Astellas Pharma Inc.

R&D Meeting (Targeted Protein Degradation)

December 9, 2022

Event Summary

[Company Name]	Astellas Pharma Inc.	
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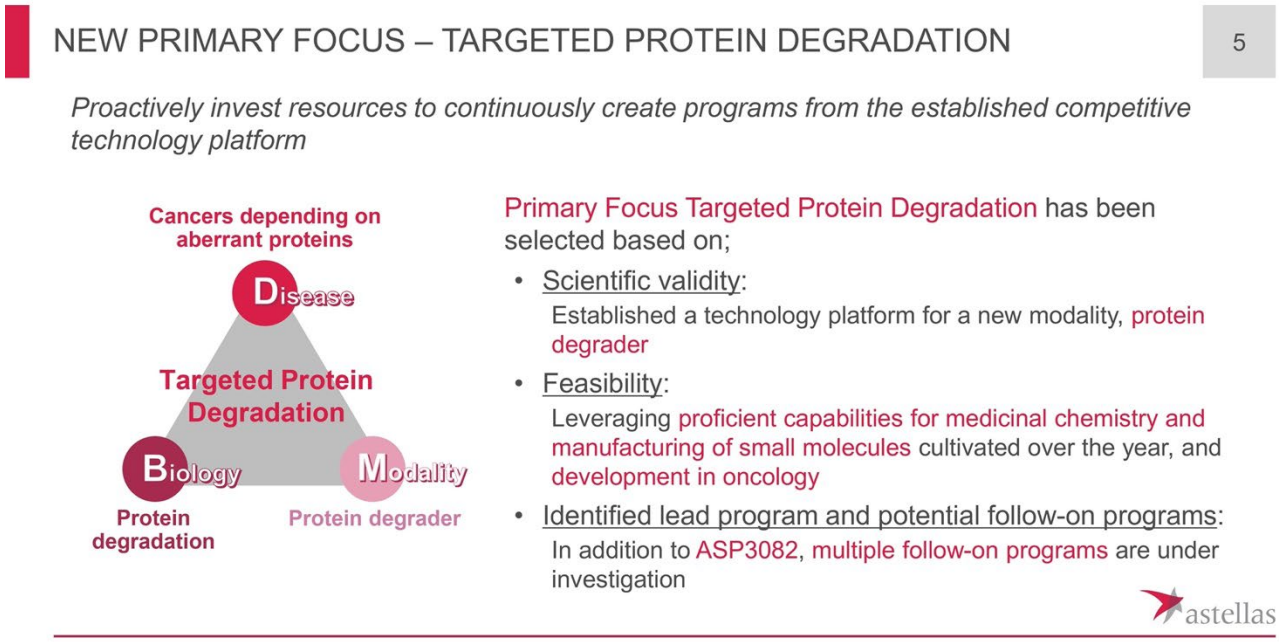
[Event Type]	Conference	
[Event Name]	R&D Meeting	
[Date]	December 9, 2022	
[Time]	10:00 – 11:14 (Total: 74 minutes, Presentation: 30 minutes, Q&A: 44 minutes)	
[Venue]	Webcast	
[Number of Speakers]	5	
	Kenji Yasukawa	Representative Director, President and CEO
	Yoshitsugu Shitaka	Senior Managing Executive Officer, Chief Scientific Officer
	Masahiko Hayakawa	Vice President, Head of Targeted Protein Degradation
	Peter Sandor	Primary Focus Lead, Immuno-oncology
	Hiromitsu Ikeda	Head of Corporate Advocacy & Relations
[Participant Names]	Hidemaru Yamaguchi	Citigroup Global Markets
	Fumiyoshi Sakai	Credit Suisse Securities
	Seiji Wakao	JPMorgan Securities
	Madoka Sato	Schroder Investment Management
	Shinichiro Muraoka	Morgan Stanley MUFG Securities
	Shinya Tsuzuki	Mizuho Securities
	Nobuaki Sawada	JPMorgan Asset Management
	Miki Sogi	Sanford C. Bernstein Japan

Presentation

Yasukawa: Good morning, everyone. I'm Yasukawa. It's December and I'm quite sure that you are very busy, but thank you very much for your allocation of your time for our R&D meeting. Page two is a cautionary statement. As usual, I would like to skip reading it.

Page three, this is our agenda for today.

There are three parts. I am going to make a very simple introduction, and then Dr. Hayakawa, the Head of Targeted Protein Degradation is going to explain the topic for today. Closing is done by Dr. Shitaka, Chief Scientific Officer.



Now page five.

I will explain the targeted protein degradation. A new Primary Focus was selected as a Primary Focus along with its characteristics. As shown in the figure on the left, this Primary Focus focuses on the biology and utilizes protein degrader as novel modality to target cancer caused by abnormal proteins. In selecting the Primary Focus, as you see on the right, the prescribed criteria have to be met.

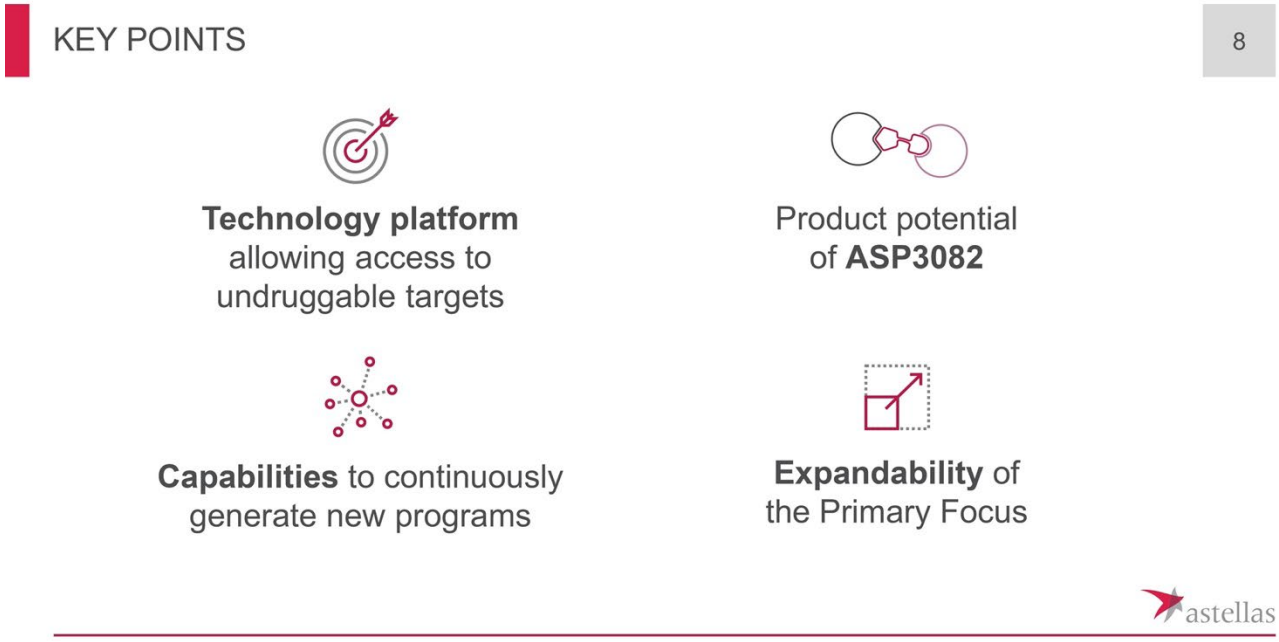
The first is scientific validity. We have established a technology platform for new modality, protein degrader, from which we can continue to generate promising assets. We believe that this is quite rational that we have selected this as a primary target or primary focus because we have such a ground.

The second is the feasibility. By leveraging proficient capabilities for medicinal chemistry and manufacturing of small molecule cultivated over the years, as well as our development in oncology, we are able to move forward quickly and efficiently with the individual programs.

Regarding the third point, the program, the lead program ASP3082 entered the clinical trial phase this year and multiple follow-on programs are under investigation in the research phase. These points were discussed at meetings such as Executive Committee and the Board of Directors and the decision was made to make this Primary Focus. We will continue to create programs from this platform on an ongoing basis and proactively invest resources to further accelerate development.

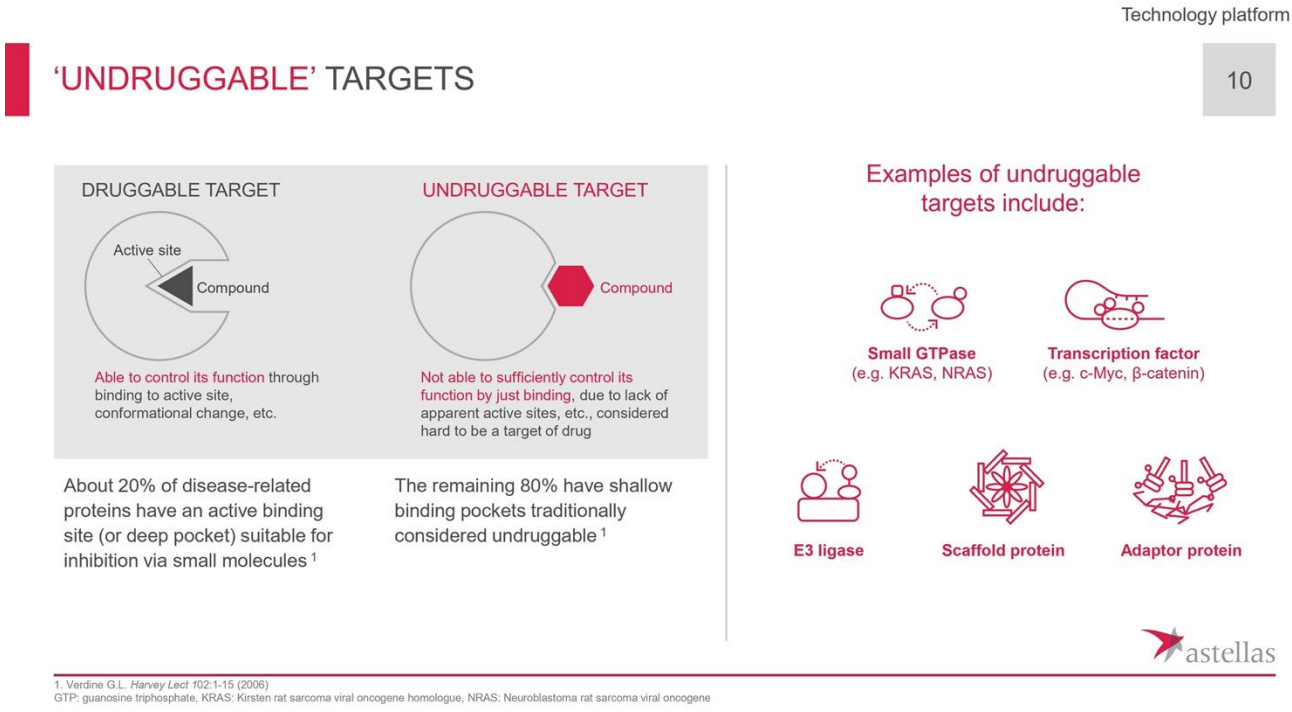
From here, the lead of this Primary Focus, Dr. Hayakawa, is going to talk about the details.

