Astellas Pharma Inc.

ASP3082/Targeted Protein Degradation Online Meeting

September 27, 2024

Event Summary

[Company Name]	Astellas Pharma Inc.
[Company ID]	4503-QCODE
[Event Language]	JPN
[Event Type]	Analyst Meeting
[Event Name]	ASP3082/Targeted Protein Degradation Online Meeting
[Date]	September 27, 2024
[Time]	07:30 – 08:40 (Total: 70 minutes, Presentation: 25 minutes, Q&A: 45 minutes)
[Venue]	Webcast
[Number of Speakers]	4

Chinatsu Sakata	Primary Focus Lead, Targeted Protein Degradation
Masahiko Hayakawa	Head of Engineered Small Molecules
Ahsan Arozullah	Head of Oncology Development
Hiromitsu Ikeda	Chief Communications and IR Officer (CCIRO)

[Questioners]	Hidemaru Yamaguchi	Citigroup Global Markets
	Seiji Wakao	JPMorgan Securities
	Koichi Mamegano	BofA Securities
	Shinichiro Muraoka	Morgan Stanley MUFG Securities
	Shinya Tsuzuki	Mizuho Securities
	Kazuaki Hashiguchi	Daiwa Securities
	Nobuaki Sawada	JPMorgan Asset Management
	Miki Sogi	Sanford C. Bernstein

Presentation

Ikeda: Good morning. Thank you very much for joining Astellas ASP3082 TPD, targeted protein degradation, online meeting out of your very busy schedule today. I'm delighted to serve as emcee today. I'm Chief Communications and IR Officer. My name is Ikeda. Thank you for your time.

Today, after the presentation, we will move on to the Q&A session. The presentation will be made based on the meeting materials posted on our website, including Q&A. Simultaneous translation is available between Japanese and English. We cannot guarantee the accuracy of the translation. Thank you for your understanding.

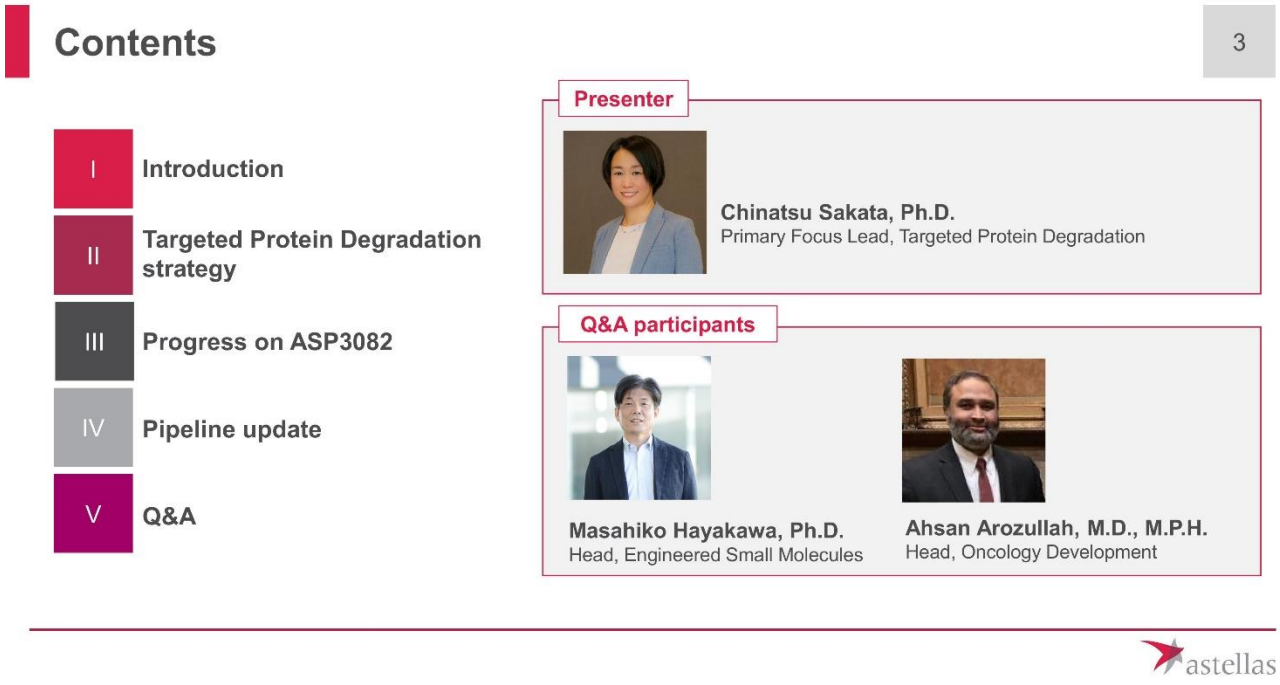
This material or presentation by representatives for the Company, the answers and statements in the Q&A session include forward-looking statements based on assumptions and beliefs in light of information currently available to management and subject to significant risks and uncertainties. Actual financial results may differ materially, depending on a number of factors. They contain information on pharmaceuticals, including compounds under development, but this information is not intended to make any representations or advertisements regarding the efficacy or effectiveness of these preparations, promote unapproved uses in any fashion or provide medical advice of any kind.

