Early Pipeline Meet-the-Management

17 December 2024 at 1pm GMT / 8am EST

Introduction | Mick Readey

Slide 1: Meet GSK Management

Hello everyone. Welcome to today's 'Meet GSK Management' event – focused on the 'next-wave' of our pipeline. This is an interactive event with the presentation sent to our distribution list by email, and you can also find it on gsk.com.

Slide 2: Cautionary statement

This is the usual safe-harbour statement.

Slide 3: Participants

Our CSO, Tony Wood will take you through the presentation before, Hesham Abdullah, Kaivan Khavandi and Luke Miels join for Q&A.

And with that, I'll hand over to Tony.

Tony Wood

Slide 4: Next Wave of R&D

Thanks, everyone. And welcome.

Today I want to talk to you about our "Next Wave" of R&D innovation at GSK. At the pace we're now working, some of these medicines will contribute meaningfully to our growth this decade, while others will reach patients in the 2030s.

At the core of our approach is deepening our expertise in science related to the immune system… taking it beyond our current understanding of its role in autoimmune disease and infection, to a deeper understanding of fibrosis and auto-inflammation, for precision treatment and, ultimately, to target interventions that support healthy immune system ageing.

We are doing this through investment in scientific partnerships and advanced platform and data technologies, to substantially increase our use of genetics, functional genomics, biomarkers and immunophenotyping – to identify the right target, the right drug, and the right patient.

Our aim is to develop significant competitive advantage for GSK, with deep expertise inside the company and the full advantage of a bespoke, world-class network of partnerships.

Data collaborations with expert partners like Oxford, Cambridge and Boston Universities, Ochre and FinnGen, together with platform tech partnerships like Flagship, WAVE and our acquisition of Elsie, are enabling us to understand underlying disease processes, reach previously inaccessible targets and better identify patients for treatment.

With the progress we have now made, I believe we have a clear path to develop a differentiated pipeline of first- and/or best-in-class medicines and vaccines – across a range of significant diseases – that will deliver benefit, at scale, to patients and, ultimately, sustainable value to shareholders.

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Slide 5: Focus for Today: Oncology and Respiratory/Immunology

Today, I will be focusing on our approach in Oncology and Respiratory/Immunology. These are two areas where we have significant opportunities for growth in 2025 – with prospective launches of Blenrep and depemokimab – and where we are increasing and prioritising capital investment to accelerate key pipeline assets.

In Oncology, our plan is to rapidly expand beyond our current focus in haematological and gynaecological cancers, to develop antibody drug-conjugates (ADCs) for the treatment of solid tumours.

And in Respiratory/Immunology, we are building on decades of knowledge in inflammatory mechanisms to lead in COPD and to target fibrotic lung, liver and kidney disease.

We plan to provide a similar update on HIV in H2 2025, with ID following in due course, but for today, let's start with Oncology…

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Slide 6: Oncology

Slide 7: Blenrep could redefine treatment in 2L multiple myeloma with exceptional efficacy, manageable safety profile and advantageous ease of administration

Just last week at ASH, we presented statistically significant and clinically meaningful overall survival results for a Blenrep combination, with a 42% reduction in risk of death over current SoC, which may translate to giving patients up to a median additional three years of life based on projections. With an acceptable safety profile, including on eye related side effects, we believe Blenrep has the potential to transform treatment for people with multiple myeloma.

We've already completed 7 regulatory filings, including in the US where we expect a decision by July 2025.

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Slide 8: Promising early results in newly diagnosed patient cohorts increase confidence in Blenrep 1L potential and further lifecycle innovation

We have already seen promising results in newly diagnosed patients as well, for example from the BelaRd trial which showed a 100% response rate. So we're increasingly confident in Blenrep's 1L potential and plan to start the phase III trial, DREAMM-10, in newly diagnosed transplant ineligible multiple myeloma this month.

The trial will compare a Blenrep combination with standard of care, looking at minimal residual disease (MRD) negativity, and progression free survival as primary endpoints. We expect initial results by the end of 2027.

Blenrep reinforces the significant potential of antibody drug conjugates (ADCs) as targeted cancer therapies.

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Slide 9: ADCs targeting B7-H3 provide multi-indication, transformational potential

In addition to Blenrep, we have two exciting opportunities with our B7H3 and B7H4 assets, as well as the potential for further BD in this space, as demonstrated by our exclusive option agreement with Duality Biologics recently announced for DB-1324 in GI tumours.

First, let's look at our GSK'227 ADC which targets B7-H3.

The B7-H3 antigen is over expressed in a wide range of solid tumours, including lung and colorectal tumours.

These tumours are sensitive to topoisomerase inhibition which means we can deliver potent medicine targeted to cancer cells, sparing healthy tissue, unlike traditional chemotherapy.

The topoisomerase payload in '227 is clinically validated and preliminary data suggest potential anti-tumour activity across a range of indications.

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Slide 10: GSK5764227 (B7-H3 ADC) has broad impact across multiple tumour types

These early data from the ARTEMIS-001 phase I trial in advanced solid tumours were presented by our partner Hansoh at ASCO in 2023.

They show promising initial clinical activity in small cell lung cancer, non-small cell lung cancer and sarcoma with multiple confirmed responses and a manageable safety profile.

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Slide 11: GSK'227 Breakthrough Designation based on 50-61% overall response rate in extensive-stage small-cell lung cancer and significant need for improved treatments

This slide shows further results from ARTEMIS-001 presented at the World Lung Conference in September this year in patients with extensive-stage small-cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

The trial showed a 61% and 50% overall response rate for two different doses of '227. For patients at this extensive stage of disease, standard of care is typically single agent chemotherapy, with an expected response rate of under 20%, illustrating the impressive nature of these results.

B7-H3's transformative potential has also been recognised with Breakthrough Designation from the FDA. Phase I/II trials will start in the coming months with a comprehensive development programme including lung, GI, GU and beyond.

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Slide 12: GSK5733584 (B7-H4 ADC) could redefine survival outcomes in ovarian and endometrial cancer

Like B7H3, B7H4 is expressed across a number of solid tumours, particularly in endometrial, breast and ovarian tumour types.

Our B7H4 ADC, GSK'584, has best-in-class potential in ovarian and endometrial cancers, with additional opportunities in other solid tumours.

We're exploring a range of potential biomarkers in our development programme to determine the patients most likely to respond to treatment and using AI/ML to understand the mode of action of ADCs in different tumours to guide and accelerate combination development, including with Jemperli.

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Slide 13: GSK'584 shows promising proof of concept with combination potential

Phase I data presented at ESMO in 2023 showed promising proof of concept for GSK'584 in patients with advanced solid tumours refractory to standard therapy.

This trial primarily enrolled breast cancer patients, with a focus on triple negative breast cancer (TNBC), but also included small numbers of patients with ovarian and endometrial cancers. Across the study, subjects were heavily pretreated, with a mean five prior lines of therapy.

As you can see here, GSK'584 showed broad anti-tumour activity in advanced solid tumours with encouraging clinical activity in TNBC.

We believe these data are representative of the type of activity expected in gynaecological tumours, an area of strength for GSK. We are moving quickly to generate further evidence, including in combination with Jemperli.

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Slide 14: Accelerating GSK'227 (B7-H3 ADC) and GSK'584 (B7-H4 ADC) development, with first phase III results expected in 2027

Given their potential, we are prioritising and increasing investment in '227 and '584 in 2025 and 2026 and accelerating their development with a plan to deliver the first phase III results in 2027.

For B7-H3:

- We are developing this asset in lung, colorectal, head and neck, and prostate cancers, and evaluating other solid tumours
- Together with Hansoh, we expect to share updated SCLC and osteosarcoma data at ASCO and dose escalation data at ESMO next year, with pivotal studies planned for Q4 2025

For B7-H4:

- We are developing this asset as monotherapy and in combination across multiple indications in ovarian and endometrial cancers
- We expect to share early ovarian and endometrial data at ASCO and ESMO in 2025.
- Dose expansion data are also anticipated during the year with a targeted pivotal study start in 2026

For both programmes, we will apply extensive biomarker work, supported by AI/ML to determine the patients who will benefit most from treatment.