Hayakawa: Good morning, everyone. I'm Hayakawa, Head of Targeted Protein Degradation. I was involved in small molecule drug discovery research, and I have been a chemist for about 15 years since I joined the Company. After that, I worked in planning for the research division and led the unit conducting research in protein degradation, and then I have been in my current position since this October.



Page eight, please.

This shows the key points that I would like to communicate with you. I will divide the presentation into four parts: the basics of the technology platform, the lead program ASP3082, the capabilities we have, and the expandability of this Primary Focus.

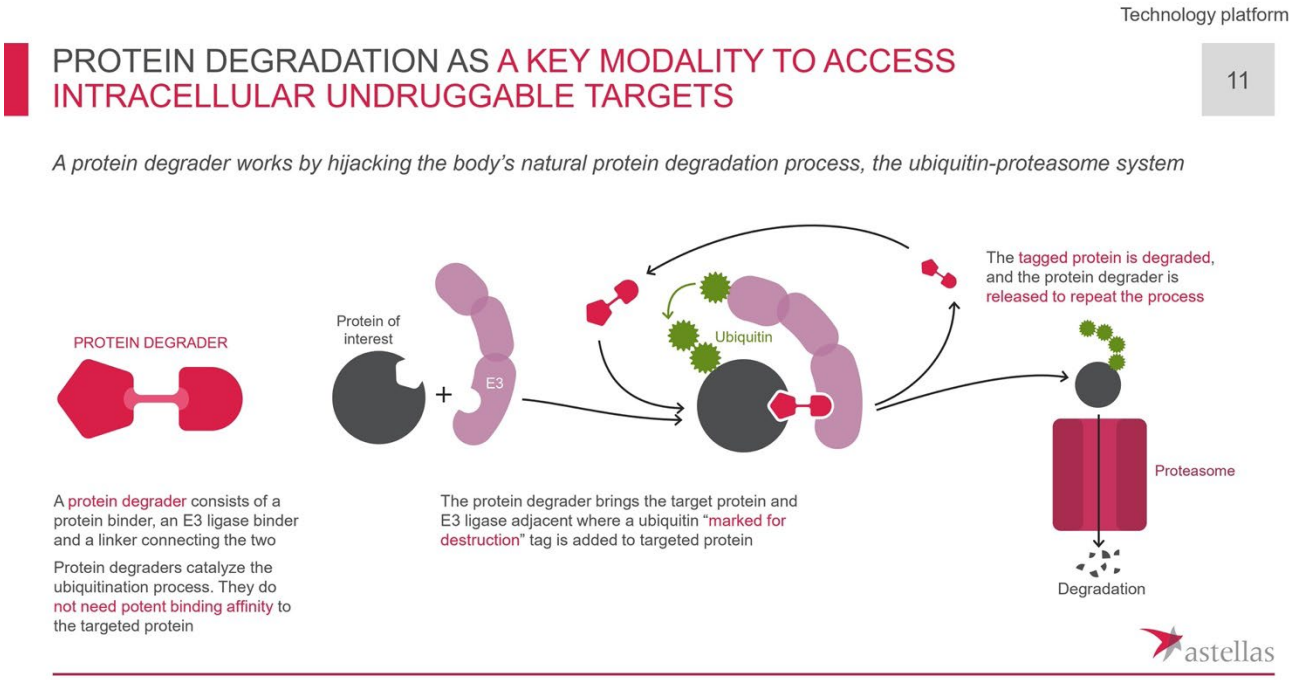


First, I would like to explain about the basics of the technology platform.

Now page 10, please.

This slide explains about the undruggable targets. The left chart shows the difference between druggable target and undruggable target. Druggable targets have distinct binding sites suitable for inhibition by small molecule compounds through which function can be controlled.

On the other hand, undruggable targets are said to be difficult targets for small molecule drugs because their function cannot be sufficiently controlled simply by compound binding due to lack of a parent active site. It is estimated that about 80% of the proteins involved in disease are undruggable targets with shallow binding pockets. Shown to the right, a variety of undruggable targets. Because of the difficulty in accessing these targets, treatment options for diseases associated with these targets are limited.

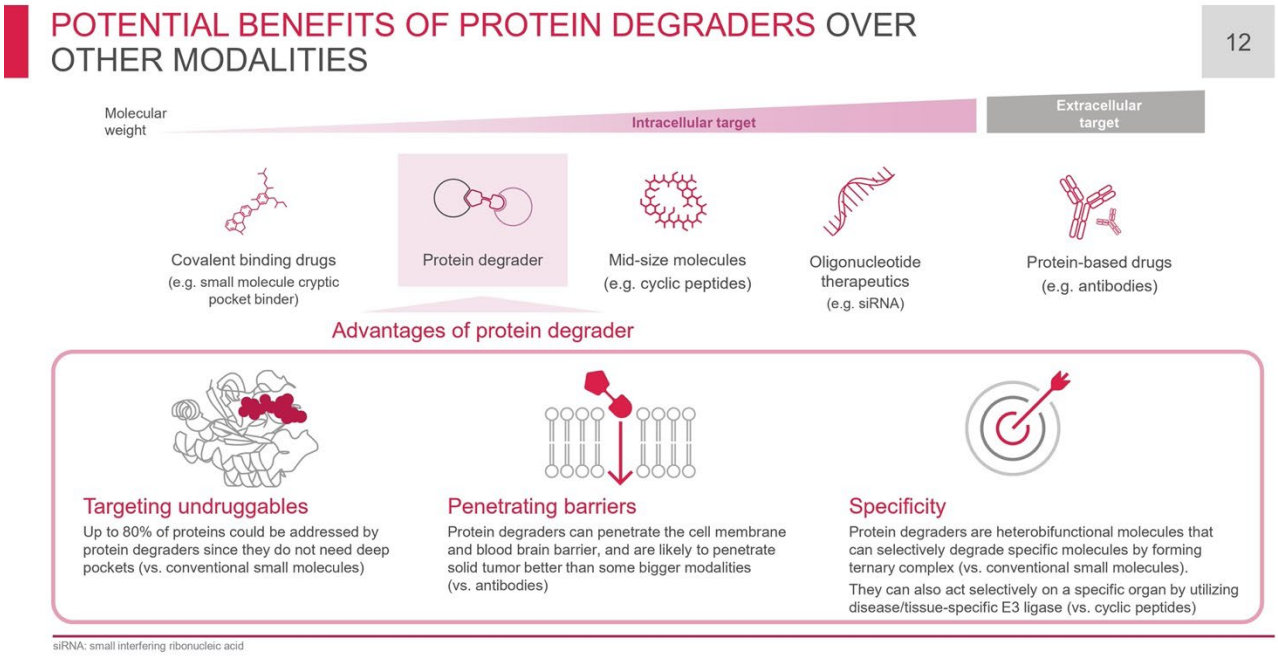


Now slide 11, please.

On page 11, we describe the mechanics of action of a protein degrader, a new modality we'll use against undruggable targets in the cell.

A protein degrader works by hijacking the body's natural protein degradation process, the ubiquitin-proteasome system. As you see on the left, a protein degrader consists of protein binder, an E3 ligase binder, and a linker collecting the two. Protein degrader is characterized by the fact that they exert their action by catalyzing the ubiquitination process rather than by binding to the target protein and directly inhibiting its function, and thus, do not require the strong binding affinity of conventional low molecular weight compounds.

As you see the right-half of the slide, the protein degrader brings the target protein and E3 ligase adjacent, where a ubiquitin marked for destruction tag is added to targeted protein. The target protein is subsequently degraded by the proteasome, an enzyme that selectively degrades ubiquitin-added proteins. Once capitalized, the protein degrader is released and triggers this process again. This is assumed to allow the target degrader to remain in the cell and continue to degrade the target protein for an extended period of time. Through this mechanism, we believe that strong and sustained degradation effect on undruggable targets can be achieved.



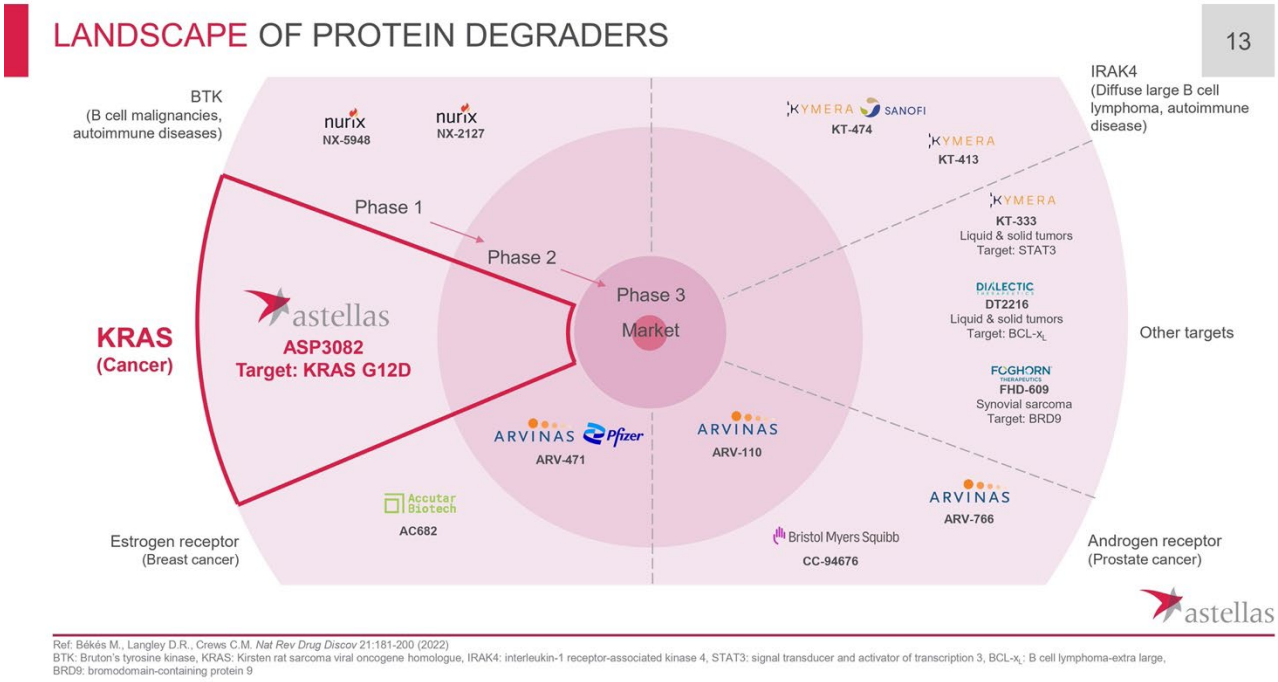
Now slide 12, please.

This slide shows the potential benefits of protein degraders of other modalities. Among the various modalities used against undruggable targets, protein degrader has three main advantages.

The first is access to undruggable targets. As explained earlier, we believe that proteins that are difficult to target with the conventional small molecule compounds can be targeted because they do not require the deep pockets.

The second is penetrating biological barriers. Since protein degraders are not very large in molecule size, they can penetrate cell brains in the blood brain barrier, and they also have excellent penetration in solid tumors where large molecules have difficulty to reach.