The presenter today is Dr. Chinatsu Sakata, Primary Focus Lead, Targeted Protein Degradation. During the Q&A session, from Research, Head of Engineered Small Molecules, Dr. Masahiko Hayakawa, and from Development, Head of Oncology Development, Dr. Ahsan Arozullah, will join.

I'd now like to go to our presentation. Sakata-san, please.

Sakata: Good morning, everyone. I am Sakata from Astellas Pharma Inc. Thank you very much for taking the time out of your busy schedule to attend this meeting.

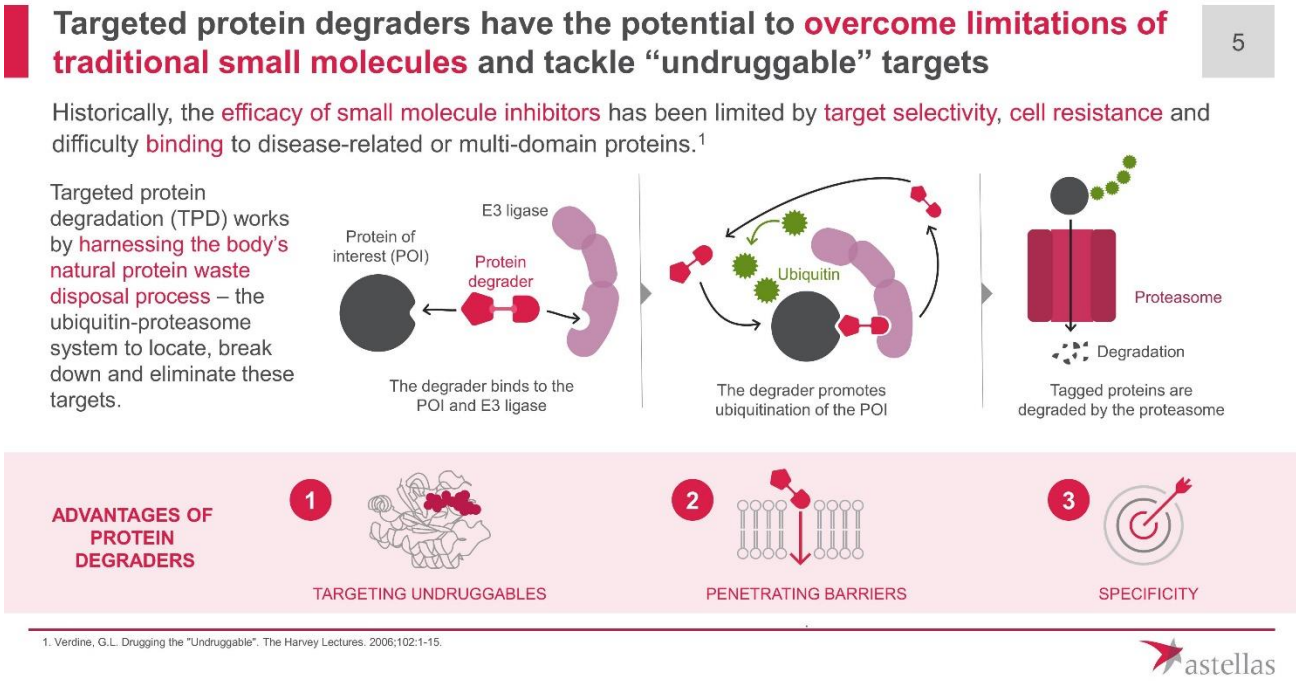
Next slide, please. This is the cautionary statement slide. Ikeda explained this already, so I will skip reading.



