Kyowa Kirin Co., Ltd.

Agreement for Global Strategic Collaboration with Kura Oncology to Develop and Commercialize Ziftomenib

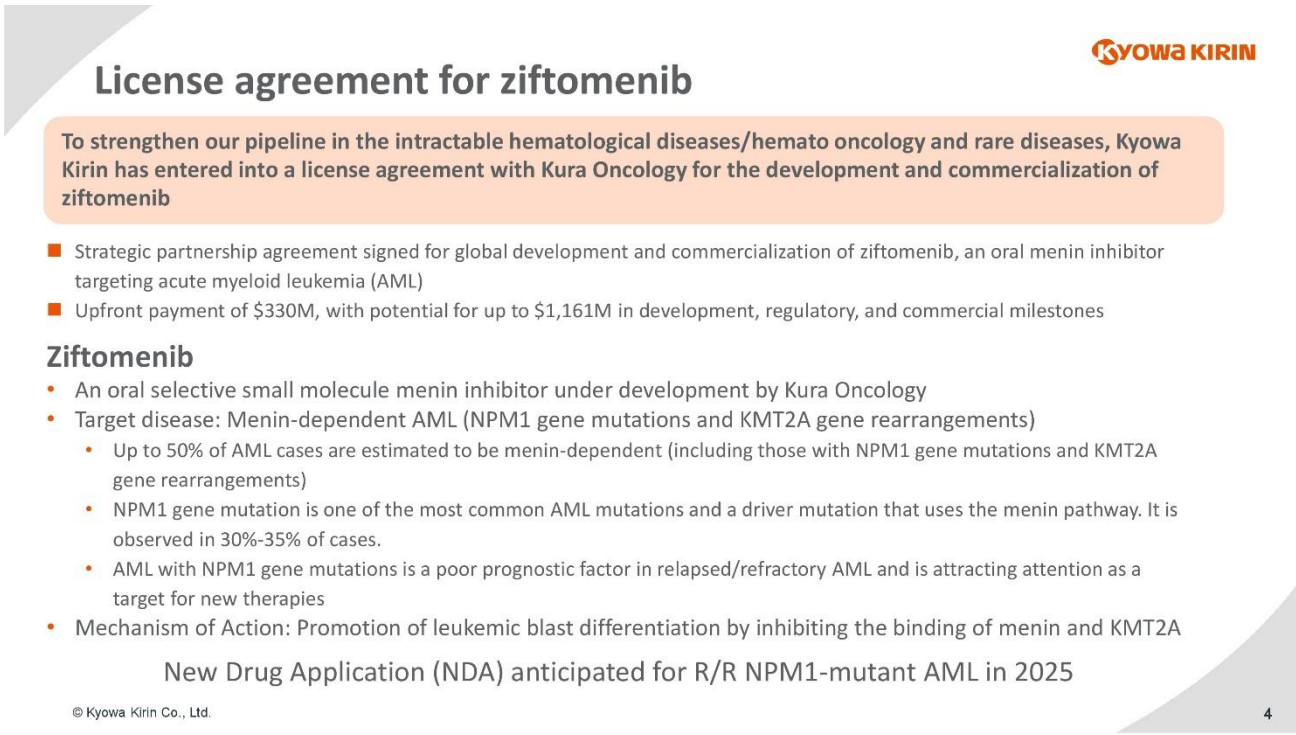
November 21, 2024

Event Summary

[Event Name]	Agreement for Global Strategic Collaboration with Kura Oncology to Develop and Commercialize Ziftomenib	
[Date]	November 21, 2024	
[Number of Speakers]	5	
	Takeyoshi Yamashita	Director, Senior Managing Executive Officer and Chief Medical Officer
	Motohiko Kawaguchi	Managing Executive Officer and Chief Financial Officer
	Yasuo Fujii	Managing Executive Officer and Chief Strategy Officer
	Abdul Mullick	Managing Executive Officer and Chief International Business Officer
	Hiroki Nakamura	Global Corporate Communications Head

Presentation

Nakamura: Thank you for your patience. We are now hosting an online presentation on our strategic collaboration with Kura Oncology to develop and commercialize ziftomenib.



Fujii: Good morning. My name is Fujii. Today, the Company and Kura Oncology of the US entered into a strategic collaboration agreement for global strategic collaboration to develop and commercialize ziftomenib, which Kura is developing.

Upon execution of the agreement, we will make an up-front payment of approximately USD330 million, as well as up to approximately USD1.2 billion in development, approval, and marketing milestone payments. Kura Oncology is a biopharmaceutical company in the US with several products in development, aiming to realize the potential of personalized medicine in the field of oncology.