Third is specificity. Protein degraders can selectively degrade their targets by forming a ternary complex with a target protein and E3 ligase, which may be advantageous in terms of efficacy and safety balance. With these advantages, we believe protein degraders are best suited among modalities to access undruggable targets in cells.

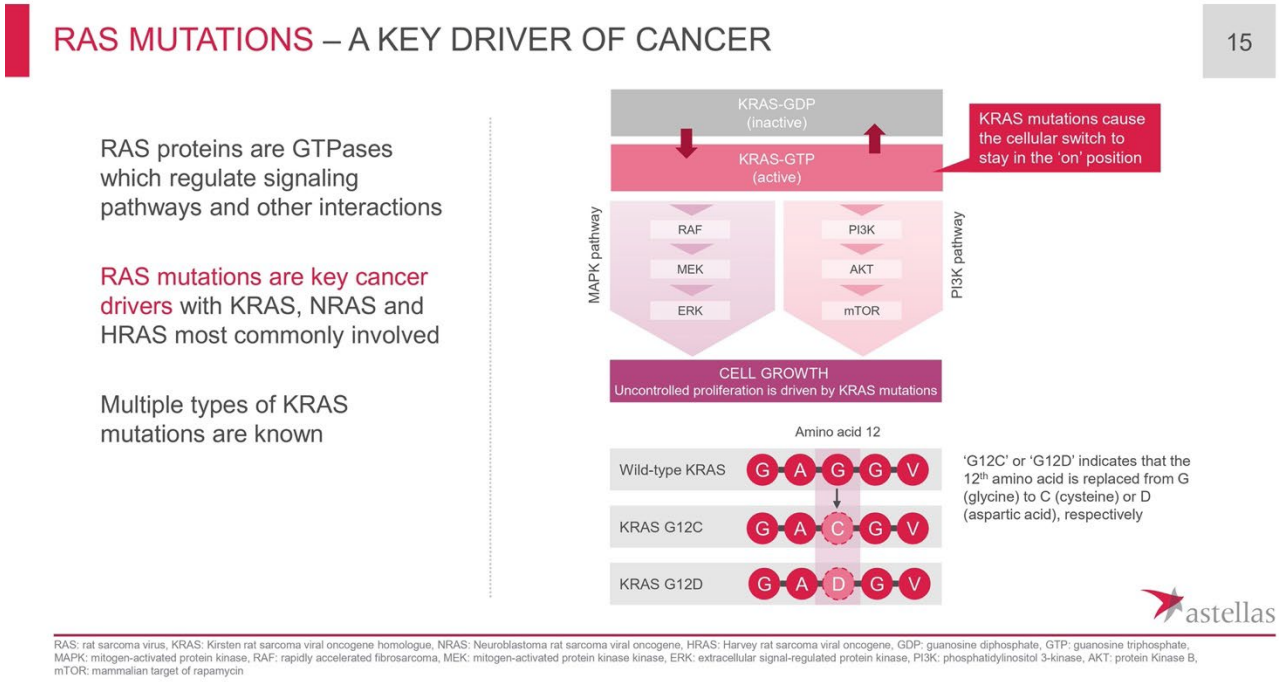


Ref: Békés M., Langley D.R., Crews C.M. *Nat Rev Drug Discov* 21:181-200 (2022)
BTK: Bruton's tyrosine kinase, KRAS: Kirsten rat sarcoma viral oncogene homologue, IRAK4: interleukin-1 receptor-associated kinase 4, STAT3: signal transducer and activator of transcription 3, BCL-x_L: B cell lymphoma-extra large, BRD9: bromodomain-containing protein 9

Slide 13, please.

We discussed the status of protein degrader development. In this figure, the programs that have entered the clinical phase are mapped based on the study phase and target classification. Moving from outside to the center of the circle, the phases are represented as Phase I and Phase II. There are currently two programs in Phase II. These are targeting the estrogen receptor and androgen receptor in breast and prostate cancer, respectively. Several other programs are in Phase I. Although it is a program of another company, clinical trial data suggesting pharmacological effects have been reported at the recent conferences and the usefulness of this modality itself is being demonstrated in the clinical trials.

ASP3082, which is currently under development by Astellas, is the world's first protein degrader for KRAS mutants to enter the clinical study and is expected to become a first-in-class drug. This is going to be explained further in the following slides.

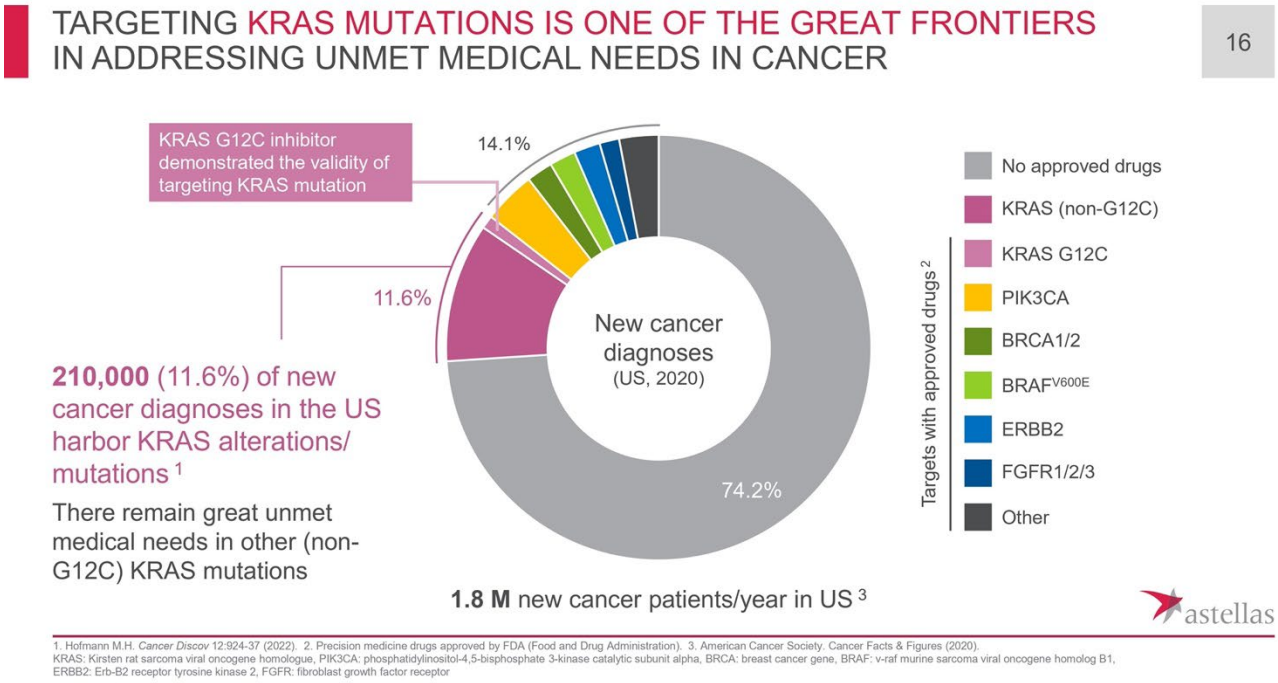


Here is about the product potential of the lead programs, ASP3082.

Slide 15.

We discuss the KRAS mutation that is the target of ASP3082. RAS proteins are GTPase that regulate signaling pathways and other interactions. RAS mutations are one of the major oncogenic factors in KRAS, NRAS, and HRAS most commonly involved. Especially in KRAS, the mutation frequency is known to be quite high. As shown in the figure on the right, KRAS is normally inactive or off-state but becomes active or on during cell proliferation. Normal KRAS switches between these on and off states in conjuncture with the cell proliferation, thus maintaining a proper cell proliferation. On the other hand, when there is KRAS mutation, the active on state persists. This results in uncontrolled cell proliferation leading to cancer.

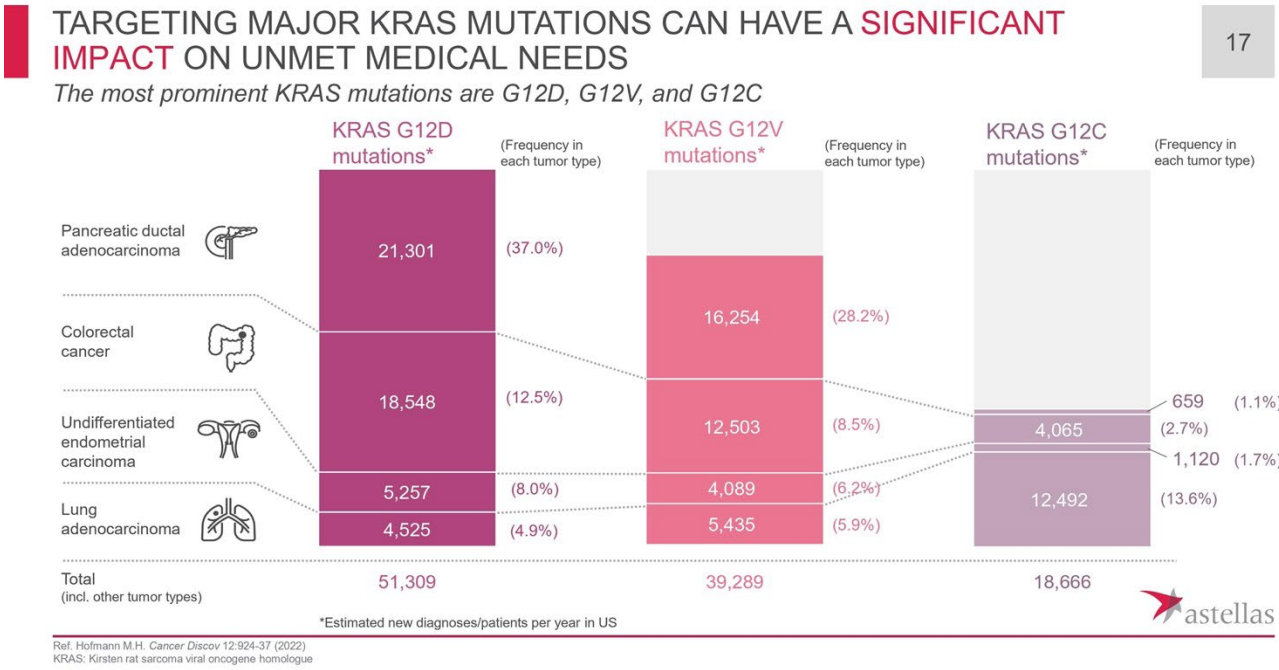
As shown in the figure at the bottom right of the slide, there are multiple types of KRAS mutations, which are denoted as G12C and G12D. This means that the 12th G, glycine, is replaced by C, cysteine, or D, aspartic acid, in the amino acid sequence of the KRAS protein.



On slide 16, we discuss the population of cancer patients with KRAS mutations.

Approximately 1.8 million new cases of cancer are diagnosed annually in the United States. The 14.1% portion of this population shown in color in the upper left indicates that our cancer-causing target has been identified and that a therapeutic agent exists for this target.