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Slide 15: ADCs enable expansion into a range of solid tumours with significant unmet need, strengthening current portfolio and unlocking new combination potential

As you can see, the ADCs compliment and strengthen our Oncology pipeline, expanding our presence across multiple tumour types with significant opportunity.

ADCs could disrupt conventional treatment regimens, alone and in combination with PD1s, complementing our *Jemperli* programmes and replacing chemotherapy in later lines

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Slide 16: With accelerated development, ADCs approvals could come 2027+

Our clear focus is to prioritise and accelerate development of assets with the greatest potential, with effective stage-gating and checkpoints in place to drive timely investment decisions.

Gynaecological cancers remain a cornerstone of our portfolio with Jemperli and now our B7-H4 ADC...

... and we are moving into additional solid tumour types including lung, colorectal and head and neck with both our B7-H3 ADC and Jemperli.

As a reminder, we expect initial results from the AZUR-1 and -2 trials exploring Jemperli in rectal and colon cancer in 2026 and 2027 respectively, with the phase III JADE study in locally advanced head and neck cancer, expected to read out in 2028.

We're confident B7H3 ADC will also serve as a significant cornerstone in many of these cancers.

Beyond these, we continue to evaluate our TIGIT monoclonal antibody, belrestotug, – mindful of data we have seen elsewhere – and our development strategy will be informed by additional data generated over the next 12 to 18 months.

With that complete, now, let's turn to our Respiratory/Immunology portfolio...

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Slide 17: Respiratory/Immunology

Slide 18: Deep expertise in inflammatory mechanisms is opening up new opportunities in Respiratory/Immunology

Our unique understanding of the role that inflammation plays in airway disease is based on decades of research in chronic respiratory conditions like asthma and COPD.

In **Respiratory,** our focus is on the underlying biology and heterogeneity of inflammation, notably in COPD, is leading to a differentiated pipeline of long-acting options with multiple MoAs.

In **Immunology**, we're researching how inflammation contributes to the development of fibrosis in the lung, liver and kidneys. Fibrotic diseases are thought to account for up to 45% of all deaths worldwide so this is a major area of need.

As I'll share through examples of our work in COPD and liver disease, we're transforming our approach with the application of advanced technologies.

Next slide please.

Slide 19: We have a deep understanding of the multiple pathways driving inflammation in COPD

As with our work in cancer, our approach starts with understanding human biology – in this case for COPD.

COPD affects more than 300 million people globally and is the third leading cause of death worldwide excluding COVID.

It is a complex and heterogenous condition, driven by multiple inflammatory pathways.

We were pioneers in establishing the role of IL-5 through our work with Nucala and were delighted with the positive headline results of MATINEE, our phase III trial in patients with COPD with high eosinophil levels.

We are applying the unique insights we've collected in the Nucala phase III COPD studies to progress our wider COPD pipeline – including for depemokimab where we aim to start phase III development in COPD next year.

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Slide 20: IL-33 and TSLP have strong genetic validation as potential targets in COPD

Both IL-33 and TSLP also have strong genetic evidence supporting their potential as promising targets for intervening in COPD.

People with naturally occurring lower expressions of IL-33 and TSLP proteins have a reduced risk of COPD and lower activity of both TSLP and IL-33 seems to decrease susceptibility to COPD in an additive manner, providing strong rationale for a combination therapy that targets both of these pathways.

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Slide 21: Insights from unique, proprietary data sets support the need for multiple modalities to ensure the right treatment for the right patient

By integrating a range of diverse data from disease phenotyping, human genetics and genomics, cell biology and insights from our own scaled clinical studies, we have built a sophisticated and unique understanding of different COPD populations.

Together with insights from partners like Cambridge and Boston Universities, we have amassed a vast dataset to help answer key questions on COPD progression, predictive outcomes, and biomarker measures for disease stability.

Factors including T2 inflammation, eosinophil levels and a host of others influence both disease progression and response to treatment and we are now using modelling to map prospective treatments to specific patient types. This work strongly supports the need for multiple mechanisms, in addition to IL-5, to help as many patients as possible.

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Slide 22: We will expand our COPD leadership exploring a suite of ultra-long-acting medicines to maximise efficacy in the broadest range of patients

This slide shows the range of MOAs in our pipeline which target different biological pathways to reach the broadest range of COPD patients. This chart is split by eosinophil levels and disease severity, but you can also map against factors like smoking status and exacerbation history.

It is important to know, that while we're already well positioned to compete in COPD with our IL-5 assets, these will only be suitable for the ~37% of patients whose disease is driven by eosinophils.

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Slide 23: Ultra-long-acting treatments have the potential to significantly impact outcomes in COPD

There remains significant need for improved biologic options in COPD to stop patients exacerbating and improve persistence with therapy. We see ultra long-acting medicines as a critical differentiator, providing sustained suppression of inflammation to impact disease progression, for new efficacy benchmarks such as exacerbation/hospitalisation reduction, as well as adherence and convenience benefits. We have deep understanding of patient, payer and HCP preferences in this space.

As the only company with this range of mechanisms in an ultra-long-acting format, we believe we are very competitively placed to extend our leadership in this disease.

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Slide 24: We are well placed to execute new COPD programmes across IL-5, IL-33 and TSLP with phase III starts in 2025 onwards

In the next 2-3 years, we anticipate a series of pivotal trial starts in COPD which could transform the treatment landscape.

Next year, we're targeting approval for COPD with Nucala and expect to begin a phase III trial for depemokimab with a potential filing by 2031.

Our IL-33 programme is currently in phase I, and we're targeting a potential phase III start in 2027.

For TSLP, currently in phase II, we expect to begin phase III around the same timeframe, while also evaluating the combination potential of these two molecules.

This is an ambitious development plan, conducting multiple large-scale pivotal programmes in parallel, but given our significant experience and strong heritage of working with respiratory investigators, we believe we are well placed to deliver.

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Slide 25: Our expertise in inflammatory pathways and fibrosis is unlocking new opportunities beyond the lung, for example in liver disease

As I laid out earlier, our work in human genetics and phenotyping is also generating insights that are informing moves into other areas, including liver disease.

One example I'd like to share our progress on is Steatotic Liver Disease (SLD), a chronic, progressive liver disease that affects 5% of the global population and has a significant health burden.

Steatotic Liver Disease includes several conditions associated with accumulation of fat in the liver, including metabolic dysfunction-associated steatohepatitis (MASH), also known as NASH, and alcoholic liver disease (ALD).

Over 12 million patients globally have MASH, and a further 26 million have alcoholic liver disease, this accounts for half of liver-related deaths in developed countries.

There are currently no pharmacological treatments available for ALD, which is associated with significant emotional and psychological issues. Many patients also struggle with alcohol addiction making lifestyle changes difficult.

These conditions have typically been seen as difficult to treat…

…but new modalities, including oligonucleotides, have shown real promise in targeting liver diseases due to their ability to specifically modulate gene expression in the liver.

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Slide 26: HSD17B13 has strong genetic validation as a target in SLD

HSD17B13 is a gene involved in lipid metabolism and primarily expressed in the liver. Human genetic studies show that naturally occurring variants in this gene are protective against both alcohol-related and non-alcohol-related liver disease – providing a ~30-50% risk reduction in carriers compared to non-carriers.

This is one of the strongest levels of genetic validation we've seen for any target. And, reassuringly, this protective effect is maintained even in the case of continued alcohol consumption.

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Slide 27: GSK'990 showed deep and durable reduction in HSD17B13 expression and reductions in key marker of liver injury

GSK'990 is our second oligonucleotide in the clinic, following bepirovirsen for chronic hepatitis B. '990 is a siRNA therapeutic designed to selectively target HSD17B13, reducing its expression and slowing or halting disease progression in ALD and MASH.

