect the subset of the PAOLA-1 competition? That's question number one; and then question number two, for Dr Martin. What are the patients for which you will recommend using a combination therapy with bevacizumab upfront? Thank you.

Luke Miels: Keyur, I would love to answer that question, and two years ago I could have, but I might get into trouble if I have a go at it now, so I will take a pass on that one, thanks.

Dr González-Martin: If I understood well, the question you were asking is in which profile of patients we will use, or I will use the combination of bevacizumab and olaparib?

After seeing the data in PAOLA, I think that it is clear that homologous combination proficient group do not achieve any benefit, so that population we shouldn't add olaparib to bevacizumab if the patient is going to receive bevacizumab, and focus more with the combination-deficient group. What I saw is that they have a ratio in the BRCA wild type, also in the BRCA-mutated that was in the range that we have seen in PRIMA, so the question that arises is what is the benefit of adding bevacizumab, in this case, to olaparib?

That's something that we cannot answer, because the trials do not have a single arm with olaparib, and it's difficult to interpret, but we have to realise that all the data that we have in second line, with the combination of antiangiogenic and PARP inhibitors will compare with PARP inhibitor, so we were asking if antiangiogenic adds something to the PARP inhibitor.

Here is the other way around. All patients have received bevacizumab, and the question is if olaparib is adding something to that, and olaparib is having what the PARP inhibitor used to have in an homologous recombination deficient population – it has a ratio between 0.3 and 0.4 … something, so, again, the question is do we need the combination of PARP and bev with more toxicity, and more cost, and more visits to the hospital? Honestly, I don't think so.

Hal Barron: Thank you, next question?

Steve Scala (Cowen): Thank you, a few questions on the ICOS, and apologies if they have already been answered, but is ICOS expression correlated with response, and, if yes, will that be a stratification factor in Phase 3?

Second, what evidence do you have that the expression relationship is not unique to head and neck?

Then, thirdly, is there a validated assay for patient selection in Phase 3? Thank you.

Hal Barron: Axel, do you want to take all three of these?

Axel Hoos: Yes, so the ICOS story actually originated from a biomarker profile that was detected in the CTLA-4 programme, ipilimumab, and there ICOS expression or up-regulation of ICOS was correlated with higher response rate, and a better long-term survival, so, clearly, there is a biologic underpinning that ICOS expression is important.

We are in the process of developing an assay that enables us to detect ICOS high expression, but we do not have enough data yet to say we will actually need that, so the responders that we have seen in the INDUCE-1 study were at this point independent of ICOS status, so consequently, this Phase 3 trial is not aiming for selection of patients based on that, but, certainly, we realise this could enrich the story further as we build out the programme, and as we learn more we will consider it.

Hal Barron: Thank you. I think we are going to have to wrap it up, but I want to thank all of you who participated on the call, my GSK colleagues here, Dr González-Martin, and a particular thank you to all of the Tesaro colleagues that might be listening for their great work on PRIMA and making an outstanding company that can result in a really very, very significant outcome for patients, so thank you for that, and we will end here.

[*Ends*]