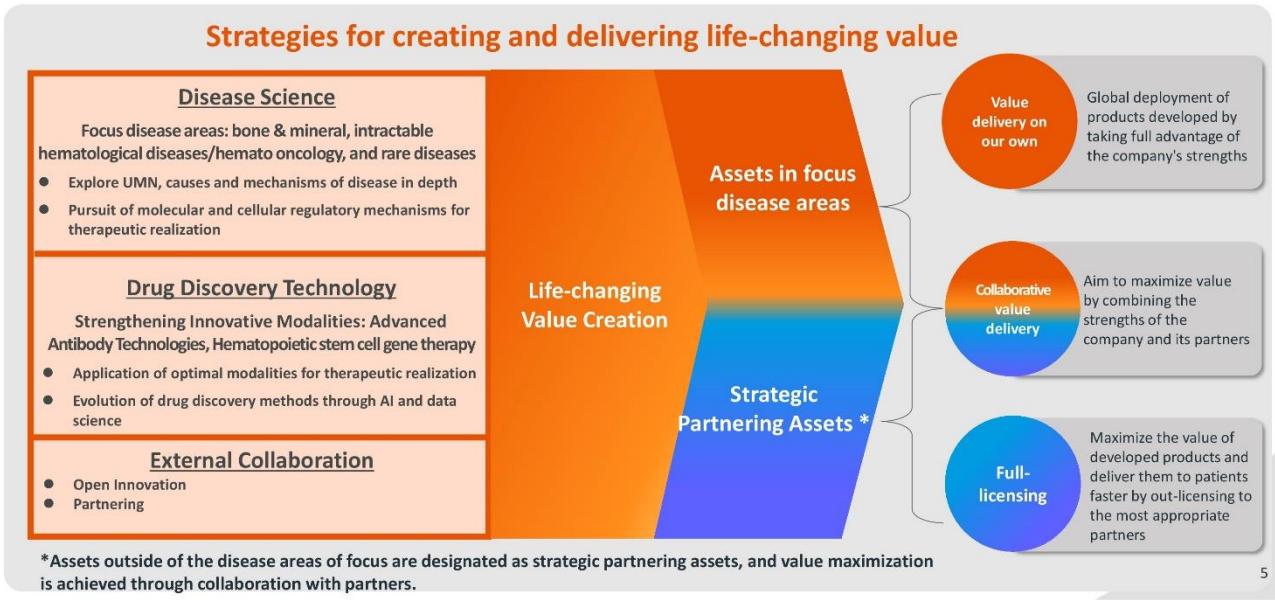
Kura's pipeline consists of small molecule developments that target cancer signaling pathways. Ziftomenib is an oral menin inhibitor being developed for acute myeloid leukemia, or AML. Up to 50% of AML cases are estimated to be menin-dependent, which is the target for the development.

In addition, the genetic abnormalities targeted in ongoing clinical trials, such as NPM1 gene mutations and KMT2A gene rearrangements, are thought to be responsible for the development of AML in many cases. The NPM1 gene mutation is one of the most common AML mutations and is a driver via the menin pathway.

AML with this gene mutation is considered a poor prognostic factor in relapsed/refractory cases. Therefore, there is a focus on developing novel therapeutic agents targeting this mutation. The mechanism of action is the promotion of leukemic blast differentiation by inhibiting the binding of menin and KMT2A.

We plan to apply for approval of this drug for R/R NPM1-mutant AML in 2025.

Story for Vision 2030



We launched a strategic initiative, "Story for Vision 2030," to realize our vision. Expanding the pipeline for late-stage development is a key management challenge, as we expect a certain level of global sales in the target disease areas while delivering life-changing value. This is the focus of our ongoing efforts.

Ziftomenib is in late-stage development for hematologic oncology, including intractable hematologic diseases and rare diseases we focus on. Notably, it is the first and only drug candidate to receive FDA Breakthrough Therapy Designation for treating NPM1-mutant relapsed/refractory acute myeloid leukemia (AML), a disease associated with poor prognosis.

Through value co-creation with our partners, we aim to expand our pipeline in our focused disease areas and accelerate progress toward realizing our vision.

Ziftomenib - Collaboration with Kura -

	US	ex- US
Development	• Kura leads development • Share global development cost • Kura funds development costs (~2028)	• Kyowa Kirin leads development
Commercialization	• Kura books sales • 50/50 profit share	• Kyowa Kirin commercializes and books sales
Sales Royalties		• Double-digit royalty to Kura
Commercial supply	• Kura supplies	• Kura supplies

Kyowa Kirin makes a $330 million up-front payment and future contingent milestone payments potentially worth up to $1,161 million in total, including $420 million in near-term milestone payments and $228M opt-in right for solid tumors, as well as royalty payments on future global sales to Kura.