Today, I would like to discuss one of the priority investment areas in Astellas Pharma's [R&D] primary focus, targeted protein degradation, or TPD.

We believe that TPD has the potential to transform the treatment landscape for some of the world's most devastating diseases, including refractory cancers with limited treatment options. As a progression of ASP3082, the lead program in TPD, I would also like to discuss the Phase I data presented this month at the European Society of Medical Oncology, or ESMO, in Barcelona.

Developed in-house, ASP3082 is the very first targeted protein degrader, which went into a clinical study phase. This TPD is targeting the KRAS G12D mutant and has the potential to become a first-in-class treatment for solid tumors associated with the KRAS G12D mutations.



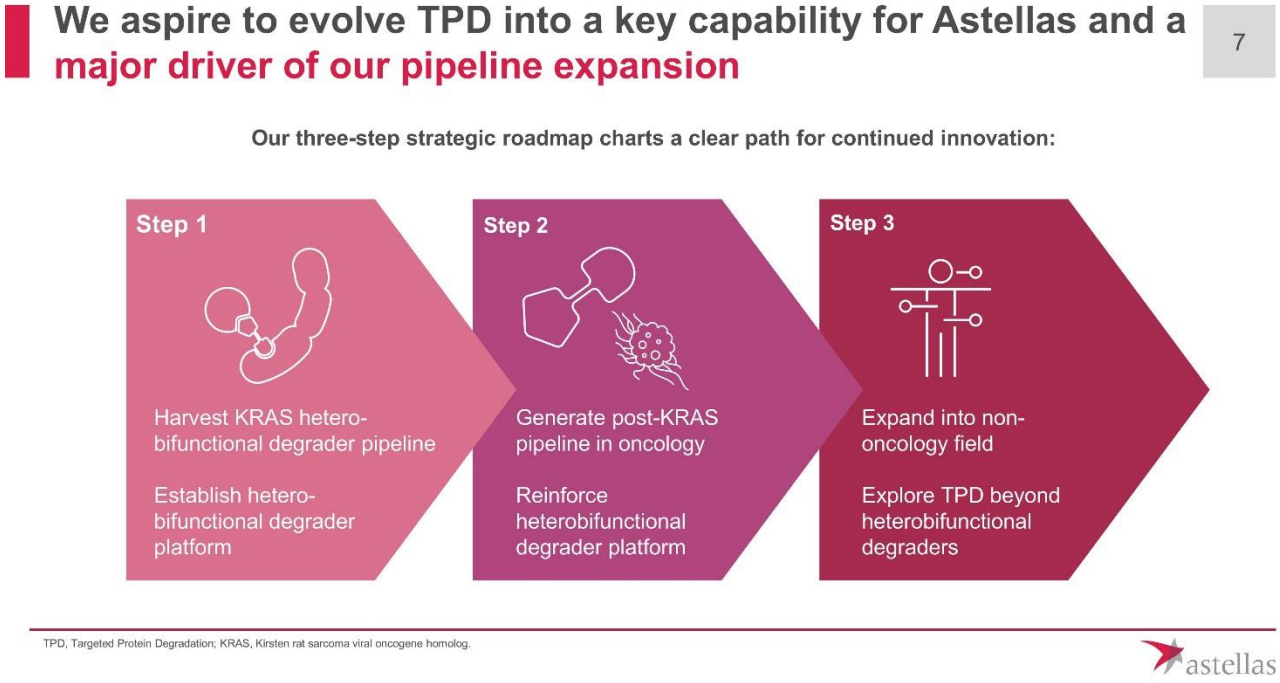
Next, page five. This shows the background of TPD.