In phase I, it has demonstrated robust target knockdown and encouraging reductions in markers of liver injury.

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Slide 28: Tech-enabled GSK'990 development programme underway across spectrum of SLD

We have now started the HORIZON phase II study in MASH patients with advanced fibrosis and we are initiating a phase II trial in patients with ALD called STARLIGHT.

GSK'990 is another fantastic example of our tech strategy in action building out our oligonucleotide platform. The programme has also been strongly informed by genetics, and we've used single cell imaging to confirm the expression of the target in liver cells – an approach which roughly triples the chance of a target reaching phase III.

Our clinical development programme for '990 is being informed by biomarkers so we're able to predict the patients most likely to benefit from treatment. We have identified several well-established and non-invasive tests that have excellent predictive value for clinical outcomes.

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Slide 29: Opportunity to develop an SLD portfolio of complementary mechanisms to reach a broad group of patients

Looking beyond '990, we see further opportunities in liver disease, enabled by our growing expertise in this space and enhanced by our collaboration with WAVE Therapeutics.

We are evaluating two additional targets which complement '990. These both have strong genetic association with a range of steatotic liver diseases and oligonucleotide tools have shown promising early activity in validation studies.

While this work is at an early stage, we see future potential for an emerging portfolio of complementary mechanisms of action informed by genetics to reach a broader group of patients and address the significant burden across SLD.

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Slide 30: Over the next decade, we expect significant approvals in Respiratory/Immunology Focused in new areas, built on our deep expertise and enabled by tech

So, we expect a growing pipeline in Respiratory focused on COPD, and an exciting evolution of innovation in new areas – just a few of which we've covered today. These exemplify our approach to science and technology.

We anticipate a flow of data readouts and potential approvals for the remainder of the decade.

In the near term, this encompasses approvals in a range of indications for depemokimab - the first long-acting biologic to reduce severe asthma attacks leading to hospitalisations by over 70% - and Nucala in COPD. New assets in COPD and liver disease offer significant growth opportunity in the longer term, amongst other early-stage programmes focused on fibrosis.

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Slide 31: Key takeaways

So, to finish, we are making strong progress in R&D with 67 pipeline assets, 18 in late stage.

Our deepening expertise in immune science, use of advanced technologies and world-class strategic partnerships is leading to a differentiated and exciting early-stage pipeline that will deliver growth to and beyond 2031.

With strong momentum in Oncology, a clear path to extend our leadership in Respiratory and exciting new prospects in Immunology, our pipeline offers significant growth opportunities and high-potential medicines.

As a result, we are increasing and prioritising investment in both Oncology and Respiratory/Immunology; whilst continuing to pursue major pipeline opportunities in Infectious Diseases and HIV. We are very confident in achieving our prospects for growth and global impact on health. Today I have shared just a few examples and look forward to sharing more in due course.

Looking forward, we have multiple data and regulatory catalysts to come – including 5 regulatory approvals next year - and an increasing flow of innovation throughout the remainder of the decade.

With that, we'll now open for questions.

Q&As

James Gordon (JP Morgan): Thanks for taking the questions. Two questions, please. One was AI machine learning. If I'm understanding right, you are going to use that to work up cut-offs for your ADCs. Can you help us out in terms of how big would the eligible treatment populations be for these two ADCs, so '227 and '584, based on the biomarkers you envisage using, and what are the actual biomarkers that you'll be looking at? Is this a bit like UCS that we've seen for data in terms of how you assess what's being expressed, so if you can elaborate on that please, how it works and what the eligible populations might be?

Then the other one was just a clarification on the biologics for COPD. Is the idea that the IL-5 TSLP and IL-33 that they are all going to be six-monthly? What do you need to see on that? Thank you.

Tony Wood: Hi James. Let me start just with the ADC point, and I'll make a broad point and then Hesham, perhaps hand over to you in terms of how we're thinking about bringing some additional precision to the ADC landscape, and then Kaivan, over to you for pharmacokinetics for the COPD assets.

James, the first thing that I'll stress is that clearly one of the attractive features of both the B7-H3 and H4 ADCs is that they are broadly expressed across various treatment populations. What we're interested in, and we're not going to give away a great deal at this point, as I'm sure you will understand, are other features associated with the cancer that might indicate a greater or lesser response.

Hesham, I might just hand over to you to add a little bit to that.

Hesham Abdullah: Absolutely. James, one of the things we've learned, certainly with antibody drug conjugates and the targets that they actually select that we go after, is the target expression levels are not the only thing that really matters. I think the field has moved beyond that.

Certainly looking at not only target expression, expansional distribution, its density and how the ADC is actually being processed within the cell, are really critical factors. As part of our translational strategy, these are elements and variables that we will prosecute and look at. I'll maybe just call your attention to the fact that, at least based on the data that's currently available to us from the Phase 1 study that's been conducted in China for both B7-H3 and B7-H4, we're seeing data that says that there is clinical activity across a broad array of tumours, irrespective of biomarker or at least target expression at this point of time.

So, we're going to learn more and we certainly have already initiated our own development programme, and we have a translational strategy set in place that helps us even go after bigger treatment effects potentially that could be defined through this biomarker strategy, but as of now, the data tells us that the drugs are active across both high and low expression levels.

Tony Wood: Thank you, Hesham. Moving over then into COPD and PKK, perhaps you might just give James and everyone listening a sense of where we are on the qualification of the pharmacokinetics for the three assets.

Kaivan Khavandi: Thank you! For depemokimab, of course, the profile has been established in the SWIFT studies as a six-monthly administration. For the anti-TSLP, the data that we had at deal signing from exposure in China and Australian participants demonstrated through modelling confidence that that would also be amenable to a twice-yearly dosing regimen. We're taking that into a Phase 2 study in asthma, which we have just had IND confirmation we're safe to proceed in Q1 next year for dose selection.

Then, for the anti-IL33 programme that's currently in a Phase 1a/b, we are moving into a patient cohort next year where we're going to do repeat dosing. The first dose will be after 12 weeks, and then we're going to follow up after the second dose, so over six months, to confirm whether it's going to be a three or six-monthly dosing regimen, both of which would meaningfully differentiate versus other anti-IL33 molecules.

Tony Wood: Thank you, Kaivan.

Simon Baker (Bernstein): Thank you everyone for the presentation. Three quick questions, if I may. Just starting off with *Blenrep*, at ASH, a week or two back, it was shown that the dose reductions related to ocular tox led to a fairly rapid resolution and did not impact efficacy. In light of that, I just wondered if you could give us the feedback you had from physicians on their enthusiasm for using *Blenrep* and their comfort with the side effects? I kind of get the sense that physicians are probably a bit more relaxed than we are, so any colour on that would be handy.

Then on '227 and B7-H3, there was a poster at San Antonio last week showing B7-H3 being targeted through CAR-T. You didn't mention CAR-T today, so I just wondered if you could give us your thoughts on that as a modality for GSK.

Then finally, moving onto the long-acting IL-33, there was work published earlier in the year showing potential utility in cystic fibrosis, I wonder how interesting that is to you given it's an obvious adjacency to your respiratory work and an adjacency which has orphan drug potential? Thanks so much.

Tony Wood: Thanks Simon, let me see if I can get through all three, please remind me if I miss any component of it. Why don't we start Hesham with you, just quickly on physician feedback with regards to *Blenrep* and the emerging profile over efficacy versus safety effects. I might then come back and just make a quick comment on CAR-T before we hand over to Kaivan, so over to you Hesham.