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Here are the areas of responsibility and financial conditions for Kura and our company.

Kura will lead the development in the US. Kura will bear the cost of global development until 2028, but after 2029, the cost will be split equally between the two companies.

We will lead the development outside the US. Kura will book sales in the US, and we will receive half of the profits through a profit-sharing arrangement.

Sales outside the US are recorded in our account, and we will pay double-digit royalties to Kura. Kura will be in charge of supply. Future contingent milestone payments potentially worth up to USD1.2 billion in total, including USD228 million opt-in right for solid tumors, and up to USD420 million will be paid in near-term.

OVERVIEW

- There are an estimated 20,800 new cases of AML in the United States in 2024[1]
- AML continues to carry a poor prognosis, where there remains a significant unmet need for additional treatments with durable efficacy and greater tolerability[13,14]
- AML is characterized by significant genetic heterogeneity due to the possible presence of multiple driver mutations, such as *NPM1*m and *KMT2A*r[8,9]
- Up to 50% of AML cases may be menin dependent, including those driven by *NPM1*m and *KMT2A*r[2-7]
- *NPM1*-m is one of the most common AML mutations, found in 30% to 35% of cases, and is an important upstream driver mutation that uses the menin pathway[7,10]
- *NPM1*-m AML is associated with poor outcomes in R/R AML[11,12] making it a potential target for novel therapies

AML, acute myeloid leukemia; *KMT2A*r, lysine methyltransfemse 2A rearrangement; *NPM1*-m, mutated nucleophosmin 1; *NPM1*m, nucleophosmin 1 mutation.

1. American Cancer Society. Updated January 17, 2024. Accessed October 16, 2024. https://www.cancer.org/cancer/types/acute-myeloid-leukemia/about/key-statistics.html **2.** Issa GC et al. *Leukemia*. 2021;35(9):2482-2495. doi:10.1038/s41375-021-01309-y **3.** Candoni A, Coppola G. *Hematol Rep*. 2024;16(2):244-254. doi:10.3390/hematolrep16020024 **4.** Bertrums EJM et al. *Haematologica*. 2023;108(8):2044-2058. doi:10.3324/haematol.2022.281653 **5.** National Cancer Institute. Accessed October 16, 2024. https://seer.cancer.gov/seertools/hemelymph/5186cf39e3e27e3994bd547d/ **6.** National Cancer Institute. Accessed October 16, 2024. https://seer.cancer.gov/seertools/hemelymph/5a7e288d1ef557f9c8636d31/ **7.** Burnews F et al. Poster presented at: AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics: Discovery, Biology, and Clinical Applications; October 26-30, 2017; Philadelphia, PA. **8.** Papaemmanuil E et al. *N Engl J Med*. 2016;374(23):2209-2221. doi:10.1056/NEJMoa1516192 **9.** The Cancer Genome Atlas Research Network. *N Engl J Med*. 2013;368(22):2059-2074. doi:10.1056/NEJMoa1301689 **10.** Falini B, Dillon R. *Blood Cancer Discov*. 2024;5(1):8-20. doi:10.1158/2643-3230.BCD-23-0144 **11.** Issa GC et al. *Blood Adv*. 2023;7(6):933-942. doi:10.1182/bloodadvances.2022008316 **12.** Ostronoff F et al. *J Clin Oncol*. 2015;33(10):1157-1164. doi:10.1200/JCO.2014.58.0571 **13.** Kumar CC. *Genes Cancer*. 2011;2(2):95-107. doi:10.1177/1947601911408076 **14.** Bhansali RS et al. *J Hematol Oncol*. 2023;16(1):29. doi:10.1186/s13045-023-01424-6

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This is an overview of the target disease, AML.

There are an estimated 20,800 new cases of AML in the US in 2024, where a large unmet medical need remains. Up to 50% of AML cases may depend on a protein called menin, including those driven by NPM1 mutations and KMT2A rearrangements. These mutations are the targets of ziftomenib.

This NPM1 mutation is one of the most common in AML, found in 30 to 35% of all cases. It is associated with a poor prognosis and was a known target for AML treatment.