The 11.6% or approximately 210,000 people shown in pink are the patients with KRAS mutations. The light colored area is the group of patients with a G12C mutation among KRAS mutations. For this mutation, small molecule inhibitors are now on the market. Therefore, validity of target KRAS mutations and suppressing their function has already been clinically proven. On the other hand, there are still no effective treatments for KRAS mutations other than G12C and there is a huge medical unmet need.

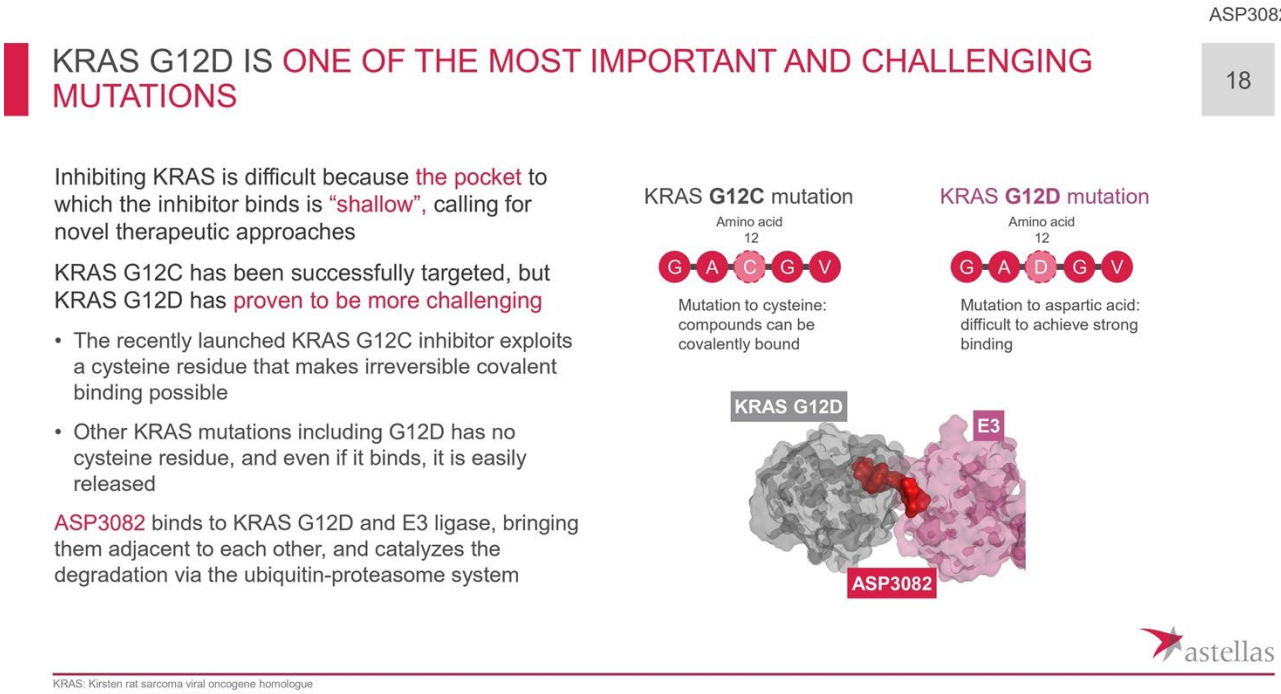


Page 17, please.

In this slide, this describes the major types of KRAS mutations. There are a variety of known mutations in KRAS, but the most prominent are G12D, G12V, and G12C.

The G12D mutation on the left side of the figure, the target of ASP3082, is reported to occur in 37% of pancreatic ductal adenocarcinomas, 12.5% of colorectal cancers, 8% of undifferentiated endometrial cancers, and 4.9% of lung adenocarcinomas, and can be targeted in many cancer patients.

For the G12V mutation in the middle, there are a very large number of patients. As for the G12C mutation on the right, as shown in the previous slide, an inhibitor has already been launched. Although the overall number of patients is not as large as for G12D and G12V, some reports predict peak annual sales of more than JPY200 billion. It is currently attracting a great deal of attention.

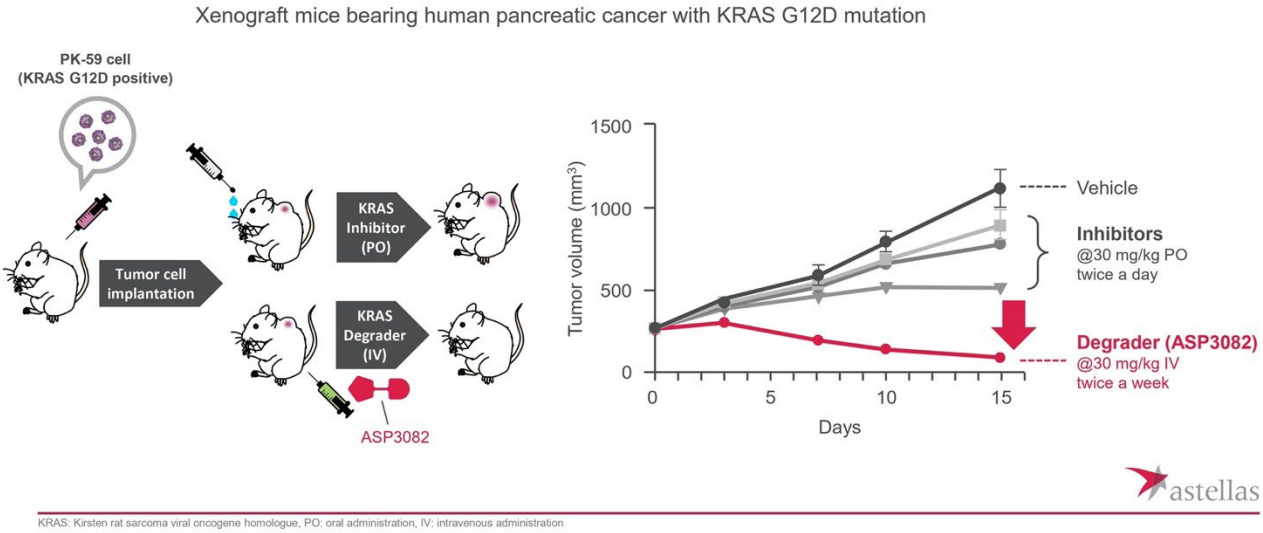


On page 18, let me explain the difference between G12C and G12D mutations.

In general, inhibiting KRAS is difficult because the pocket to which the inhibitor binds is shallow. As was mentioned before, for KRAS G12C mutation, a small molecule inhibitor has been launched already. In KRAS G12C mutation, a highly responsive cysteine residue exists. The drug can inhibit the KRAS function through strong binding here.

On the other hand, other mutations, including G12D, do not have such sites, so it's challenging to create compounds which can inhibit the function by strong binding. To address this issue, we considered the targeted protein degrader approach and created ASP3082, a compound which specifically binds to KRAS G12D and E3 ligase and catalyzes the degradation.

ASP3082 DEMONSTRATES SUPERIOR ANTI-TUMOR EFFICACY VS INHIBITORS IN PRECLINICAL STUDIES



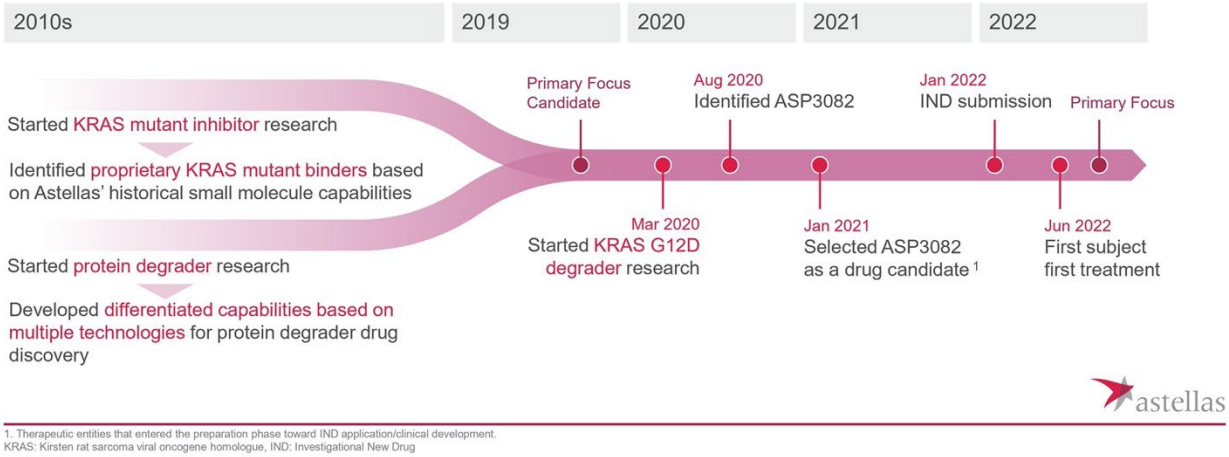
On page 19, I will explain the efficacy of ASP3082 by using animal model experimental data.

Xenograft mice bearing human pancreatic cancer with KRAS G12D mutation were used to compare the anti-tumor efficacy of the conventional small molecule KRAS G12D inhibitor and the ASP3082 KRAS degrader. The small molecule inhibitor could suppress the tumor growth to a certain degree, but its efficacy was not enough.

On the other hand, ASP3082 demonstrate very strong anti-tumor efficacy and tumor regression was observed. Based on these results, it is expected that ASP3082 can demonstrate high clinical efficacy against cancer with KRAS G12D mutation, which was considered to be undruggable target. We presented more detailed non-clinical study data of ASP3082 at an academic conference in October. At that time, there was a great reaction. The profile of this compound is drawing strong interest from researchers around the world.