Hesham Abdullah: Certainly the feedback that we have been getting from physicians that have had experience with *Blenrep* is it's relatively easy to administer, especially given the context around of course the fact that we

have 70% of patients, multiple myeloma patients, that are sitting in the community, so the ability to be able to administer this on an outpatient basis, the ability to not require hospitalisation is really important and critical for them. The fact that it can be given immediately, so there is no need to wait for patients going through apheresis lymphodepletion, or of course, for them to really have to experience some of the side effects that are associated with other therapeutic modalities like CAR-T's or T-cell engagers. Now again, it's a familiarity that the physicians have to acquire of course, just as is the case of course with any new class of drugs that emerges in oncology. You think back to let's say, for example, checkpoint inhibitors, and this was a class of agents that initially, when it came on the scene in 2014, was associated with these immune-mediated adverse events, not everyone was very familiar with them, but once everyone realised that they were inflammatory in nature, can be managed by steroids and that they can certainly interrupt the dosing until they resolve and then resume it afterwards, you look at it now at least, no one is really talking about them at this point in time when they are thinking about checkpoints.

The same holds true here, in terms of starting out with the 2.5mg dose, induce the depth of response and we have seen that, whether it be with the MRD negativity or with the duration of response, and then basically over time, increase the dose and extend the schedule. You saw the data at ASH when the dosing intervals were extended to every eight or 12 weeks, the response was sustained and maintained and you saw that the ocular toxicity in terms of its incidents and discontinuations resulting from it, decreased over time. So I think that's the message and the feedback that we are getting from the physicians as well, is their ability to effectively use the dose reductions, the dose interruptions, help them to manage the ocular side effects quite well.

Tony Wood: Luke, I will give you a chance to speak to this feature of developing and understanding and managing the treatment population as well, but before I go there, Simon, just quickly on the CAR-T question. Obviously whether it's ADC's CAR-T or TCEs, what we are doing is exploiting the same antigen proposition but bringing a different feature associated with the cytotoxic component. One of the things that we find particularly exciting about the B7-H3 and H4 ADCs is that we're able to deploy them to cancers which we already know, topoisomerase inhibitors are effective, so we feel given that background, the ADC approach is the one that is likely to bring the most effective therapeutic index and indeed as Hesham stressed earlier in the comparison, more straightforward process for treatment. With that, Luke, I don't know if there is anything you want to add?

Luke Miels: I think, Simon, I completely agree with the direction you're taking. Practising haematologists, oncologists, they are empirical by nature, and I think firstly, the overall survival, the profile that we have for DREAMM-7 and DREAMM-8, potentially resets the discussion in the mind of many physicians.

The other thing is – and Hesham, correct me if I'm wrong – if you look at the percentage time that a patient actually experiences blurred vision or ocular events, it is single digit percentage of the total time you're on the drug. It's not an ongoing, durable disturbance, blurred vision, etc., it's a relatively confined point of time. As Hesham has said, it's reversible.

I think the other thing is, if you just print out the PI, the safety profile of CAR-T where you've got all sorts of novel things, Parkinsonian excess, early mortality, unusual and partly irreversible AEs with CAR-Ts, so you have excellent efficacy but they are sophisticated and difficult to use as Hesham said, in the community it's just practically not accessible. If you look at the bispecifics, we are really getting a sense of the profile there. The MajesTEC 2 data, okay, there was a difference in terms of the rates of infusion, but that had 22% infusion deaths, right? Other data, earlier, neutropenia was around, a third of the patients had Grade 3.

I just look at this and I try to be as objective as we can in talking to experts using the drug. In that context, *Blenrep* is looking increasingly like an accessible product, and as Tony said, we are going to do a lot of work to manage that interface between the optometrist and the ophthalmologist. We need to see what the REMS we get from the FDA is, but the benefit/risk of the product is dramatically changed now that we have overall survival against the CD-38 regimen.

Tony Wood: Thanks, Luke. Simon, we will now move over and deal with IL-33 in cystic fibrosis. Kaivan, I guess we might talk more broadly about obstructive lung disease and what we see in the opportunities from the phenotypes there.

Kaivan Khavandi: Absolutely. I think in our team schematics, you often see TSLP and IL-33 occupying the same space together as upstream alarmins, but actually Tony presented some of the multiomic approaches that we're able to prosecute. What we see is that whilst TSLP 430 and IL-5 map together, you get a clear bifurcation where IL-33 is clearly moving towards more Th1/Th17 pathways, and therefore maps more closely to this neutrophilic COPD obstructive lung phenotype.

We are actively exploring the possibility of evaluating IL-33 in non-CF bronchiectasis, and we are fully enabled to start that study next year if we wish, and of course, consideration can be made whether we include CF patients within that same trial design.

Seamus Fernandez (Guggenheim): This is Abdan, I'm on for Seamus Fernandez. Thank you for the questions. Just to start off with, it looks like you're not pursuing combination strategies with IL-5. Can you explain the rationale behind this? Then shifting over to MASH afterwards, do you believe that your pivotal trials will require a biopsy, and more broadly speaking, what do you see for the opportunity in MASH as this market evolves?

Then, third and last question, I'm just curious, Tony, what you think is the most under-appreciated asset that you presented on today? Thank you.

Tony Wood: Thanks for the questions. I think I'll hand straight over to Kaivan on the IL-5 and MASH on questions. Obviously if you can include the context of the sort of temple nature of the evaluation of all of that, and in the context of MASH, address the fibrotic components in post-GLP 1, and I will in the meantime, take a look amongst all these exciting assets and figure out which one I like the most!

Kaivan Khavandi: Tony presented earlier a genetic risk score that we created for IL-33 and TSLP, and you saw there that the combination of activity results in additivity for those pathways. I just described some convergence of TSLP 4, 13 and 5, therefore it's unlikely we would pursue a TSLP anti-IL5 combination. However, there is a rationale for an anti IL-33 and anti IL-5 combination strategy and that is something that we would consider.

Moving onto MASH, we are conscious that there are a number of mechanisms that are exploring anti cirrhotic mechanisms in MASH. The unique differentiated value of HSD17B13 is that we have quite exquisite human causal data from genetics that we presented, showing that this pathway is most relevant in advanced MASH and fibrosis and cirrhotic segments of disease and those are the segments, the natural history, that are going to be underserved by emerging standard of care. What we see is that we are able to pair that genetic confidence with a cell level understanding of what the pathway can do to ballooning of hepatocytes, inflammation, and fibrosis. The population we are studying, the Phase 2b Horizon trial, is MASH patients with F3 fibrosis, F3 stage disease and we also include an F4 exploratory population that study, we will be biopsing of course because we need to demonstrate either MASH resolution or improvements in fibrosis. Given that therapeutic hypothesis, that's particularly relevant to alcohol related liver disease where you see a very fast progression through to fibrotic phenotypes and where of course there's currently no pharmacological treatments for what is the number one cause of liver transplantation in the US.

Tony Wood: In answering your question with regards to which ones we are most excited about, I think the first point I would make is the one I did right at the beginning of the presentation, in that these are all areas in which we are investing in because we see the potential for significant growth, driven by a combination of the medical need and indeed the underpinning science. If you don't mind, I am going to answer with two examples, because

I think they illustrate nicely the sort of features that science and programmes which are now emerging from our research activities into clinic or from our BD focus, are going to carry for the future.

Obviously B7-H3 represents a very exciting opportunity, Hesham laid out the broader context of that, but what we have there is through form studies, the opportunity to look for early efficacy, the confidence that the TOPO inhibitor brings and then a range of additional either genotyping or phenotyping approaches that will in time begin to disclose, which will give us a sense of who is going to be the most likely patients to respond, even within the breadth of the antigen expressions. Very excited about that one, given both the opportunity and the link back as well to the translational science that we're building within Hesham's group under Tony Ng for example.

With regards to Kaivan's world, well for me HSD17B13 is a really great example of something that carries tremendously strong genetic credentials. You can think about this one as being PCSK9-like but what we have on top of it and we didn't have time to go into detail, is single-cell work through spatial transcriptomics that then links the transcripts that are expressed as a consequence of that genotype against the cell types, ballooning hepatocytes and indeed, looks at it relative to alcohol as for example a given event.