Protein dysfunctional mutations responsible for numerous serious and life-threatening or life-altering diseases that interfere with daily life, including cancer, central nervous system diseases, metabolic diseases and immunological disorders.

Traditional small molecule inhibitors have difficulty in sufficiently inhibiting the function of undruggable proteins, which lack active pockets or have flat surface and no characteristic structure. The efficacy of the drug was also limited by factors such as selectivity and cellular resistance.

TPD, by utilizing the ubiquitin-proteasome system—a natural protein disposal process in the body that identifies and degrades and eliminates targets—has the potential to trigger the degradation of undruggable target proteins that cause various diseases.

TPD has three distinct advantages over other modalities. First, unlike conventional small molecule inhibitors, they do not require deep pockets for binding, allowing access to targets that are currently considered undruggable. Second, because of their small size, they can penetrate biological barriers and more deeply into tissues, including solid tumors, allowing them to access targets that are difficult to reach with large molecule therapeutics. And third, because of their high specificity, they can selectively degrade their targets, which may reduce potential toxicity.



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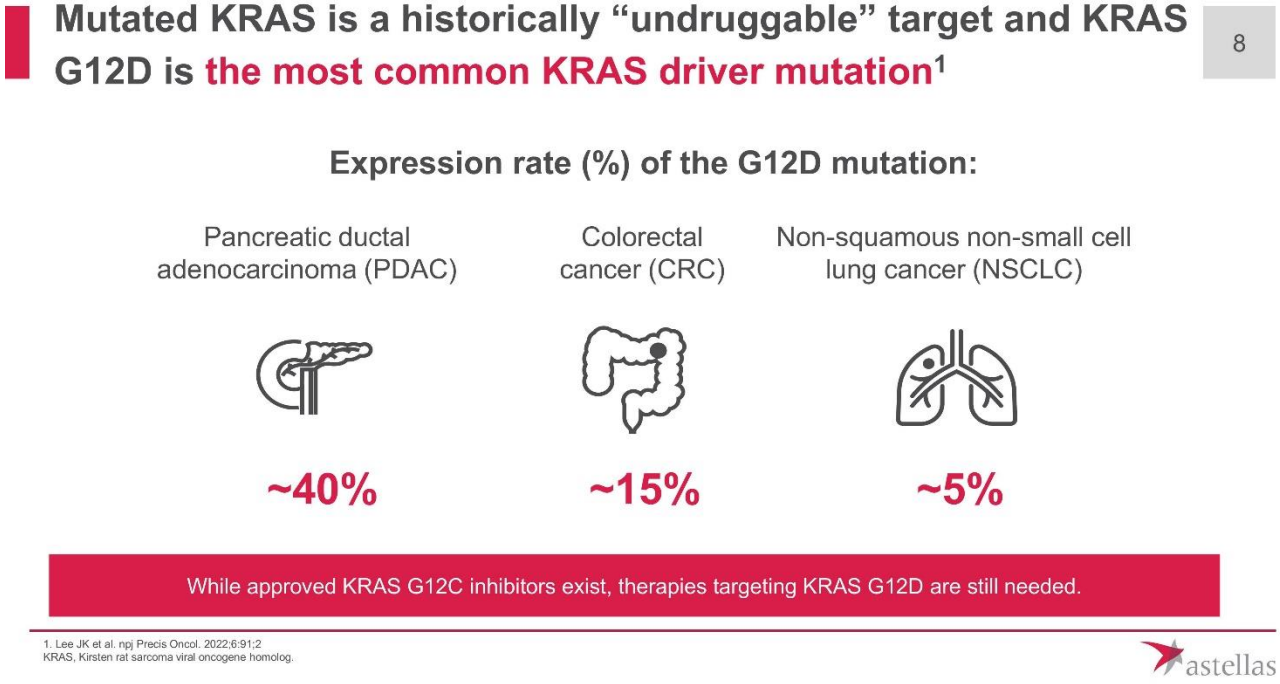
Astellas currently has four primary focuses, and we are confident that we have the expertise and capability to deliver significant impact and meaningful value for patients. As part of primary focus, we are making strategic investments in TPD to accelerate our R&D and making an effort to maximize the potential of our platform.