HISTORY OF IN-HOUSE CHALLENGE IN TARGETED PROTEIN DEGRADATION TO ADDRESS KRAS G12D

Accumulated proprietary binder assets and capabilities enabled us to create and advance a potential first-in-class protein degrader in an accelerated manner

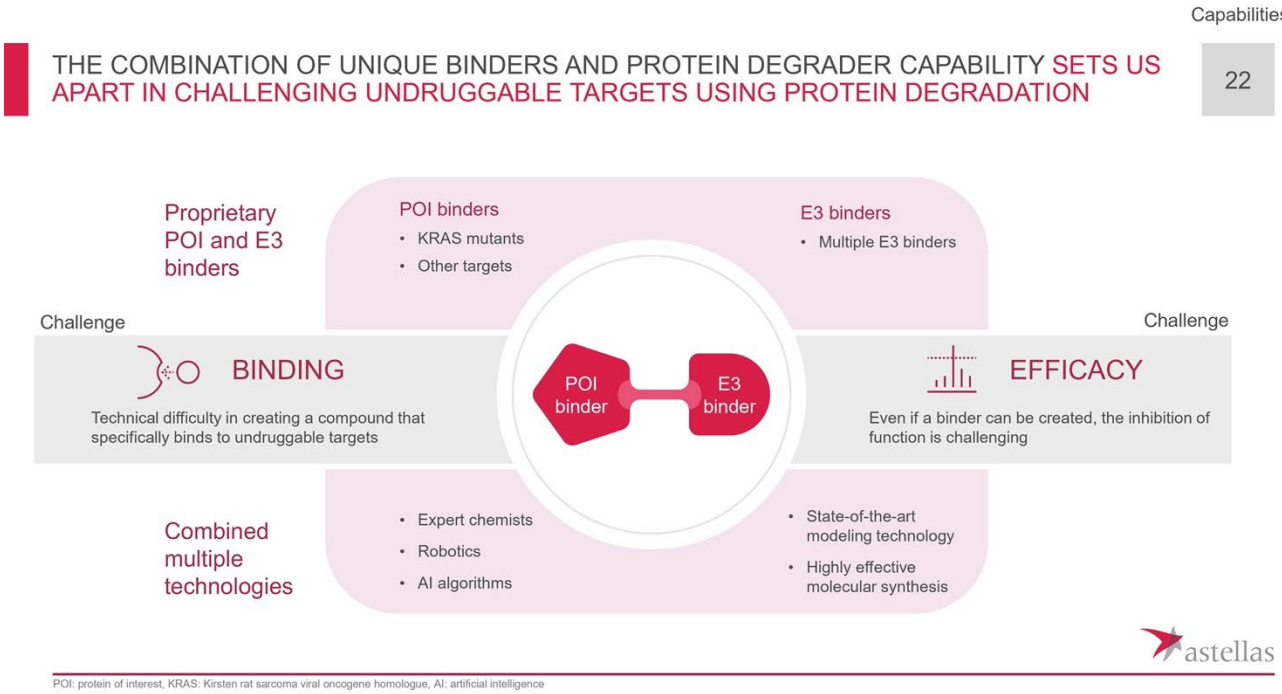


1. Therapeutic entities that entered the preparation phase toward IND application/clinical development.
KRAS: Kirsten rat sarcoma viral oncogene homologue, IND: Investigational New Drug

Next, let me explain our drug discovery capabilities. On page 21, I will explain the history of related research Astellas has conducted by now.

First, in the 2010s, we started our research aiming to generate conventional KRAS mutant inhibitors. It was technically difficult to create binders that binds specifically to KRAS mutants such as G12D, but we identified proprietary KRAS mutant binders based on Astellas' historical small molecule capabilities.

Independently from this inhibitor research, we also started protein degrader research in the 2010s. Through this, we built various technologies for drug discovery using this modality. By combining these two, we started research on KRAS G12D degraders in 2020. Since then, as is shown on the slide, this has advanced at an unprecedented speed as a compound aiming to be a first-in-class product. In just five months after the start of a research, we identified ASP3082. Furthermore, after selecting ASP3082 as a new drug candidate, we achieved IND submission in just one year.



On page 22, let me explain the capabilities we have developed in creating ASP3082.

Until the creation of ASP3082, there were two major challenges. The first one was to bind the compound to targeted proteins. The second was to enhance the efficacy so that we can achieve sufficient inhibition of function. It took quite a lot of time and efforts to create a compound which binds to KRAS G12D mutant, but we were successful by leveraging our capabilities for small molecule synthesis, which we have been good at from before.

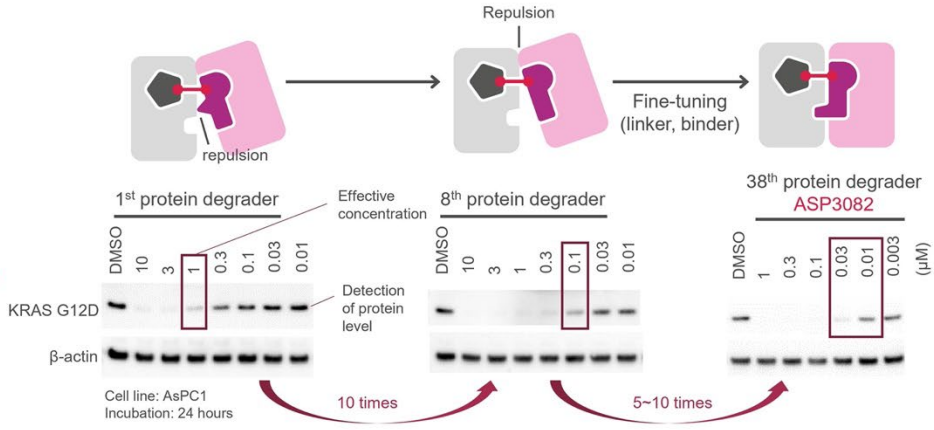
On the other hand, even if a binder can be created, due to shallow binding pockets of targeted proteins, we couldn't achieve sufficient inhibition of function. So by using protein degrader as a modality, we enhanced the efficacy successfully.

The upper and lower part of the diagram are the capabilities we have developed through this process. First, we have proprietary binder compounds against KRAS mutations. We can utilize capability technologies in chemistry synthesis to create binders for expansion to other targets. I will explain this later, but regarding the E3 binders, in addition to the one created by Astellas on its own, we also acquire next-generation technologies through partnering.

At the bottom, you can find examples of the technologies we utilize in drug discovery for this modality. It's not just enough to create a targeted protein binder and E3 binder to be connected with the linker. It's important to optimize the structure including the three parts. In addition to the conventional chemical synthesis, we can leverage robotics and AI algorithm. We also have state-of-the-art modeling technology and highly efficient molecular synthesis technologies as well. By combining these, we can create optimal targeted protein degraders quickly and efficiently.

SPEED AND POTENCY: AN EFFICIENT PROCESS OF OPTIMIZATION

Our modeling system is an integration of human expertise and computer modeling. It is highly effective, requiring only five months of optimization to identify ASP3082.

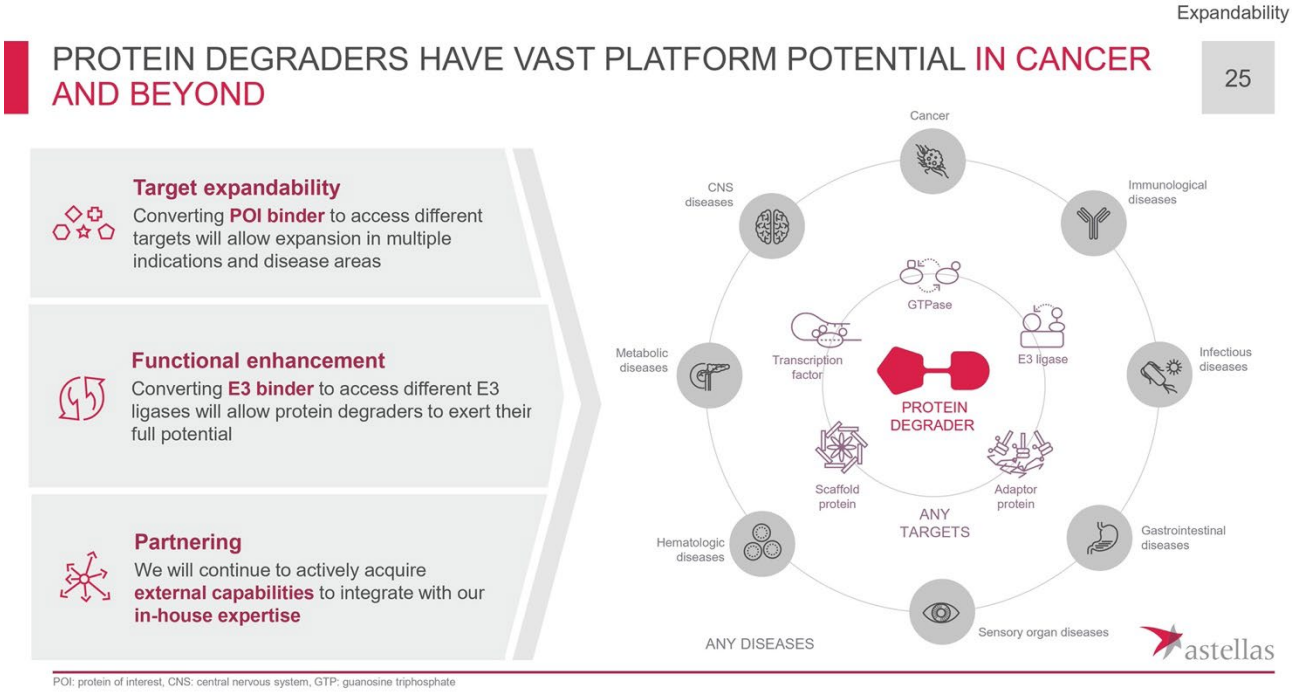


KRAS: Kirsten rat sarcoma viral oncogene homologue, DMSO: dimethyl sulfoxide

On page 23, let me explain the process to create ASP3082 as a specific example.

The modeling system we use to generate ASP3082 is unique as it's an integration of researchers' expertise and computer modeling. Usually, it takes multiple years to optimize for small molecule drug discovery, but only five months were required to identify ASP3082 successfully.

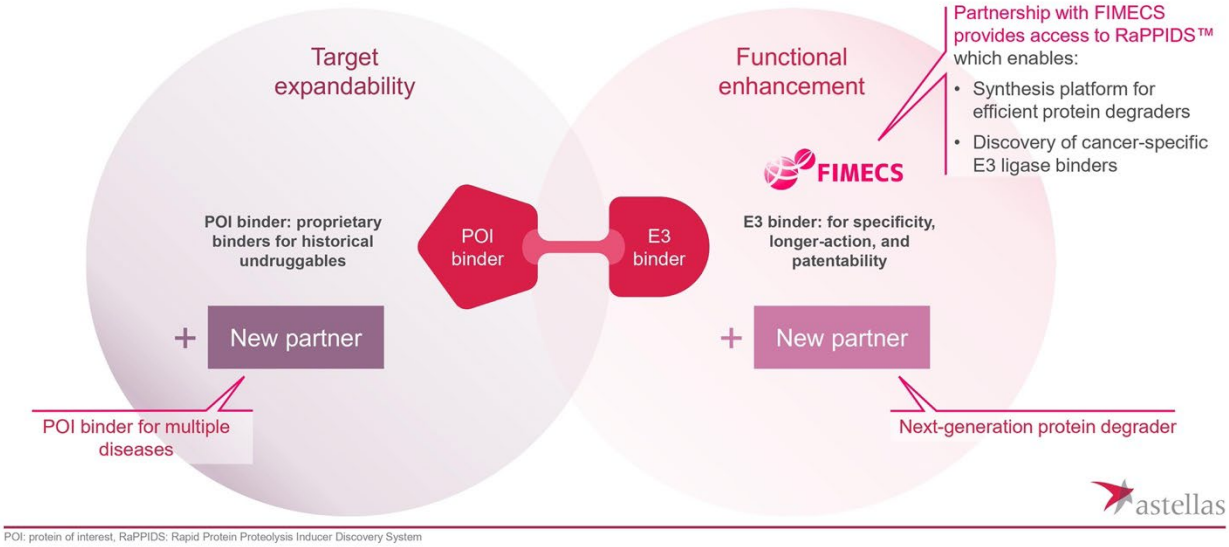
As is shown in the diagram, we started optimization from hit compounds and the 38 compounds we synthesized was ASP3082. Given the fact that in usual optimization process, synthesis of hundreds to thousands or even more compounds is necessary, we were able to create a new drug candidate very efficiently with less steps. By leveraging the capabilities we have accumulated, we think we can create new drug candidates in a short period of time in our follow-on programs and can expand our pipeline continuously.