So we are reaching a degree of precision and understanding target modulation and the patients who are most likely to benefit from these agents, in both oncology and in MASH, which is going to characterise the approach that we take in the future. For those two programmes, for me they represent probably the pinnacle of what we've presented today but it's important to stress that this is not a portfolio against which I am making relative choices.

Emmanuel Papadakis (Deutsche Bank): Thank you for taking the questions, a few if I may please. Firstly on oncology, the pipeline, if I recall correctly, *Blenrep* was discovered internally but you've now largely had to resort to in-licensing the next wave of assets from Chinese companies both ADCs, even beyond B7 molecules we talked about today, cobolimab, dostarlimab and all the rest, they all came from outside the company. What's been the hold-up on building upon the early success of *Blenrep*, either within ADC or beyond in oncology in the last few years? That is question No. 1.

Question No. 2: 990 MASH - thank you for the evidence on genetic validation. What about translational rationale, so what does the B13 protein actually do? Do you suggest it should deliver a functional benefit when modulated and do any better than previously promising genetic targets outlined in things like CCL-17?

A very quick one on IL-33, is that totally a new molecule or is it the same backbone as the molecule you discontinued several years ago for asthma? Thank you.

Tony Wood: Thank you. Again, I will give some brief answers and in this case, I'll hand over to you, Hesham, to talk about the internal build in oncology discovery.

I would say first of all, this is not a reflection of a lack of internal effort, but rather a reflection of a deliberate strategy in which we recognise that by focusing on the sort of technologies that we have just been describing that enables us to make better choices of targets in patients and combinations, then our efforts are more effectively deployed there, and it gives us an insight into what, as you are, I'm sure, fully aware, is a very active potential BD landscape.

Now, sitting behind that, of course, we are continuing to develop internal programmes and follow-ons, for example, in the Pol-Theta arena that, Hesham, you might just briefly mention. I'll take up the genetics and translational rationale in a moment. But why don't you mention just a little bit about the internal earlier portfolio, Hesham.

Hesham Abdullah: Thank you very much for the question. I'll start off by saying, even industry leaders in oncology have relied on, certainly in-licensing to build parts and complement parts of their portfolio, including certainly other organisations have, for example, leading PD-1 inhibitor as well. I think we just have to keep that in mind.

The ability to have the right mixture and balance between business development, but also inhouse research and development activities is really important and critical. With that mind, the one you highlighted of course, *Blenrep* was developed internally. We have complemented that now with B7-H3 and B7-H4, and then of course the recent deal that we're doing, an option deal that we're doing with Duality on another ADC with another validated linker payload technology for a target that's directed towards gastrointestinal tumours.

With that in mind, in parallel, we have been developing an internal linker payload platform as well, and you'll be hearing more about this over the next 12-18 months as you see the first asset from that platform come into the clinic. That's one.

Two, we do have T-cell engagers, and we have access to them or are in the process to developing both bispecific and trispecific T-cell engagers that will be applied across prioritised tumour types and areas, whether they be solid tumours or key malignancies for that matter.

Then three, to highlight Tony's point, we are continuing to look at small molecules as a means of synergy and as combination partners for some of our assets, including antibody drug conjugates. I think one area to highlight of course is DNA-damage response and the potential for that, of course, to synergise with the topoisomerase warheads, in our ADCs - the Pol-Theta programme is one example of that. It's currently in the clinic and being explored in combination with niraparib across gynaecologic malignancies and breast cancer as well. But you can imagine, it could certainly be a key combination partner for antibody drug conjugates moving forward, along of course with dostarlimab no doubt.

We've found a good balance between giving time for us to be focused and selecting the right technology platforms within our research portfolio, but then complementing that with clinical stage assets that we can certainly get access to through business development.

Tony Wood: Just to reiterate then, of course, it's not unusual for late stage clinical pipelines to come in, at least 50% from BD-related activities and a deliberate choice on our behalf to focus our early stage work on technologies which will give us a better opportunity to make those selections, based on an understanding of the patient landscape and potential combinations, coupled with very focused internal working areas where we already have a clinical lead that informs discovery programmes.

As far as moving on to the other two questions or concerns, let's do the oligonucleotide programme first. Kaivan, you can add a little bit more to this but one of the big advantages of oligonucleotides is that we don't need to understand fully the biology associated with the target. I am sure you probably are aware that for HSD17B13 actually that still remains to be fully illuminated but the key advantage we get from oligonucleotides, once we understand the direction of the effect, is one can re-capitulate the phenotype simply by addressing the target at a message level.

As far as IL-33 is concerned, it is the same molecule that we had earlier that carries some half-life extension technology, I know there's no basis given the profile that we had accrued of the molecule to want to search for an alternative but, Kaivan, anything else you would like to add on HSD-17?

Kaivan Khavandi: Whilst the mechanism is not fully identified, what we do understand is that it's able to target the lipid particles that sit on the surfaces of hepatocytes. I briefly described some spatial transcriptomic work that we've done in primary tumour hepatocytes that shows that targeting that pathway reduces ballooning,

which is the most powerful agnostic cell phenotype that is linked to outcomes. That really represents quite a distinct pathway from any other mechanism to target inflammation and fibrosis in those advanced stages of the disease.

Peter Welford (Jefferies): Thanks for taking my questions, apologies if these have been asked but I joined a bit late, so firstly just on *Jemperli*, I think you mentioned for AZUR-1 and AZUR-2 but I may have missed this, was it 2026 and 2027 that you said the readouts for that or was it 2027 and 2028? I guess I'm curious given your recent breakthrough therapy designation you've for rectal, is this possible to file based on just one of those readouts or is it even possible based on an interim read before then do you think, to potentially consider discussions with the FDA?

Just moving on then to the respiratory portfolio, for depemokimab, presumably we should be assuming for COPD there are two Phase 3s planned and you cannot possibly piggy-back on any of the *Nucala* data for depemokimab at all? I just wanted to confirm that.

Then, just for IL-33, two things here, one is when you talk about the combination, am I right to understand that is two separate drugs, you are not considering a bispecific or any single moiety that hits both of those targets? Have you looked at all at the biologic rationale when you think about the Phase 3 trial for IL-33, are the targeting the ligand and if so, have you potentially looked at whether or not you should be targeting a prior smokers population? Thank you.

Tony Wood: Thank you Peter, let me start Hesham with timelines for the *Jemperli* programme and the clinical strategy for rectal and straight over to you on that one.

Hesham Abdullah: Thank you Tony, I think let me start off by first reiterating the data of course which is extremely promising, great news for patients that was presented at ASCO 2024 and specifically 42 patients with locally advanced dMMR-MSI high rectal cancer, all had a clinical complete response, a 100% clinical complete response, which is quite of course unheard of, but just shows how exquisite the science is here is terms of the sensitivity of these patients to checkpoint inhibition.

With that in mind, of course we designed the AZUR-1 and AZUR-2 studies. The AZUR-1 study of course is a Phase 2 study, it's a single-arm trial in locally advanced dMMR MSI-high rectal patients. Then AZUR-2 of course is a Phase 3 study in neo-adjuvant locally advanced colorectal cancer patients. So the readout for AZUR-1 anticipated in 2027 and then the same holds true for AZUR-2, so both of them actually are planned for 2027. Bear in mind of course that if AZUR-1 data is available early, we will plan on of course being able to file off of that, so both studies are not necessarily required, we can make a filing on only one of them. If you may recall of course, we did have a discussion at an Oncologic Drugs Advisory Committee meeting in 2023, whereby we got agreement on the single arm design of AZUR-1 as well.

Tony Wood: Thank you, Hesham. Just moving over then to the questions on COPD, where we might start actually, obviously the standard will be two Phase 3 clinical studies, but it might be worthwhile commenting on what we have learned or how we will be designing that, relative to lessons from *Nucala* at a high level, bearing in mind that we've yet to disclose that. Data will come in the first half of next year, in May.