*NPM1*m: ONE OF THE MOST COMMON AML MUTATIONS AND AN IMPORTANT DRIVER MUTATION IN THE MENIN COMPLEX

***NPM1*m is present in up to 35% of AML cases**, making it one of the most common genetic alterations in AML[1]
- Approximately two-thirds of patients with *NPM1*m carry a co-mutation[2]

- **NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)** recommend expedited testing for *NPM1*m at diagnosis to inform prognosis and guide treatment decisions[3]
- Most patients (~97%) **retain** *NPM1*m after first-line therapy[4,5]
  - Suggests that detection of *NPM1*m, as early as at diagnosis, can be referred back to when making treatment decisions during initial therapy and beyond

AML, acute myeloid leukemia; NCCN, National Comprehensive Cancer Network® (NCCN®); *NPM1*m, nucleophosmin 1 mutation.

1. Falini B, Dillon R. *Blood Cancer Discov*. 2024;5(1):8-20. doi:10.1158/2643-3230.BCD-23-0144 **2.** Sharma N, Lieseveld JL. *Cancers (Basel)*. 2023;15(4):1177. doi:10.3390/cancers15041177 **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.3.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed August 27, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for their application or use in any way. **4.** Issa GC et al. *Blood Adv*. 2023;7(6):933-942. doi:10.1182/bloodadvances.2022008316 **5.** Falini B et al. *Blood*. 2011;117(4):1109-1120. doi:10.1182/blood-2010-08-299990

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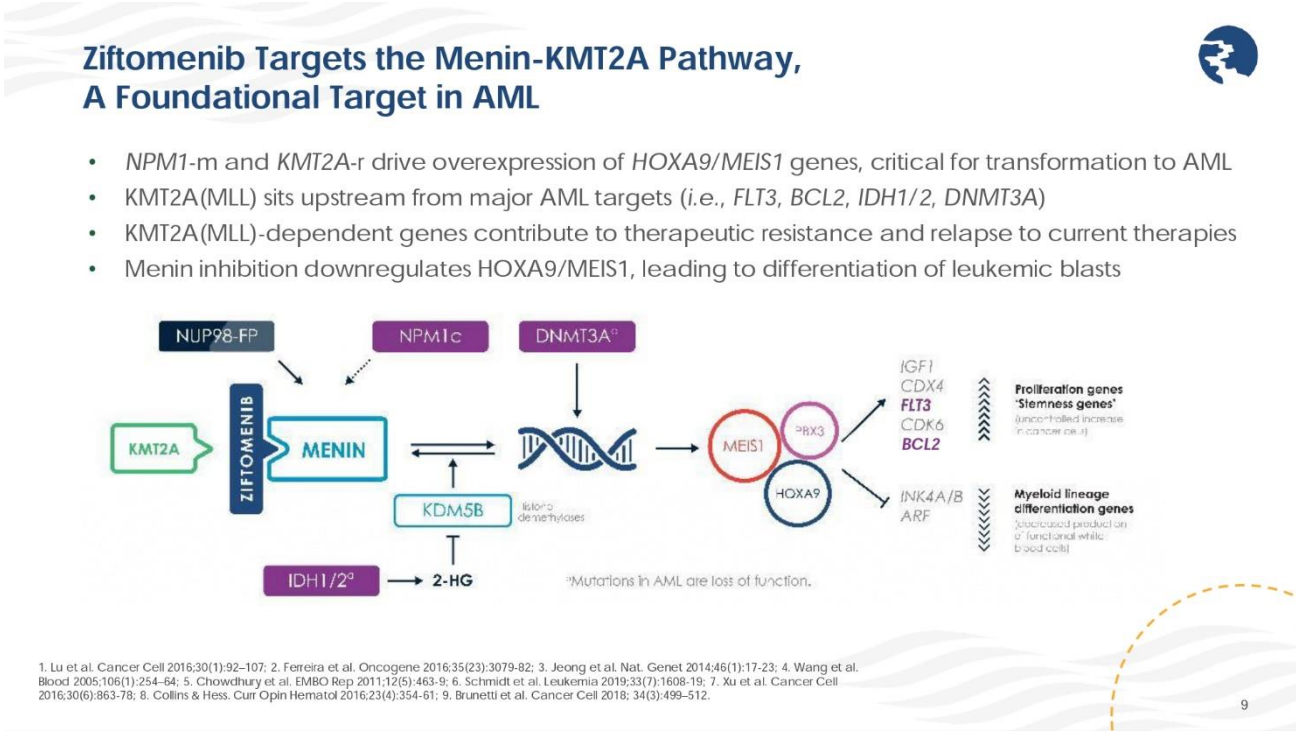
Let me explain a little about the NPM1 mutation.

Guidelines proposed by the NCCN, a nonprofit organization in the US, recommend expedited testing for NPM1-m at diagnosis to inform prognosis and guide treatment decisions.