Starting with our first target, the mutated KRAS protein, we are expanding our capabilities through the acquisition and combination of [various] binders to design compounds with the potential to treat a wide range of diseases.

TPD has a three-step strategic road map for continued innovation. First, we will establish a heterobifunctional degrader platform through a successful program targeting KRAS, which will serve as the foundation for expanding the range of applicable targets. Next, we will leverage our knowledge and experience to build a pipeline of [TODs] following KRAS in oncology. We will then explore further potential for TPD beyond the heterobifunctional degrader.



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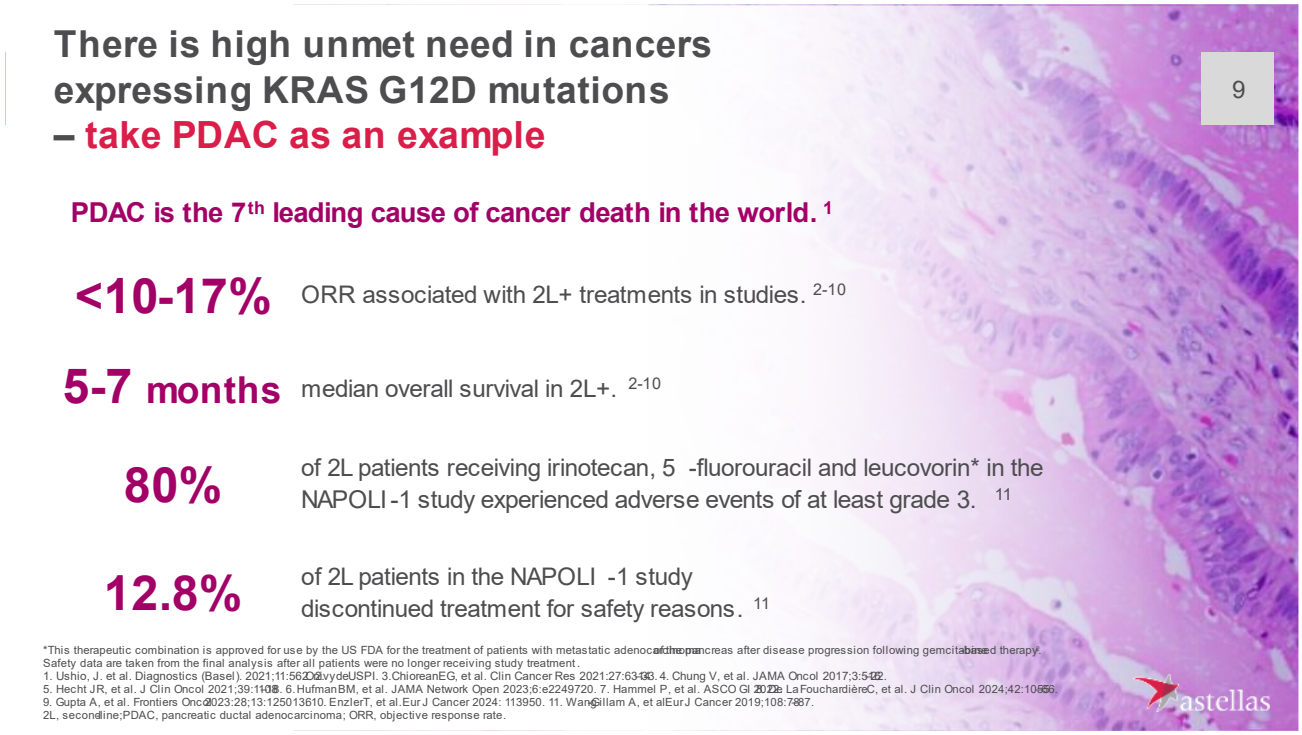
I will explain the background of our initial focus on KRAS, which has traditionally been known as an undruggable target.