As far as IL-33 is concerned, perhaps you might talk a little bit about what we see with regards to the behaviour in COPD for the non-smoker and ex-smoker populations, and our view of whether or not they are distinguished phenotypes for the future.

I might just say one thing with regards to targeting a ligand versus a receptor. Obviously you will appreciate from our experience with IL-5 that one can make arguments on both sides of that equation. Typically though, when

you are targeting the receptors, it is often the case that you see higher turnover of those molecules, and given that we are focused on a long-acting portfolio, that was a factor in our decision, although the total pharmacology associated with each side of that axis obviously remains to be determined, and we will continue to examine the phenotypes associated with the diseases in question as the development programmes proceed.

Kaivan, over to you in terms of high level lessons, thinking about the depth of the COPD programme.

Kaivan Khavandi: Just to re-emphasise, given that depemokimab is a different molecule, the assumption would be that we would have to replicate pivotal studies, but what we are exploring is whether we could use one of those studies to evaluate populations that could provide a differentiated label. One area that we are exploring is earlier disease and predicting those at risk who either had no exacerbations or one exacerbation in the year prior to enrolment. Obviously we are expecting the variables that we identified at the MATINEE study with *Nucala*. What I'll say is that if you have a like-for-like comparison with, here, mechanisms of COPD were very competitive. There are variables, that we will take through as learnings for the design of Phase 3 for depemokimab.

As regards anti-IL-33, what you will have seen is varied data across, again, peer companies that may be targeting receptor or ligand, and then reaction, I'd say, to small empirical datasets for sub-groups in Phase 2. What you saw in Tony's presentation is that we are taking a much more data-driven approach and using these proteomic and multi-omic and genetic approaches to be able to evaluate, explainability rather than reacting to small datasets.

In our Phase 1 study of anti-IL-33, we are stratifying by smoking, and we are doing a number of mechanistic assessments within that, including our inhouse clinical unit in Addenbrookes in Cambridge. I think that we're going to be making data-driven decisions that might be based on more mechanistic rationale than just reacting to small sub-groups and clinical studies.

Tony Wood: Thanks Kaivan. I wonder, Luke, if it's worthwhile giving you an opportunity just to talk about how we see the long-acting portfolio in lung disease at this stage.

Luke Miels: Thanks, Tony. I think there is a degree of natural synergy of course in having others validate using short-acting programmes to target, as we've done ourselves obviously with mepolizumab, *Nucala*, with depemokimab, which we are attempting to do that with TSLPs, and if we can replicate that with the IL-33 programme, yes, there's also synergy of course in terms of eos and T2 inflammation positioning, the IL-5s and 33s, obviously in people who are former smokers, and then stratifying them based on their eosinophil level.

Yes, the market research that we have is that there's the potential to disrupt. It's a relatively low penetration of biologics in respiratory disease. It is still below 30% which I think is somewhat disappointing considering the profile of these assets, so shifting into products which can be administered in the US context by physicians in office, obviously has a lot of benefits in terms of just barriers to injection, compliance and other parameters which are favourable to that method of adoption for physicians and also the patient, so the market research is very encouraging but we now need to get out there and I think the profile of depemokimab is very, very competitive in what we're seeing so far.

Graham Parry (Bank of America Merril Lynch): Thanks for taking my questions, a few on respiratory actually, so depemokimab, the Phase 3 data I think you showed 74% reduction in exacerbations leading to hospitalisation which looks like the best comparative to the existing data, so when you go out with that one, this is a question for Luke, do you see that as a best in class or is it just a convenience argument you'll being looking to commercialise that on?

Then are you looking to match existing COPD data that we have seen in the COPD study or do you think again, that could be a best in class asset there? Are you looking at a broad population in COPD, so across all biomarker sub-types?

Then on the IL-33, I was just wondering if you had any data to say whether it works on both oxidised and reduced forms of IL-33, does it prevent oxidation on IL-33, so any impact on RAGE and EGFR pathway, which is one of the differentiating points that one of your peers points out for their product?

Then on your combo strategy on IL-33 TSLP, is it co-formulation or is it actually just the safety efficacy data in combination that is the rate limiting step in taking that any further forward? Thank you.

Tony Wood: Thanks Graham, let's make a start with the depe-data in Phase 3 and I presume then Graham there is a bridge from asthma into COPD and it might be worthwhile just emphasising Kaivan before I have you a chance to speak to that.

As I have said on a number of occasions, what we see there is more the advantage associated with the breadth of coverage and across different phenotypes. When one looks at comparable populations, the efficacy is probably slightly lower than for dupilumab for example in the high eosinophilic bronchitic population but you'll see when we disclose the data next year, that we have advantage with breadth of coverage. I will come back to Luke at the end to talk about the advantage for best in class for the longer-acting agent, please remind me to go there.

Before we go to Kaivan, to just make a point on this co-formulations versus bispecifics because I forgot to answer Peter's question in that context. At the moment we very much see this as a matter of first of all establishing a clear understanding and proposition for the contribution of components, both in terms of appropriate doses and the most responsive patient populations and taking that then into co-formulation will obviously depend on understanding just exactly what the doses are, one really can't make a start on that until you have a solid grasp of that. In terms of bispecifics, we have evaluated these as potential areas, they always bring the challenge of how one gets the dose proposition accurate on both of the arms and so we prefer at the moment, to take a more optimised approach, particularly in an area where it maybe the different patient sub-groups are more responsive to one pharmacology versus another.

So Kaivan you might want to add a little bit more just in terms of COPD and a comment on the oxidised IL-33 pathway.

Kaivan Khavandi: I think you hit the main point Tony that the MATINEE study included patients with chronic bronchitis and those with emphysema. If you look at the group with chronic bronchitis, again, you will see this data in detail next year, it's competitive and comparable with the best data that is available for other mechanisms but really, the differentiator here is that we recruited these patients with severe distil airway disease and emphysema, and we are seeing efficacy in that population and those are patients who of course have the worst outcomes. Importantly of note in the recent Gold Guidelines, there was a stipulation for IL4-IL13 being recommended for those with chronic bronchitis and of course the data set that we had generated for *Nucala*, wouldn't have that same restriction in terms of societal guidelines.

For IL-33, again, I think I touched on it earlier, that some of the perhaps overly-simplified arguments around smoking, oxidisation and what we're seeing clinically, might require a more nuanced description. Our molecule binds to IL-33 in its reduced form, and therefore blocks the ST2 signalling pathway and the direct pro-inflammatory effects of the cytokine. We are seeing the same data pre-clinically, that we do have the ability to modulate oxidised forms, and therefore in the EGFR RAGE. We would say within our own data there are caveats

around those translational models and where we have the correct expression of EGFR RAGE in the relevant airway and tissue.

In summary, I think that we've got the correct molecule with respect to not being limited to a single receptor, binding the ligand and also of course, most importantly, a population that's got multi-morbidities with the dosing administration, which is very clinically important to COPD.

Tony Wood: Of course, Graham, you will recall that, for example, RAGE is something that has been actively targeted in the past, without a great deal of success as well. Very much part of the emerging picture we have, and understanding the precision of the disease phenotypes.

Why don't I hand over to Luke – any comments you would like to add in terms of how we see the depe positioning.

Luke Miels: Yes, I think, Graham, if you look at the pooled data of 52 weeks, it's about 54% from memory, which is in the range of *Nucala*. It's very consistent which is no surprise, considering the heritage. If you then look at that with Fasenra, it is very much in the range, their 41-week data in the 300 EOS population. I think Dupixent have been a little more creative in terms of how they cut their data in terms of eosinophil level, and 24 versus 52 weeks, but our feedback through market research is it is seen to be comparable.

The fact is, it's exactly as you say, the main driver is the frequency of administration, but also what we have learned from *Nucala* is once you take these drugs into a real-world setting, we know there's a huge drop-off of biologics once patients get to after about six months of treatment. It's a big drop-off and there's a lot more control of course in a medical benefit physician-administered context, where you potentially lock in six months of compliance for a single shot and you look at two shots a year versus Dupixent, at 26 shots.