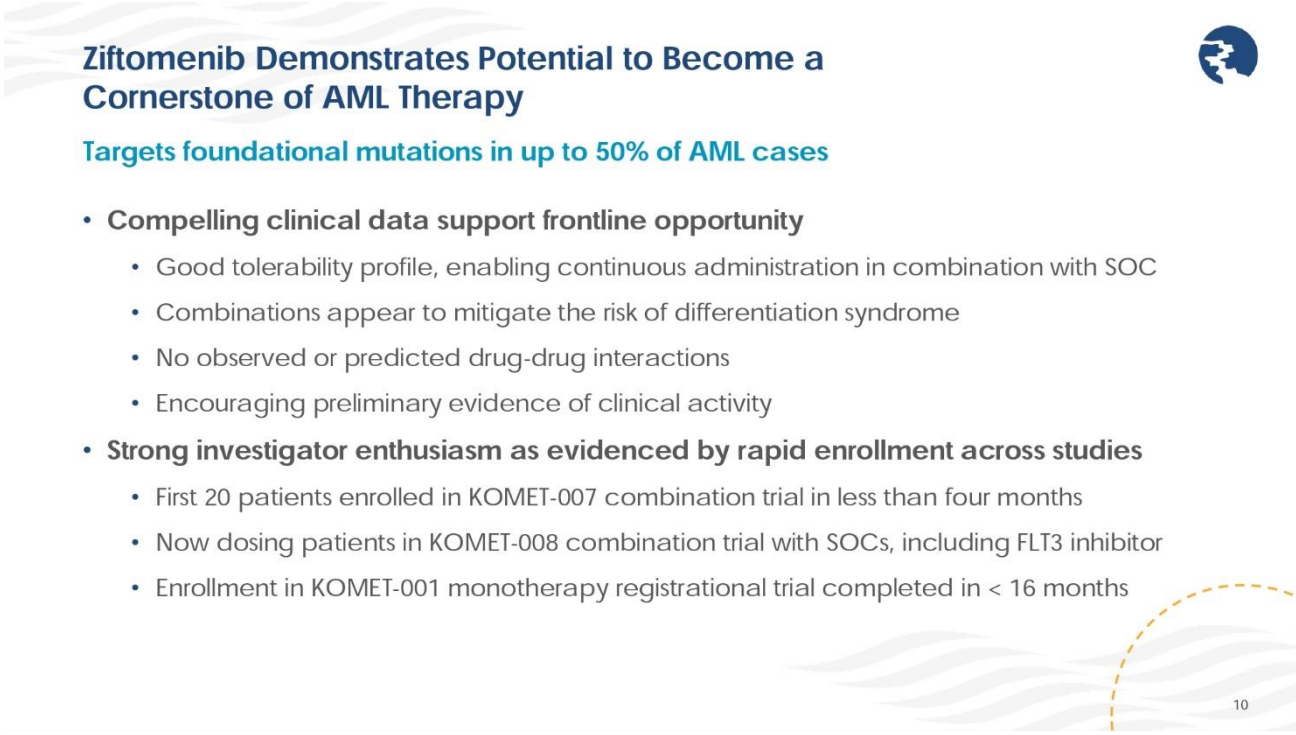
In addition, approximately 97% of patients retain the NPM1 mutation after first-line treatment. This suggests that early detection of NPM1 mutations is necessary to make initial and subsequent treatment decisions.



Here is a slide on the mechanism of action of the drug.

NPM1-m and KMT2A-r drive the overexpression of genes in normal blood cells, leading to the development of AML. This protein, KMT2A, sits upstream from primary AML targets.

Genes affected by this molecule contribute to therapeutic resistance and AML relapse. Inhibiting menin and its binding to the molecule induces the differentiation of leukemic blasts, resulting in a therapeutic effect on AML.



Lastly, this is a summary of the ziftomenib's potential.

It has a good tolerability profile, enabling continuous administration in combination with standard of care (SOC). In addition, combinations appear to mitigate the risk of differentiation syndrome and drug-to-drug interaction. We believe that this will enable us to expect clinical efficacy.

The speed of case enrollment in clinical trials is also favorable, with a targeted 20 patients enrolled in KOMET-007 combination trial in less than four months. Patient dosing has begun in the KOMET-008 combination trial with SOCs. Enrollment in KOMET-001 monotherapy registrational trial was completed in less than 16 months.

As mentioned above, we believe ziftomenib is a highly promising compound. It aligns well with our pipeline for hematological oncology and intractable hematological diseases, which are key areas of our focus.

That's all from me.

Question & Answer

Nakamura [M]: Now, I would like to move on to the question-and-answer session.