Mutations in KRAS protein are known to cause a variety of cancers, and of the approximately 1.8 million new cases diagnosed annually in the United States, 210,000, or 11.6%, have KRAS mutations. The types of these mutations vary, and many are referred to as G12C or G12D mutations.

Drugs for KRAS G12C mutations already exist. On the other hand, G12D mutations are frequently found in pancreatic ductal adenocarcinoma, PDAC, and colorectal cancer, CRC, but there are currently no approved therapies targeting these G12D mutations. We hope to address this significant unmet need.



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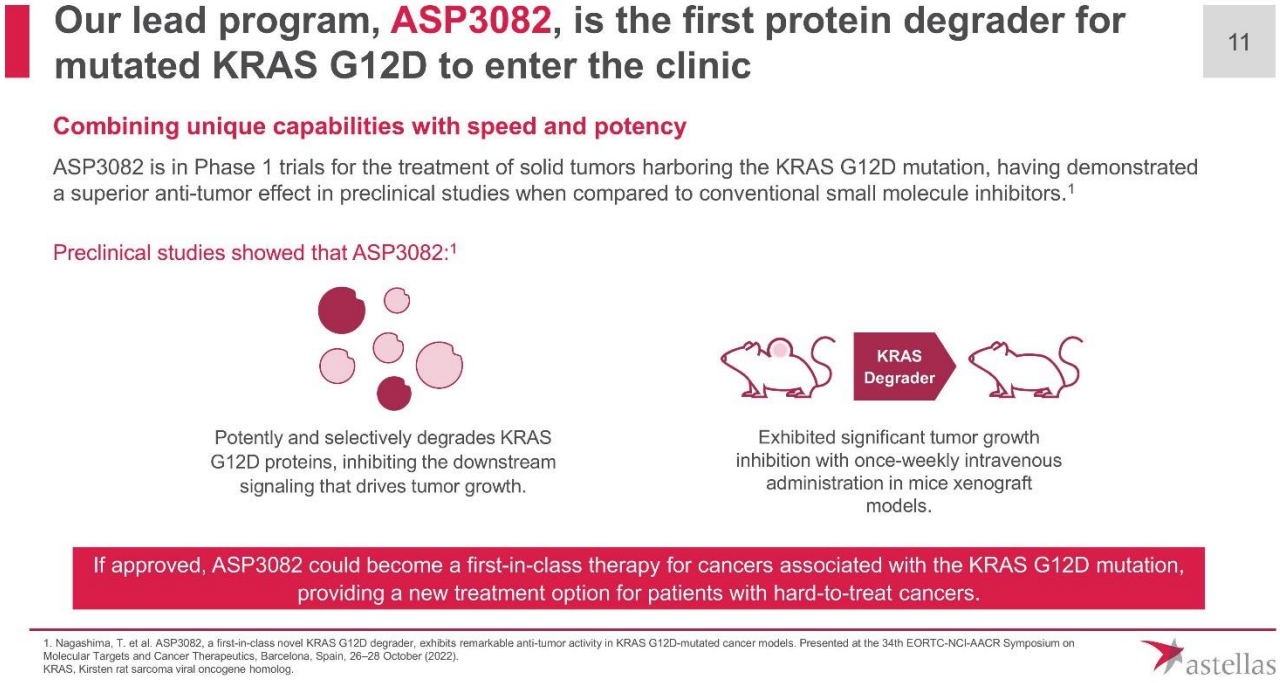
Here, I will discuss PDAC as a representative example of a cancer that is common among patients with KRAS G12D mutations.

PDAC is the seventh leading cause of cancer death worldwide and is known to enjoy limited efficacy with currently available therapies. Even with chemotherapy, which has a relatively high response rate, the median overall survival is only five to seven months. And because these are all chemotherapy regimens, they can cause serious toxicity.

For example, in the NAPOLI-1 trial, 80% of patients receiving irinotecan, 5-fluorouracil, and leucovorin had grade 3 or greater adverse events, and 12.8% discontinued treatment for safety reasons.

Clearly, the patients' needs are not being fully met by the current standard of care.