Lastly, I will explain the expandability of this primary focus. As is shown on page 25, various applications can be possible with regards to the targeted protein degradation technologies.

By converting POI binders in line with different purposes, it will be possible to access various targets. By also modifying the design of E3 ligase binder and linker, we can aim to enhance the power of degradation and strengthen functions such as tissue specificity. In proceeding with these, we will not just depend on our own existing technologies, but we will also actively combine them with external capabilities.

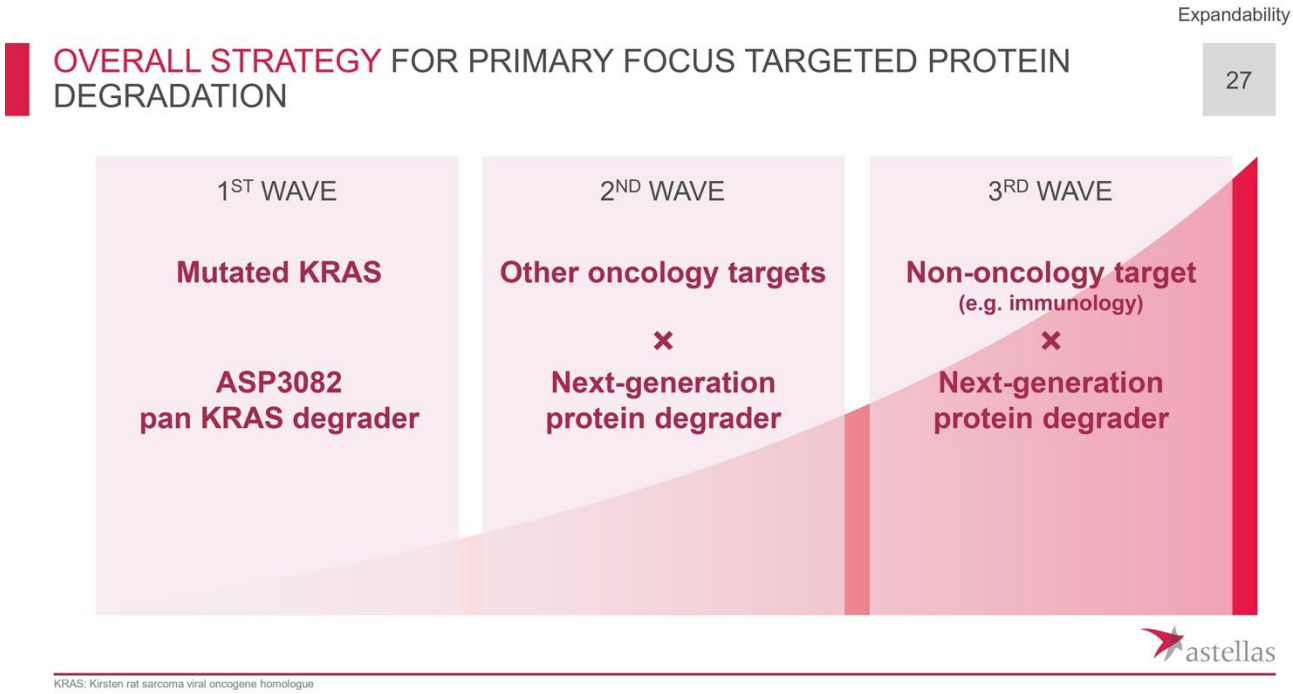
ACCELERATING OUR PROGRESS THROUGH COLLABORATIONS WITH INNOVATIVE PARTNERS



Next, page 26.

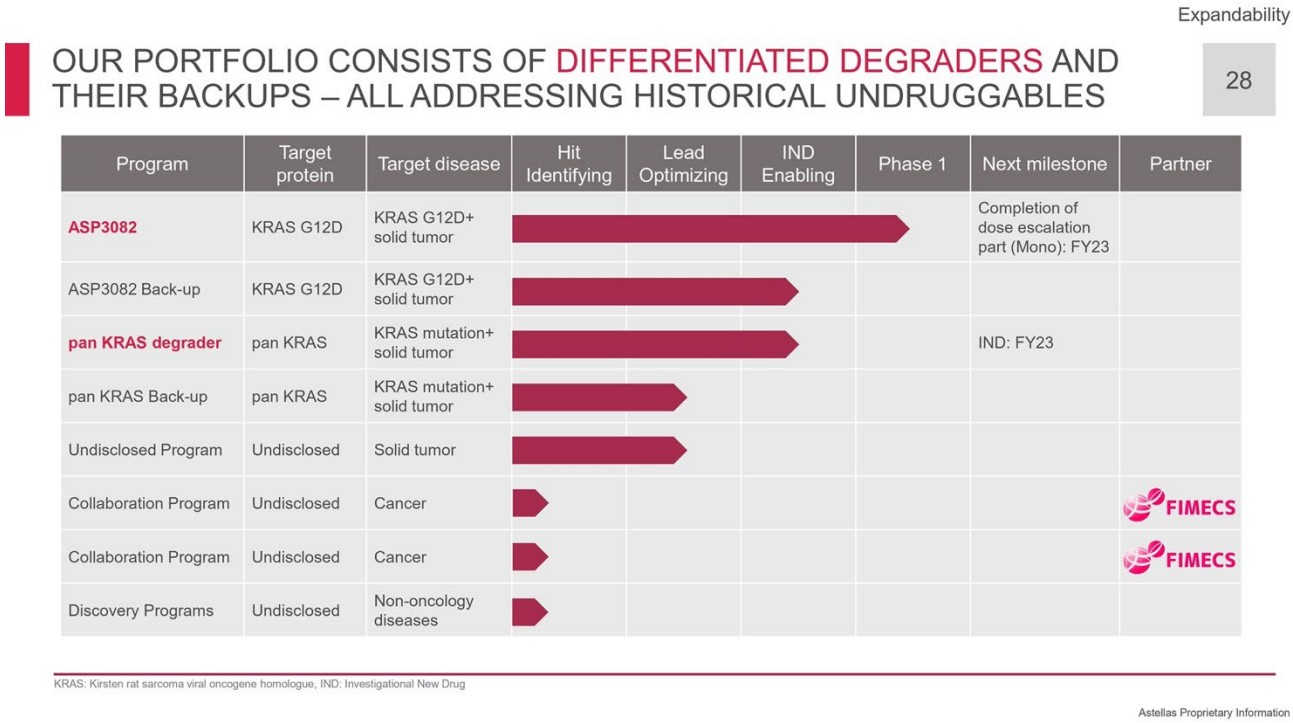
Let me explain the direction of a partnering. As I mentioned on the previous page, we are considering two directions: expandability to various target proteins and to strengthen functions by design, and modification of the entire modality. We are exploring partners actively in both.

We already have a partnership with FIMECS, which has synthesis platform for efficient protein degraders and cancer-specific E3 ligase binders. We'd like to use their state-of-the-art technologies and aim to create next-generation protein degraders. We'd like to expand partnering in the future, incorporate external capabilities, and further enhance our competitive edge.



On page 27, I will explain our overall strategy for this primary focus.

As the first phase, we will aim for the launch of KRAS-targeted protein degrader. In addition to ASP3082 targeting G12D mutant, programs targeting other KRAS mutants are also ongoing. As the second wave, we will utilize both partnering and our own technologies to expand to oncology targets other than KRAS and promote the creation of next-generation protein degraders. Furthermore, as the third wave, we will aim for expansion to non-oncology targets, such as immunology and other target diseases.



On page 28, let me explain the current pipeline.

Regarding our lead program, ASP3082, in the Phase I study, monotherapy dose escalation part is ongoing with data readout expected in FY2023. For KRAS G12D mutation, we are studying a backup compound in parallel as well. The next program we are considering is pan-KRAS degrader, which is the third one from the top. Pan-KRAS means various KRAS mutants. We are discussing this as a compound with the potential to be applied to a broad range of patients. Our lead program is now in the IND preparation phase, aiming for IND submission in FY2023. We cannot disclose the details, but as the second wave, we are also working on cancer-related programs targeting non-KRAS proteins, including two collaboration programs with FIMECS.

Also, for non-cancer diseases in the third wave, we are conducting exploratory research. We are working to generate continuous programs broadly from initial stage of research to clinical stage in this primary focus as a whole.

That's all from me. Lastly, Chief Scientific Officer, Dr. Shitaka, is going to explain from the viewpoint of our research and our new organization structure. Shitaka-san, please.

Shitaka: Good morning, everyone. Shitaka, Chief Scientific Officer. At the end of our presentation today, as a background leading to the creation of this new primary focus, I'd like to explain the changes brought about by the new research organization structure we implemented in the last fiscal year.

Page 30. By modifying the research organization structure in October last year, we changed the structure from functional-led hierarchical structure to objective-based agile organization shown on the left. We created an agile organization by objective such as immuno-oncology and targeted protein degradation, assigned researchers with regard expertise, and delegated authority. We wanted to change mainly the three things shown in the middle, namely, the speed of decision-making, mentality and behaviors of our researchers, and timely decision for investments.

One year has passed since the reorganization. We're feeling the great effect of changes and improvements we wanted to realize occurring in the research organization as a whole.

First, our daily decision-making has become much faster. In a flat organization, researchers' original ideas and ambitious plans have been proposed and shared. In the ASP3082 creation process, breakthrough proposals and decisions were made on site by those in the research labs rather than by top-down. Mindset change spills over from research to manufacturing and clinical development divisions as well, resulting in entry into clinical trial in a record time of just one year from the identification of a compound and our promotion of ASP3082. In my capacity, investment effects are much more visible in each objective, so we can change the allocation of our investments in the other organization in line with the performance even during the middle of our fiscal year. In reality, we have checked the progress of our research on targeted protein degradation at an appropriate timing, judged the potential, and expanded investment flexibly. As a result, as we presented earlier, ASP3082 achieved the world's first IND by targeting KRAS G12D. We were also successful in creating multiple promising follow-on programs to accelerate the primary focus selection this time.

In the R&D meeting last year, we told you that we are adopting the framework where an organization can grow or maybe shrink. According to its performance, the organization to execute targeted protein degradation has gone from a small venture unit to a research engine to promote the primary focus. Going forward, we will more significantly delegate authority and reinforce investments in this area so that we can further accelerate our research and generate programs continuously into the future.

This concludes our presentation. Thank you very much.

Question & Answer

Ikeda [M]: Thank you. This is all from us. Now we would like to entertain questions from your side. The questions are entertained only from the Zoom webinar but not from the live streaming. You can ask questions either in Japanese or English. If you have any questions, please refer to the raise hand button that you can find at the bottom of the screen. From the smartphone, you can find the details icon and tap it, then you can find the raise hand icon. When your name is called upon, please unmute yourself. Please mention your name and affiliate first to ask questions.

At this time, from overseas, Primary Focus Leader Peter is attending here together with us, so sometimes the answer will be in English. For those in the Zoom, you can select original language as well. Depending on your necessity, please adjust your channel. Now let's start Q&A.

Thank you very much for waiting. First question is Mr. Yamaguchi from Citigroup Securities.