If you have any questions, please click the “raise your hand” button at the bottom center of the screen and wait. We will call on you in order. When prompted to unmute yourself on the screen, please do so and ask your question after stating your company name and your name. If you wish to cancel your question in the middle of a question, please click on the "hands down" button.

Yamaguchi [Q]: Thank you. I am Yamaguchi from Citi. The first question is about financial impact. Rather than a total of USD1.2 billion, I believe initial or second milestones will be paid to start with. Could you explain the impact of this on your P/L?

Kawaguchi [A]: Thank you for your question, Mr. Yamaguchi. Kawaguchi will answer.

P/L impact. As for this year 2024, there will be little impact. However, the USD330 million up-front payment will be paid in December, so that a negative amount will be recorded in cash, but there will be little impact on P/L.

Then, beyond 2025. First, if the monotherapy for relapsed/refractory AML is launched in 2025 in the US, the share of gross profit from this will be recorded as revenue. The amount there will not be that big yet.

On the other hand, the market preparation cost will start in 2025. So, we will share 50:50 of the preparation cost in the US. Additionally, the up-front and milestone payments to be made in the future will be recorded as intangible assets. However, amortization will begin once the application is approved. So, the part of this amortization will also occur after the application is approved.

Another point is the development cost. As for development costs, we will not incur any global development expenses until 2028, as Kura will bear all costs under the agreed scheme. On the other hand, a few, for example, exam fees to bridge that will be incurred other than this global exam. In Japan, for example, we will have some development costs, such as bridge costs to apply to the authorities.

This is how it works. In terms of the amount scale, it will not be like JPY10 billion. The negative impact will remain at a scale of a single-digit billion yen, and is expected to continue for several years

Yamaguchi [Q]: Thank you. My second question is about the competitive environment. This area, the menin inhibitor landscape. Your company has taken breakthrough therapy designation and is ahead of the pack. Syndax is also applying for revmenib, maybe H1 of next year, I think. There seem to be drugs that come out at the same timing.

I think one topic of discussion is the characteristics of these drugs, especially QT prolongation and differentiation syndrome. I think you bought it because you are confident, including its differentiation points and timing. What is your view?

Fujii [A]: Thank you for your question. My name is Fujii.

As Mr. Yamaguchi just mentioned, we believe this drug offers superior safety, including tolerability, compared to those from other companies.

We intend to expand the first-line indications for this drug in the future. We currently believe that this will be a primary differentiation point compared to other companies.

Yamaguchi [Q]: Regarding timing, will you beat Syndax? Or is it difficult to say?

Yamashita [A]: This is Yamashita. We are not clear about the timing. Recently, Syndax announced that their application for monotherapy of KMT2A rearrangement was approved, and they are working on this NPM1.

I think they will be in the application process in the next year. So, I don't know the exact details, but as I mentioned earlier, we have received breakthrough therapy designation, so I think the process will proceed promptly after the application is submitted. I am not sure about the competitor in this regard.

Yamaguchi [M]: Yes, that's right. I understand. Thank you very much. That is all.

Wakao [Q]: My name is Wakao from JP Morgan. Thank you very much.

I also would like to know about the competitors' situation. Now, regarding Syndax, you explained to me that the incidence of QT prolongation or differentiation syndrome would be lower than that of Syndax.

What I would like to ask is how it compares to Sumitomo Pharma's enzomenib. I think enzomenib has similar characteristics in terms of low incidence of QT prolongation and differentiation syndrome. I have an impression that their product has a better safety profile than the one you are partnering with. Please let me know your view against enzomenib.

Also, the Syndax product includes a boxed warning for differentiation syndrome. Is it correct to assume that your partner's product will not come with a boxed warning? Please tell us about this area. This is the first one.

Yamashita [A]: Yamashita will answer. First, we do not know Sumitomo Pharma's product profile, which is under development. So, it is difficult for us to make a clear comparison.

Regarding differentiation syndrome, it tends to occur more prominently in monotherapy. However, in first-line combination therapy, blast cells, the source of differentiation, are eliminated during pre-treatment and the combination phase. Regarding differentiation syndrome, I believe the issues associated with it will be significantly reduced in combination therapy.

Then, for the box warning. As far as I can see, Syndax seems to have grade five in differentiation syndrome. I think this is the main reason they got the box warning.

Under Kura's development, severe differentiation syndrome has not been observed. I believe this sets us apart from them.

Wakao [Q]: Thank you very much. I understand very well. Second. I would like to know how you position this alliance and plan to strengthen the pipeline further.

When you acquired Orchard [Therapeutics], I understand that you took it as a long-term contribution to your company's performance. In contrast, you said that you were considering purchasing or making a partnership that can contribute to your profit in a shorter term, like in a few years. Can we assume that this partnership is in line with what you have said in the past, and that it is in your plan? Could you share if you are considering any additional partnerships or acquisitions? That is all.