I think personally short-term it's comparable, and it will be shot-burden. Secondly, over time, as we deal with real world evidence, as we see how patients operate in the wild, I think we will see the frequency of injection and injection burden translate to efficacy, but we need to do those studies, and we have a big programme that is starting up to do that.

Jo Walton (UBS): I have three quick questions. Can you talk a little bit more about biomarkers, because you mentioned them as being important, but then you go on to say, well, there are other things. How are you going to decide what the appropriate populations are? Are they going to biomarkers, or does everyone have to have some complex genetic profile taken to support the drug that you should try first?

Secondly, to go back to Simon Baker's question about other modalities, beyond ADCs, do you have any interest in radiotherapy because that seems to be the flavour of the day?.

Then finally, in your presentation Tony, you talked of technologies you used that tripled your chances of getting a product to Phase 3. I wonder if you could tell us a little bit more about that and how you've measured that? If you've tripled your chances in getting things to Phase 3 you must have used this on quite a lot of products to get those sorts of statistics out, so please tell us a little bit more about what this is and whether it is just you, or do you think everybody is doing it now, or will be doing it in the next few years?

Tony Wood: Thank Jo, look we couldn't hear you very well, so I am going to make my best my attempt at directing the question. I think the first one was about biomarkers and how one really navigates the journey of first of all identifying and then making them a practical proposition when you reach later stage studies and patient selection. I might actually just begin Hesham, you could describe the journey we have been on in the context of the dMMR positive cancers for *Jemperli* and in both, particularly across the endometrial setting. I think Jo, that sort of illustrates the general path here that one starts in early translational studies with a range of hypotheses

that are tested and then validated in later stage studies with different instruments, which are more amenable ultimately to the market setting.
Hesham, you can make a quick comment on radiotherapy and our focus. Jo, essentially we have an exciting portfolio in front of us with regards to the areas that I described and Hesham has answered questions on and we don't see radiotherapy as an area of interest for us at the moment.

Let me just quickly deal with the comment on the improved survival in early Phase 1 studies from the single-cell data, this is work coming from Sarah Teichmann's lab and it's a broad assessment of the performance of industry portfolios with and without an ability to localise targets into expression in individually very carefully characterised cell types, Mick we can send Jo the reference. That data very clearly identifies an improvement and survival in Phase 1 associated with targets that carry those characteristics. Let's go back first of all Hesham, perhaps you could make a comment on biomarkers in the context of our oncology portfolio and Kaivan, you might just describe the journey for IL-5 and eosinophilia as an example and how that might develop elsewhere as well, so over to you Hesham.

Hesham Abdullah: Thank you Tony. I think probably a really good example is of course of the RUBY study, and specifically looking at dostarlimab when it was combined with chemotherapy in first-line endometrial cancer. I think everyone is well aware of course that early on we were really exploring two different hypotheses. The first is how the combined assessment of dostarlimab plus a platinum-based doublet chemotherapy regimen could have a treatment affect relative to chemotherapy in the dMMR MSI high segment. We saw a tremendous treatment affect there, in terms of the interaction between the biomarker and the combination affect and then of course the outcome in patients, whether it be on progression free survival or overall survival, quite dramatic treatment effects.

We didn't stop there as well too, so we also looked at the combination in the intent to treat patient population, which basically included the remainder of the broader patient segments, about 75% of patients which are the MMRp or MSS patient segment as well too. We also saw a treatment affect for PFS and OS, now while not necessarily as dramatic as that seen in dMMR MSI-high, it was clinically meaningful. So I think Jo, what we really have to do is really look at each tumour type and the patient segments that exist, whether it be based on certainly molecular … characterisation of those patient segments, whether it be based on proteomic characterisation of those patient segments and really ensure that we have different treatment options available and to better characterise the treatment effect of different types of therapeutic modalities.

I believe you were referring to antibody drug conjugates in terms of how we would think about biomarker selection for them. I think it wouldn't be necessarily any different, there may be certain patient segments that require cognitive based approaches based on their biomarker status, there may be patient segments that require monotherapy based approaches, there may be patient segments that require combinations with current or existing standard of care agents; that is the way that we are thinking about and choosing to evaluate and assess biomarkers, in terms of best tailoring treatment options for patients. At the end of the day we are in the era of precision medicine and certainly oncology is leading the way there and hence how we are trying to make sure that we provide options to patients.

Just one point around the ligands, to Tony's point as well too. We don't necessarily have any interest there. I think the bottom line for us as an organisation is we are really focused on making sure that we impact 2.5 billion patients by the end of this decade of course. If you bear that in mind, I think what we're thinking about is treatment options that are scaleable and accessible. That is very important, and so when we think about the therapeutic modalities that we are introducing across the Oncology portfolio, it is a priority for us that treatments are scaleable and accessible.

Some of the challenges that exist with radio-ligands, whether it be manufacturing of the isotopes or the supply chain, whether it be the facilities that are required to potentially manage these isotopes and the radiation, it's a difficult space to navigate. It's important of course to continue to look at different treatment options that utilise different technologies for patients.

Tony Wood: The only other thing I would add to that, Hesham, is of course we have an advantage with the collaboration that we have with Tempus, which helps us understand across a broad range of tumours, the molecular characteristics that feature in the early identification of potential biomarkers.

Let's just finish with a quick comment on eosinophilia and on the T2 and adjacent populations. Kaivan, again an example of how this is worked out in practice.

Kaivan Khavandi: Just one comment if I may on the forward-looking view on how we are approaching this in the pipeline. With *Nucala* of course, using the eosinophils and the surrogate for T2 high inflammation allowed for the correct patient selection and of course represented the first precision medicine approach in respiratory medicine and even actually in COPD metrics and that really did pave the way across the industry for that approach within COPD.

Coming back to that broader point around genetics reducing attrition, I think the key development at GSK is that we are now able to match genetic confidence with what Tony described from Sarah Teichmann's work which is the cell-specific confidence. That's really important because it allow you to prosecute those questions in clinical developments, and if you think about the HSD17B13 programme, we had genetic confidence, but then we were able to match that with a cell phenotype and then an organ phenotype and a clinical phenotype, and so when we look at our correlated LIBERTY study, we're looking at digital pathology evaluated using machine learning, but then able to pair that with spatial transcriptomics, to look in the clinic at what the treatment effect is to the cell, and then looking at other clinical measures such as fibroscan, which is able to predict outcomes and compensated our correlated liberties and MR elastography. So you have that continuum from genetics to cell to patients.

Tony Wood: Jo, just to finish off, of course that continuum as well and increasing, and hopefully, simplification over time as we recognise the reality of treatment decisions that will be made in a more distributed sense in the future.

I think that probably answers your questions, Jo.

Rajan Sharma (Goldman Sachs): I have two questions on the Oncology ADCs. Tony, and I guess, Hesham as well, we begin to get your take on the mechanistic rationale of PARP and topoisomerase combinations and whether that's actually feasible from a safety perspective. I guess ultimately the question is whether there is combination potential with '584 and *Zejula*?

Then the second one was just on B7H3 and how you expect '227 to compare with the other assets that are in development, and I guess the most advanced looks like it's Merck and Daiichi Assets. Do you think there is an efficacy or a tolerability advantage there? Thank you.

Tony Wood: Let me just quickly deal with the PARP comment, and Hesham, you can add any more detail, and I'll leave you for the competitive positioning relative to Merck/Daiichi which is simply placed in the context of combination opportunities and the focus within areas of our Oncology portfolio where we are building a presence.