Yamaguchi [Q]: I have a couple of questions here. First of all, this research team group or the members of this research group. Are they all internal members?

Hayakawa [A]: Yes, that's right. They are all internal employees and members. But of course, external capability is utilized. We have these double approaches.

Yamaguchi [Q]: Thank you very much. Also, you have three factors. This might be too simplified away, but the binder to the target protein, E3, and in between, you see the linker. I think each of them is, of course, important, but which one shows you the most difficulty? For making it a platform, of course, the left is going to be changed, but the right one, E3 linkers, they have to be always generated in very different types. In order to expand this project, you have to go through such process each time.

Hayakawa [A]: Thank you very much for asking your questions. I think what you point out it's quite important. What is important is the component that is about the left side and also the right side that is connecting E3 and the binders. Both are very important components, as I said. For each of them, sometimes it differs depending on the programs, but it is necessary to have such capabilities.

What is the common capability that assemble all these components? We have good modeling and expertise. We have those as a common platform that we can use. Thank you very much.

Yamaguchi [Q]: Lastly, for the future in this area, various companies are making their reports in this field. Competition is going to intensify into the future, and you're doing your development under circumstances, particularly ASP3082, the initial asset. With the speed to reach the market, this is going to be very important for the expansion of the franchise into the future.

Erbitux combination is used in the Phase 1 study. In pancreatic cancer, I think, which tumor types are you going to use in those initial studies? What's your tumor type strategy because competition is going to intensify?

Yasukawa [A]: Regarding ASP3082, CRC is the initial target. But also, as you can see on page 17, higher onset pancreatic cancer, CRC, and pancreatic ductal cancer, lung cancer, ovarian cancer, and also the uterine corpus cancer, we'd like to consider. Thank you very much.

Yamaguchi [M]: Thank you.

Ikeda [M]: Next, Credit Suisse Securities, Mr. Sakai, please.

Sakai [Q]: Sakai from Credit Suisse. Thank you very much. This might be two simple questions. Phase 1, that is an on-label study with 270 subjects. I think that's a relatively reasonable size. Looking at ASP3082 alone, this is the undruggable world, so what's your focus expectation about the probability of success that you had?

Shitaka [M]: ASP3082 probability of success is your question?

Sakai [M]: Yes.

Shitaka [A]: Well, yes, it's an undruggable field, but the pathological involvement, we believe this is the target with a high level of the evidence. We believe that this is quite degradable and degradation level is quite high, so we have a high probability of success set.

Sakai [Q]: I see. But I think, of course, internally, you look toward the level of the success, right? But for example, if you refer to page 28, some information is disclosed. But regarding the sense of the speed, are you going to wait for the result of ASP3082? I believe you are working on backup program as well. But other than those, you mentioned you are going to put the resources further. In your earlier phase, you also shift toward a Phase I. Do you have such a plan? And what level of the speed or sense of speed do you apply for this?

Shitaka [A]: Well, without waiting for the result of ASP3082, we work on the follow-on projects one after another. ASP3082, the optimization study is finished after just one year. ASP3082 got into the clinical phase. That is the level of the speed we are thinking about for follow-on products because this field is quite competitive.

Yasukawa [A]: Sakai-san, Yasukawa speaking. Regarding the first question, let me make additional comments. If you refer to slide 12, there are three benefits described here. Biology, ubiquitination is introduced, and that is quite robust. But of course, compared to the ordinary low molecule weight compounds, the molecule weight is larger. On the production side, well, when we adopted this thing as Primary Focus, the middle one is the focus. If it's really penetrating into the tissue, although it resides within the vessel or before getting the tissue, PK goes up or not, those were part of the concerns that I had. But looking at the result of the initial clinical trial, it was confirmed that it was absorbed and distributed systemically. The first hurdle that I thought was the highest among this project was what we were able to overcome. But of course, we have a backup for the preparation. If Phase 1 went much further, and we can learn about the level of the concentration if that achieves to the target level. If the target level of the blood concentration is achieved, we would not think about the backup.

Sakai [Q]: Thank you very much. On page 19, compared to inhibitors, was this published? What is the comparator? I would like to explain. Here, as you pointed out, what is compared against what directly?

Hayakawa [A]: Yes, I understand your point. Inhibitors are used as a component to develop degraders. The left side inhibitors could work as inhibitors and also the degraders were compared against inhibitors. As for the inhibitor part, 30 milligrams oral BID almost to the limit, it was dosed. Still, the tumor could not be controlled sufficiently. But if you add the degrader function, tumor was almost cleared by injecting twice a week. Very powerfully, the tumor shrunk. That's the comparison here.

Sakai [M]: Understood. Sorry to say this, but you didn't expect a lot of efficacy here in this model to begin with.

Hayakawa [A]: Going back to the history, originally, we were doing inhibitor research with a lot of focus initially. Compared to other companies, from the initial stage, we identified inhibitors, but even if you optimize

during in vivo model, it did not demonstrate sufficient efficacy. We had such a long time in research. We switched to a degrader profile, then we were able to accelerate

Sakai [M]: Understood. I have great expectations on you. Thank you very much indeed.

Ikeda [M]: Next, JPMorgan Securities' Mr. Wakao, please.

Wakao [Q]: Thank you very much. Wakao, JPMorgan. First question. There's protein degraders developed by other companies as well, and looking at the technologies, what's the difference of the technologies between other companies and yourself? Thank you.

Hayakawa [A]: First of all, assets. KRAS, as you see on the screen, we have various types of the target possible because we have such tools on our hands. Therefore, we can have a variety of the approaches that can work on others than KRAS as well.

Three-component assembly, that design is a very special technology base, so that is what we have great confidence.

The other part that is expanding these days is E3 binder technology on top of the ordinary binders, but also we have our original binders. From FIMECS as well, they have a very interesting unique technology so we would like to expand this further. That's the difference of us from others.

Wakao [Q]: Against the target, as you explained, you have to tune up. It's difficult to compare the technologies just simply.

Hayakawa [A]: Correct. We have these technologies, and it's difficult to make an apple-to-apple comparison. But we have chemical drug discovery activities, and we accumulated our design, our manufacturing capabilities and technologies. They can be said as something very good.

Wakao [Q]: Thank you very much. Secondly, on this page, in the end, the initial target is undruggable. But this time, what you have is having binding. The thinking behind here, it can bind, but it's not as much as to show inhibitory effect. Regarding the binding site, your binding capability is not so high, but by having a degrader, it's supplemented. How is it being bound?

Hayakawa [A]: Thank you for the very important point. In the case of degrader, the binding can be very weak, which is enough. That's the difference compared to the usual small molecules. It's like a keyhole. It's like you insert a key to inhibit the function with a small molecule. In the case of degraders, protein A to target degradation and ubiquitination protein B can be close to each other. That's enough. In the case of a degrader, there can be just weak binding with each other. Binding is very different compared to the conventional ones in terms of the science.

Wakao [Q]: In line with that, well, if the specificity is low, it sounds like it binds in variable places, and therefore, E3, it is very important to show the specificity. In the first program, I just wonder at the level of the specificity. You mentioned there are various types. But what is the current expansion reach?

Hayakawa [A]: Thank you very much. For specificity, to put it simply, the specificity is to be quite high compared to the low molecule products and activator. As we mentioned, deeper lock with the key. That is a very limited interaction where you have to come up with the specificity. Within the body, there is the same type of philosophy is applied for the key and the lock. That's why the specificity is very difficult to achieve.

But this time, the protein degrader, proteins are shaking hands each other, and interface contacts in a wider area. Therefore, generally speaking, specificity is likely to be high.

On top of that, as has been pointed out, this is quite an important point. This E3 binder, this protein, there are more than 600 kinds within our body. For example, some are specific to cancers or specific to some tissue and they are known. We can make use of those of them to realize the required specificity or improve the value of the substance.

Shitaka [A]: Thank you. One additional comment. ASP3082 specificity, proteomics is utilized, and selectivity is very high. That's confirmed with the experiment.

Wakao [Q]: Next fiscal year, the initial part is going to complete for ASP3082. Are you going to show us the data in the next fiscal year?

Yasukawa [M]: Peter, what is the current status of Phase I study? Please explain.

Sandor [A]*: The current Phase I study is in dose escalation. We expect the data out of Phase I in FY2023, and this will guide us into the next step of the program to design and decide on which more types to develop it further and how to expand the monotherapy and/or combination. We will decide at this point then and there to disclose the data. It will likely be disclosed at academic meetings or conferences.

Wakao [M]: Thank you very much. Very clear. That's all for me. Thank you very much.

Ikeda [M]: Next, Schroder Investment Management, Ms. Sato, please.

Sato [Q]: This is Sato. There are a couple of questions. First of all, from the scratch, you started the research, and it's been only two years and three months to achieve the first in patient. I think this is unprecedented speed. Why would this modality, this speed was achieved? Is there any background that you can share with us for this quick achievement?

Shitaka [A]: Thank you. From the identification of compound to IND, it took one year. This is very fast. I believe this is the shortest record for us as well. We conducted several studies in a parallel manner. We took risks. That's one of the contributors for this.

For optimization, as has been repeatedly mentioned, we have accumulated know-how for that and also modeling the accuracy for that is extremely high. The forecast or prediction of the modeling achieved a very high accuracy level. That's another reason.

Hayakawa [A]: Right. From the perspective of actual research field, as Dr. Shitaka mentioned a little while ago, agility is high and a flat and object-wise organization was established. That contributed a lot, that your making was quite quick. Within the organization, the decision was made quickly, and internal-external collaboration went in a speedy manner. That's why we were able to accelerate the speed from the research to IND.

Yasukawa [A]: This is Yasukawa. Let me make additional comments. On this page, the 38th compound is what we achieved utilizing computer technologies. One year from ASP3082 discovery to IND. This is actually based upon my request. Low molecule compounds and synthesis experience is so much accumulated internally. What is done, then what is triggered, that is kind of a rule internally. If you just follow that, yes, we can minimize the risk, but it would take a longer time. It shouldn't be in that way all the time. Once the promising thing is identified or when we have to win the competitor, you shouldn't think about only the low-risk approach. When we find something good, we have to take risks and several tasks should go on in a parallel manner to achieve the IND in the shortest time. That's the recourse that have been placed into the research people. That was achieved with this ASP3082 team. This is a good precedent for us. The same thing could be applied for the following good compounds if those are identified. This brings the confidence to other teams as well, to the Company as a whole as well.

Sato [Q]: Thank you very much. Also, the delegation of authority to people in the field, reorganization, and taking risks to have programs in parallel, if that's the background, not just in this modality, but for others as well, I think you can apply this to other areas as well. What do you think?

Shitaka [A]: Yes, your understanding is correct. There is a change in such a mindset for the entire Research division and also for the entire company. It's spreading now. This is going to be a very good precedent so that we can have a great sense of speed for the follow-on programs as well.

Sato [Q]: Thank you very much. I'm checking ClinicalTrials.gov, IV infusion is once every three weeks, is this correct? Once it's bound, it's going to be released and then go back to bind to the receptor with one dosing. The efficacy is going to last for a long time with one dosing?