Fujii [A]: Thank you for your question. My name is Fujii.

We have been aware that late-stage development is a management challenge for us, which others have also pointed out. I believe this will help address that issue.

We are also planning to file a second-line application next year. So, if we can get approval and proceed to market launch, it will give us a short-term positive impact. In the long run, we also have a first line* of indications to expand. I expect that this compound will lead our future business in the long run.

Moving forward, we remain dedicated to the strategic investments we have made and the direction we have committed to pursuing. We continue to actively explore opportunities for strategic partnerships to strengthen our portfolio, focusing on late-stage development products.

*Revised by Kyowa Kirin in the transcript

Wakao [Q]: Okay. So, I understand that this strategic partnership is not the last one. Is it correct to understand that you will continue to actively seek opportunities if there are good ones?

Fujii [A]: Yes, that's right. We are not waiting for opportunities to come to us. Instead, we are proactively seeking them. If we find promising ones, we are keen to actively communicate.

Wakao [M]: Thank you very much. I understand very well. That is all.

Muraoka [Q]: Thank you very much. Morgan Stanley, Muraoka.

I would have a similar question. You mentioned that a prolonged negative impact in the range of a few billion yen will be seen in the next fiscal year and beyond. Could you provide more details about this?

I think you did not exclude intangible amortization in your core OP. Amortization of intangible assets will probably be more than JPY10 billion per year. I didn't understand how the calculation was run by adding launch costs. Can you break down the logic that led to those billions a bit more?

Kawaguchi [A]: Thank you for your question. I guess your question suggests the scale of intangible assets amortization we mentioned earlier differs slightly from what you are calculating.

As for intangible assets, this up-front payment of USD330 million and a maximum of USD420 million will be recorded as intangible assets.

However, there are payments for the US and ex-US. We categorize payments excluding the US. The relapsed/refractory monotherapy in the US will begin to undergo amortization. If this is approved, the amortization for the portion of the payment to the US will begin.

Moreover, the amortization period is more than 10 years. So, the calculation will not result in JPY10 billion being amortized annually.

Muraoka [Q]: Okay. Thank you very much. So, are you saying that the billions of yen deficit is mainly due to the annual depreciation, which is below JPY10 billion? And that this business will start with a small but positive profit after the 50:50 profit share arrangement and then gradually expand? Is that the scenario you are envisioning?

Kawaguchi [A]: In the first part, it is possible that the portion of the sales cost is slightly higher than the share of gross profit earned through profit sharing. So, the timing will depend on the sales situation of the second line.

For our part, we are most excited about the first line. If this product is launched and contributes to earnings, it will be in the pipeline to fill the patent cliff of Crysvita, especially after 2030.

Of course, KHK4083 and rocatinlimab are one of the main pillars of our business. Adding one to these pillars, we hope you will understand that our greatest expectation is that ziftomenib will make a significant contribution to profits, especially in 2030 and beyond.

Muraoka [Q]: Thank you very much. I have a question in that area. It's kind of asking about the potential of peak sales figures, but what do you see for the second-line alone? A few hundred million dollars will be the ceiling, but if you look at the first-line treatment, Kura has also mentioned that it could generate multibillion-dollar revenue, as I recall from their materials. I've been looking at Syndax's materials, and they also descrithat it will generate sales of a maximum of USD4 billion.

For second-line treatment, reaching USD500 million is considered great, but you are aware that moving into first-line treatment could make it into a multibillion-dollar business. That is why I see it as a near-term milestone for an up-front payment of this scale, though I am not sure if my view is off the point.

Kawaguchi [A]: I do not think providing peak sales figures at this stage is appropriate, so I will refrain from doing so. However, as I see it, the significance of our investment lies in the substantial first-line potential, as you understand.

Muraoka [M]: Okay. Thank you very much. That is all.

Sakai [Q]: My name is Sakai from UBS. My question is about the first-line you just discussed. In Kura's press release, there is an expression saying that Phase III will be starting in the front-line setting in 2025. It says, "fit and unfit front-line AML."

So, as Mr. Kawaguchi just said, the first line is important, but is it correct to say that it is about to start?

Yamashita [A]: Thank you for your question. Regarding the first line, as you just pointed out, Kura announced it will start in 2025. This will be up to negotiation with authorities, but we will proceed in such a manner that we can get approval as quickly as possible.

Sakai [Q]: I see the figure of USD3 billion in the front-line setting. This is what Kura is saying, but your company decided on the financial terms of this partnership based on that. I don't know to what extent this USD3 billion is accurate, but is that your understanding?