On the PARP/topo combination, there is clearly a pathway over that when you look at the mechanism of PARP inhibitors and topoisomerase summaries. One might envisage potential synergies but what we are seeing from the PARP class in general is that that type of effect is occurring right at the top of the dose response, and therefore it introduces questions with regards to therapeutic index. It is an active area for us actually in terms of our detailed translational research going on in Hesham and Tony Ng's teams but not something that we are necessarily actively pursuing as a foundational thesis in clinical evaluation at the moment. Hesham over to you.

Hesham Abdullah: Thank you Tony and just to close the loop on that, we certainly look at, for example, what could be a second generation of DNA damage response, especially with our Pol-Q or Pol-Theta inhibitor as well too, better therapeutic index, more well-tolerated and potentially lends itself to being a more combinable agent as well too and especially with an antibody drug conjugant, so something to consider and evaluate, especially as we think about development of these ADCs across certain patient segments, including those patients who could have homologous recombination deficient profiles as well too.

With that in mind, the question really around the B7-H3 ADC and its competitiveness relative to other assets or compounds that are currently also in the clinic, I would first and foremost of course, just draw your attention to the fact that there was data that was previously presented from the Phase 1 study conducted in China that showed broad - I would say - clinical activity across a number of different tumour types. You may have seen of course that certain health authorities have recognised that, so we were granted a breakthrough therapy designation by the FDA, based on the small-cell lung cancer data that was presented at the World Lung Cancer Conference in September 2024. Then just yesterday, we were also granted a prime designation in Europe, again for the same patient population as well.

I think the development programme is progressing well, I think for us, combinations are really going to play a key part in this and of course dostarlimab, which is an asset that has been well benchmarked to the leading PD-1 in the class, gives us confidence in our ability to have combinations with checkpoints across different tumour types. Then also, like I said, with small molecules potentially lending themselves as being key combination partners.

We are also exploring potential external clinical collaborations, we know that the current clinical landscape is beginning to evolve and there may be additional assets that we may want to combine the B7-H3 ADC with, stay tuned on that front. Then of course, the tumour types that we're moving into, you've seen the expression profiles. So these tumour types have certainly key capabilities that strengthen, so they lend themselves quite well in terms of the infrastructure that we've developed there. Then of course some of the biomarker work that we currently have ongoing, which we think will be very unique, but also provide hopefully over time, a level of differentiation as we think about our development strategy going forward.

Tony Wood: At the highest level, the competitive environment is something obviously that I am very attuned to, together with Hesham and Luke and will be a feature of capital allocation to ensure that we are moving forward in a competitive frame. Okay, super I think we are on the last question now.

Richard Parkes (Exane BNP): Thanks very much for taking my questions, just three quick ones hopefully. On B7-H3 and excuse me if I missed this because I dropped the line for a while, you are talking about a first pivotal study in Q4 next year, so is that going to be small-cell lung cancer and can you give us a view on how that clinical design is likely to look and will you have biomarkers integrated into that clinical study? I am just looking for visibility on what that first Phase 3 programme looks like.

Then on cobolimab, which I think is down as 2026, it's not really been talked about so should we just see that as a high-risk asset or are you still very confident about that readout?

Then finally on *Blenrep*, can you just help me understand how the FDA might deal with the likely dosing recommendations for physicians in the prescribing label? I am just wondering how that algorithm or how they will describe how physicians should conduct dosing, if you could help, that would be really helpful, thank you.

Tony Wood: Super, so Hesham these are all coming to you. I guess in terms of small-cell lung cancer, obviously we are not going to disclose the details of our clinical programmes but perhaps Hesham, you can give some broad-line guidance and similarly for COSTAR. What I would say for COSTAR is obviously the second line setting is tough and we very much view this as an opportunity of looking at *Jemperli* in that setting as well. Again Hesham, you might describe a little bit about how that will play out and indeed the features associated with the study and then lastly, a brief comment on the prescription opposition, obviously we are very early on with regards to label conversations, so broad considerations there only, Hesham.

Hesham Abdullah: Thank you Tony and I will start off first with B7-H3 and I will just say we have more than I would probably say one shot on goal to start a pivotal study at the end of 2025. To Tony's point, unfortunately we cannot necessarily disclose which tumour type but what I can tell you is there more than one shot on goal and so there could be one possibly two, so stay tuned for that to happen in 2025.

The second really around cobolimab, I believe probably Richard you are referring to the COSTAR study specifically and this is actually a Phase 2/3 trial that we had initiated a few years ago in second-line non small-cell lung cancer post PD-1, post chemotherapy. So with that in mind, what we do know and this is something that we actually had communicated back in September 2022, that the study actually was gated by certain criteria to move from Phase 2 into Phase 3.

We know that those criteria, when the IDMC, which is an independent body, looked at this data, they basically recommended that both investigational arms in this study actually get expanded and move into Phase 3. The two investigational arms in the study of course are the triplet of cobolimab, dostarlimab, and docetaxel. Then the other of course to Tony's point which is dostarlimab plus docetaxel and of course the control arm is the docetaxel.

We are just awaiting of course now the overall survival data readout, this is an event driven trial, so bear in mind that timelines can shift, they can shift upwards, they can shift backwards, depending on how fast or how slow events are going. We have no knowledge of course of the data and we are waiting the data readout of course from that trial.

I think what is probably important to highlight in second-line non small-cell lung cancer is that we have continued to see certainly a key unmet need emerge in this area and while other ADCs, and specifically TROP-2 targeting ADCs, necessarily haven't demonstrated the success that everyone had hoped for but continue to be an opportunity for novel agents to be introduced into this space.

Then finally of course, if we think about *Blenrep*, and labelling of course, we cannot necessarily comment on the ongoing regulatory submissions which have been made and accepted in the US, Europe, China, Japan, and other key markets and regions, but what we can say is, at the end of the day, the dosing and the labelling will be driven by how the drug was administered and of course the data that's emerged from both the DREAMM-7 and the DREAMM-8 results.

I think probably as you look at other drugs that have been used in oncology effectively, no doubt the dosing decisions being driven by the toxicities that patients experience and how prescribers are able to manage those toxicities on a per patient, individual patient basis, is really important. We've seen that with other labels, I think certainly looking at for example the label with palbociclib as an example here. The ability to be able to again, titrate the dosing, introduce the dose interruption as the reductions and each patient should be managed individually based on the set of toxicities they experience and how they respond to treatment as well.

Tony Wood: Against ultimately of course, the simple framework that it is easy to deliver and in the clinical setting and as Luke mentioned earlier, that's clearly part of the work that we are doing but it's a bit premature to get into those conversations I would say. Okay, I believe we have one more question and since it's Christmas we should entertain it, the final one.

Eric Le Berrigaud (Stifel): Thank you very much for that Christmas gift! One last question on the financial aspects, you were talking a lot about prioritising oncology and respiratory, how should we think about this in the context of the R&D budget going forward?

Does that mean that you will prioritise those two over others that will be de-prioritised or should we think about the R&D budget going up with those two taking a lion's share? Should we think about any step change in R&D investment going forward to support those two areas? Thank you.

Tony Wood: I am not going to get drawn on individual capital allocation to specific areas, there are sort of two comments I would make in principles rather. That is, we will continue to fund the portfolio in line with the expected growth of the areas in question, so this is very much a competitive process across the portfolio.

As I mentioned in the past, it's done at the highest level, by the committee that Luke and I chair together. Long term in terms of our R&D budget, right now, I am very well positioned I would say in terms of supporting the opportunities that we've described and of course, we've also mentioned throughout the year that as the overall company aspirations continue to grow that there will be an allocation into R&D budgets. For me, the same principles that we've described, continue to apply here and what I would say though is I am really delighted with the shift and the broad potential value in the later stage R&D portfolio as I mentioned at the beginning, we are now starting to see our focus really shift into areas of greater medical need and opportunity.

With that we can finish the call. It just remains for me to thank you all for joining us for what I know is a busy day. I wish you all a restful period over the holidays and I look forward to seeing you in San Francisco if you are there, and at our subsequent interactions, thanks everyone.

[*Ends*]