Hayakawa [A]: Yes, you're right. Once-a-week IV administration, but as you said, it's a protein degrader. KRAS mutant would be gone completely. It takes time to regenerate. The efficacy would be prolonged. Also, the distribution of the drug in the tissue cancer, it's superior compared to the conventional small molecules. That's why we can use this kind of a dosing regimen.

Yasukawa [A]: Peter, when you wrote the protocol, how did you determine the dosing frequency? According to the data you have by now, once-a-week dosing seems to be good or not, or what do you think? Anything you can share right now?

Sandor [A]*: It was designed based on the preclinical pharmacology data. What we have seen so far confirms the preclinical experiments and expectations completely. Right now, it seems that we are on the right dosing schedule and frequency as well.

Sato [M]: Thank you. Anything you're going to continue?

Sandor [A]*: As dose escalation, we don't know what the exact final dose will be, therefore, the monotherapy or for the combination.

Sato [Q]: Thank you very much. It is the 21-day cycle. This is once-a-week administration, and after that, you will have the drug holiday. That's the image of the administration cycle?

Sandor [A]*: Yes, that is the design.

Sato [Q]: Thank you very much. Phase I primary completion date that is March 2026. It's a bit far ahead, but the first part is planned to be completed in the next year. I think you have a bit of the leeway for your scheduling. Is there any background for that? Is there any reason for that?

Sandor [A]*: Yes, the primary completion describes the time when all the patients have been dosed and followed up for the predefined period. As we mentioned earlier, we expect to finish the dose escalation next fiscal year and we will have safety information about the job and then we will have the dose for the next phase of the clinical study. Our expectation is that we will start to see the first proof-of-concept type data in the 2024 to 2025 timeframe.

Sato [M]: That's all from me. Thank you very much.

Ikeda [M]: Thank you very much. Next, Morgan Stanley MUFG Securities, Mr. Muraoka. Please unmute yourself.

Muraoka [M]: Hello.

Ikeda [M]: I can hear you.

Muraoka [Q]: Thank you. This is Muraoka speaking. Listening to the presentations and discussions today, I understand that it can be used for an undruggable target. For the drugs that had been given up in the past because of the lack of efficacy or insufficient blood concentrations, if you can restart the research on such drugs using this technology, it's like a dream. Is it possible to take such a strategy?

Shitaka [A]: Yes, you're right. KRAS too, but you see the pipeline table in page 28, it is "undisclosed", but I can tell you that these are very well-known targets. In terms of the disease biology, these are targets with a high probability but couldn't be turned into drugs. But we would be able to produce with this technology, and once you are able to produce, it's going to be very efficacious. We'd like to address such targets.

Muraoka [Q]: Thank you. Your partner, FIMECS, that's Takeda's spin-off company, right? This is my own imagination, but they were overlooked in Takeda. But with a partnership with Astellas, the development is taking place in a very interesting manner. That's out of my imagination. But is this understanding right?

Hayakawa [A]: Well, I don't know if the company was overlooked in Takeda or not. But it's a spin-off and FIMECS has a technology called RaPPIDS. This has a very synergistic effect with our projects, so we have a high expectation on the collaboration with them.

Muraoka [Q]: Well, did you think that this is a good company and technology, but it was inaccessible within Takeda, so the spin of timing was most appropriate and optimal for you?

Hayakawa [A]: Yes, we believe so.

Muraoka [Q]: Thank you very much. My last question, I know this is deviating from today's theme, but any comment on the success of zolbetuximab?

Yasukawa [A]: Yasukawa speaking. Zolbetuximab, as you know, it was originally something we purchased from a European venture. Before our purchase, they did a small-sized Phase II study. A few years ago, there was an impairment loss, you may remember. We wondered whether we could file for accelerated approval with the results of Phase II study, considering the level of the results. However, it was a small-sized study and the study itself was mainly done in Eastern Europe. So just with that data, we thought we could not file our submission. If we want an accelerated submission, if that was possible after filing, after conditional approval, confirmatory study was to be conducted. That study is now being done as a Phase III study. Personally, I believed that this Phase III was going to show the same result as the Phase II. We obtained such data exactly as I thought. These are the results we expected so there was no surprise about the results. That's the situation right now.

Muraoka [Q]: The other one will be at the beginning of next year?

Yasukawa [A]: It's an event-driven study but we are in the final stage. We will make the announcement when we disclose the results.

Muraoka [Q]: You were able to reproduce the results. In the previous Phase II, OS and PFS has that ratio, 0.4 to 0.5. This result was great. So the Phase III results are comparable to this?

Yasukawa [A]: Regarding which study, the one with results that are already available?

Muraoka [Q]: Yes.

Yasukawa [A]: Yes.

Muraoka [M]: Understood. That's all from me. Thank you very much.

Ikeda [M]: The study results, once available, will be reported to you.

Muraoka [M]: Thank you very much.

Ikeda [M]: Thank you very much. Next, Mizuho Securities, Mr. Tsuzuki, please.

Tsuzuki [M]: Thank you very much. I'm Tsuzuki from Mizuho.

Thank you for the presentation and explanation. This is quite interesting. I'd like to ask you a question about the rate limiter for this degrader. You make the target, the protein linker, and also E3 ligase. I think these three are important components. Out of these three, which is likely to be the highest bottleneck rate limiter? Of course, it differs depending on the project. But regarding this ASP3082, for the optimization of the linker, in page 23, you have to go through the fine-tuning process or identifying the target protein, what was the rate limiting factor for this project? And what is likely to be the rate limiting factor? This is the first question.

Hayakawa [A]: Hayakawa speaking. That is a very important question. Thank you very much. KRAS G12D degrader case, as has been pointed out in my presentation, the left side, that is the original G12D binder. Making that took a long time. But the process of assembling, and the part of E3 binder, that match went quite well. The ultimate molecule establishment was considered based upon our design technology, so it was accelerated. But just like you pointed out, it's case-by-case. For KRAS, currently, we have mostly the sufficient binder set. Therefore, the degraders are produced as we want in an accelerated manner.

Regarding the assets other than KRAS, for a longer time, the small molecule binder research has been long ongoing, so we can make use of that. I think we'll have other projects designated as undruggable. In that case, we would work on them as soon as possible so that we can gain a new interesting asset. Maybe this is the rate limiter.

Tsuzuki [Q]: Thank you very much. One more question about the linker. If I'm wrong, please correct me. E3 ubiquitin ligase, the lysine residue in the protein is going to be important. On page 23, from the first to 38th compound you created, lysine residue access was a rate-limiting factor? As you have a lot of assets in your pipeline, you can solidify your know-how and will this be faster in the future? I'd like to know more.

Hayakawa [A]: Thank you for the very deep question. We don't know everything in science yet, but we believe ubiquitination of lysine residue is done in parallel as well. The speed of ubiquitination is very fast. That is repeated, and it goes into a proteasome degradation. It does in a reversal fashion. We are assuming such a catalytic mechanism. I don't know how much I can say. But what's important is the targeted protein, POI, and E3 ligase. They must be brought to be close to each other.

Tsuzuki [Q]: One more question. Another is the selection of the silent binder. Mega pharma has many of those that could not be either antagonist or agonist, so mega pharma has the favorability in this project. Also, are you thinking about the collaboration with a company with having the most silent binders for intracellular targets for the next project, because this is degradation in the proteasome system? Logically, I think that will be the way.

Hayakawa [A]: Well, thank you very much. It seems that you are covering our intention already. What you pointed out is quite right. Therefore, not specific to internal development, but we are always looking for the attractive partner. That is going to be quite important.

Tsuzuki [M]: Understood. Thank you.

Ikeda [M]: Thank you very much. Next, JPMorgan Asset Management, Mr. Sawada, please?

Sawada [Q]: I'm from JPMorgan Asset Management. My name is Sawada. I have a few questions. First of all, to begin with, E3 binder, ubiquitin ligase. If you change the types of ubiquitin ligase, target protein could not be degraded well. Which ubiquitin ligase should be selected? Is such know-how already available in your hands? As for KRAS, I'm sure you know this already. But depending on the targets, what ubiquitin ligase would degrade? Are there some things you don't know yet?

Hayakawa [A]: Thank you for your question. We have not understood everything yet. Regarding KRAS, E3 binder, what types should be the best to be combined, we have such information. But with modeling, we can get some information to a certain degree. Tissue or disease specificity could also be achieved with certain E3. Molecular design would tell us certain information, but we have to go through a trial-and-error process still.

Sawada [Q]: Understood. If that is the case, you mentioned there are about 600 kinds, and they are always existing in our cells? Depending on the cell, the ubiquitin ligase that it wants to bind is sometimes not available.

Hayakawa [A]: Thank you for the question. You are right. Depending on the cell, there are E3 available and not available. There is a localization taking place. There is a tissue where you would like to degrade or the pathological status so you can degrade. I think that kind of approach will be available.

Sawada [Q]: Understood. If so, where is it localized? Is that kind of information now available?

Hayakawa [A]: Yes, including ourselves, bioventures, pharmas, we collect the data and strategically reasonable combination is what we are always thinking about.

Sawada [Q]: If that is the case, then this ubiquitin ligase that is targeting a certain cell, but the ubiquitin ligase is not available for a certain cell, not available in other cells. Therefore, even with this technology, it's very difficult to target or if you work on in a creative manner, then the ubiquitin ligase you would like to target exists within cell whatever shape it will be.

Hayakawa [A]: Right. If you look at the certain cell and if you like to degrade a certain target, then some optimal one is available somewhere. We can find something. Of course, the selection is important.

Sawada [Q]: There is know-how, and you have to explore well in this field. Is that going to be one important area?

Sawada [A]: Yes, you're right.

Sawada [M]: Understood. That's all for me. Thank you very much.

Ikeda [M]: Thank you very much. Next, Ms. Sogi.

Sogi [Q]: Thank you for the great presentation today. KRAS targeting is the topic I'd like to ask a question about. Amgen, in the presentation, there was a mention, Amgen's LUMAKRAS is already launched into the market. This summer, Phase III data was published as well. As a target, KRAS G12C mutation, so the target is different. As you said, target is NSCLC. It's different, but still, the pharma industry and scientific community have rate expectations to target KRAS. As the clinical data, I believe the efficacy was not achieved compared to what was expected. I think that's the overall view. Reflecting this LUMAKRAS sales and penetration in the market, it's not so fast in the actual market. KRAS target, I understand the difference was based on this. Why does LUMAKRAS has these results? For you, there can be a different clinical impact you may be assuming. I'd like to hear your view.

Company Representative [A]: Thank you for the question. That's something we carefully watch. As for LUMAKRAS, it's an inhibitor. First of all, we have to say it's an inhibitor. Ours is a degrader. In terms of efficacy,

the target protein is eliminated or degraded. We can enjoy the benefit because of these data expectations. On the other hand, can we realize those expectations? There are still some uncertainties. LUMAKRAS is faced with issues like resistance occurring in a variety of ways. We have follow-on programs we'd like to refine on combination therapies, and the strategies for that are going to be very important as well.

Sogi [M]: Thank you very much.

Ikeda [M]: Thank you very much. We have a couple of people still waiting to ask questions but it's time. With this, we would like to close this meeting. Everyone, thank you very much for your attendance.

[END]

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