Fujii [A]: This is Fujii. Yes, we have an estimate that is close to what Kura mentioned. If we let [inaudible] on the first line, it is a USD3-billion market opportunity annually in the US alone. So, we believe that there is a market opportunity.

Sakai [Q]: Okay. Thank you very much. Second question. This time, you will apply with mono. You mentioned plans to apply for approval in 2025, but when I checked ClinicalTrials.gov, it appears that most clinical trial sites are based in the US, with very few, if any, conducted outside the US, which is an area your company is responsible for covering.

How will your company promote development outside the US in the future? I don't know if there is a way to bridge this type of disease. Can you tell us a little bit about your development strategy in this area?

Yamashita [A]: This is Yamashita. The 2025 approval is just another indication of the US timeline after receiving breakthrough therapy designation from the FDA. We are very keenly examining the situation right now outside of the US. We will announce when we are ready.

Sakai [Q]: So, until the front line is released, how do you say it, sales or profit contribution will be very limited? Certainly, I understand the number of patients for the target diseases. In terms of market penetration, you expect it will achieve 2030 and beyond, after Crysvita's patent expires. Should I have a vision that it will take until then?

Kawaguchi [A]: I am Kawaguchi. We think that it will start to have a significant impact on our profit around 2030. This is an image we envision.

Sakai [Q]: In terms of profit contribution, are you saying that profit will start to emerge after covering the amortization you mentioned earlier?

Kawaguchi [A]: Yes, that's right. Also, development costs will be split 50:50 from 2029. So, if we look at the total impact, including such costs, we can expect a large contribution to profits in 2030.

Sakai [Q]: So, you have an assumption that the first line will be out by then, of course.

Kawaguchi [A]: We have an expectation that it will be out by then.

Sakai [M]: No, I mean, I was a little concerned that it might not be profitable if it didn't show up. I understand. Thank you very much.

Wakao [Q]: I'm sorry, this is the second time. I would like you to summarize the development timeline one more time.

In Kura's material, which was not in yours, the top-line data of monotherapy, KOMET-001, will be available at the beginning of next year. I understand that you are going to apply for it.

Then, there are combinations in related areas. You mentioned the first-line will be out after 2025, but can you explain again about the development timeline, including monotherapy, combination, early timeline and such? I am a bit confused and do not understand it correctly.

Yamashita [A]: This time, what we are referring to as the second line is the one for which, as mentioned earlier, the top-line data will be released, and we aim to submit the application for approval next year. This is monotherapy for the NPM1 mutation.

The other thing we are saying is that what is important is the first line of so-called combination therapy, where we are currently under Phase I. That is where the data will come from in the 007 trial.

With that, we will go for the test to get first-line approval in 2025, as mentioned earlier. Kura says it will be mid-2025, including patients with NPM1 mutation and those with KMT2A rearrangement mutation to start first-line trials.

Wakao [Q]: Okay. Then, it would mean that the KOMET-007 data will be available at some point next year, right? If you are starting a first-line trial in mid-2025, would it come out in H1 of next year?

Yamashita [A]: Yes. I think Kura commented on this area.

Wakao [Q]: So, you can't give a specific timing at this point?

Yamashita [A]: Yes, Kura has disclosed the present preliminary data from Phase 1b, KOMET-007, and 2025.

Wakao [Q]: Okay. Thank you very much. It's a similar question to the one I asked earlier, but I understand from your explanation that the first line is important and will contribute to business performance immediately after 2030.

We saw, and I think you recognized, that your company's performance over the next few years would be on a plateau, with no new drugs coming on the market. You also mentioned that you were looking at acquisitions that would contribute to business performance in the short term. Is it correct to understand that you are considering it as well?

Fujii [A]: As I answered earlier, we have presented our "Story for Vision 2030," and we have identified our areas of focus. I believe that enhancing the late-stage pipeline remains a challenge for our management. So, we would like to actively search for opportunities, and if there is a good fit, we would be happy to promote it.

Wakao [Q]: Okay. So, it seems that the importance of factors contributing to short-term performance is still high, but you just do not have a project that fits the bill right now. Therefore, it is still highly important. We can recognize that reinforcement is highly important, right?

Fujii [A]: Yes, of course it is.

Wakao [M]: Okay. Thank you very much. That is all.

Nakamura [M]: Thank you very much. We will now conclude our online presentation on the agreement for global strategic collaboration with Kura Oncology to develop and commercialize ziftomenib.

So, thank you very much for your participation today.

Thank you for your continued support of Kyowa Kirin.

[END]