Next slide, please. I will now describe the progress of ASP3082.



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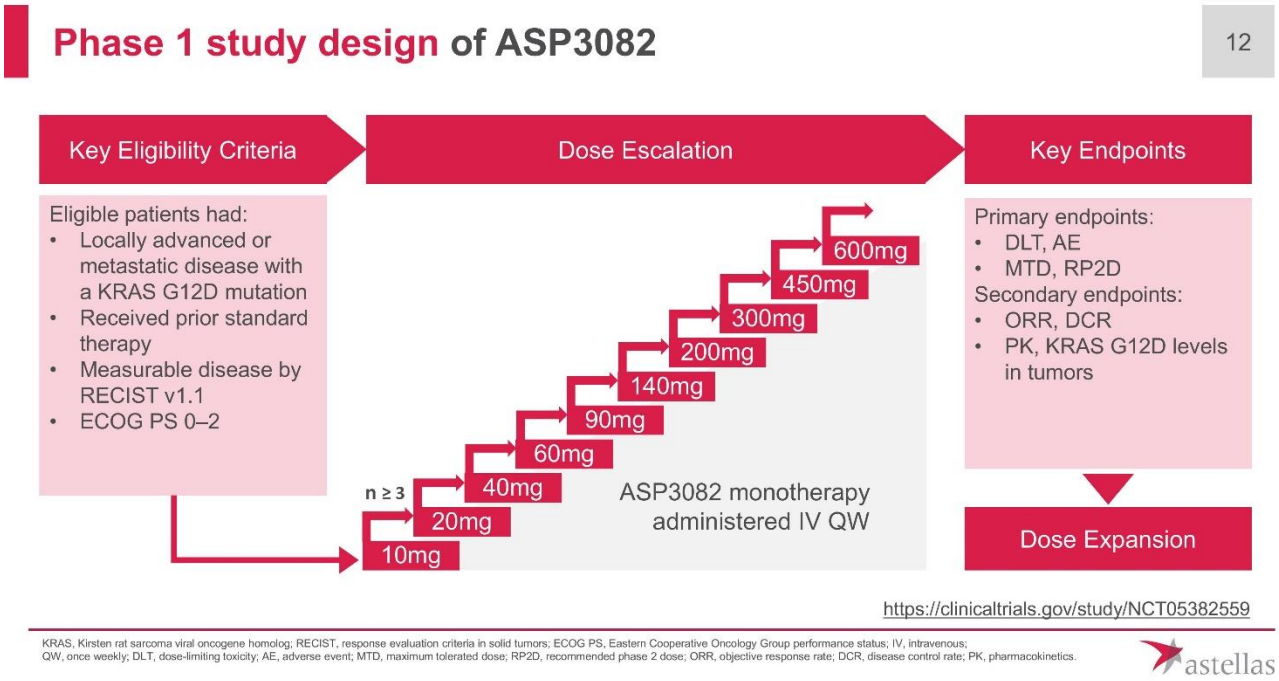
Our lead program, ASP3082, is the first compound to enter the clinical study phase as the TPD targeting the KRAS G12D mutant. A Phase I trial is currently underway in patients with solid tumors having KRAS G12D mutations.

In preclinical studies, ASP3082 has been demonstrating to potently and selectively degrade KRAS G12D proteins and inhibiting the downstream signaling that drives tumor growth. In mice xenograft models, once weekly intravenous administration of ASP3082 demonstrated significant tumor growth inhibition.

We believe that ASP3082 has the potential to become a first-in-class therapy and significantly change the treatment paradigm for cancer patients with KRAS G12D mutations, and we have initiated a Phase I study.



Next, page 12. This slide shows our first Phase I trial design.

This study enrolled patients with locally advanced or metastatic solid tumors who have KRAS G12D mutations and measurable disease. Subjects had previously been treated with systemic anticancer therapy, and there was no upper limit on the number of lines of prior therapy. Therefore, some subjects have significantly been pretreated.

In the dose escalation part of the study, subjects received ASP3082 intravenously once a week over a three-week treatment cycle. The first group received 10 milligrams, and doses were gradually escalated up to 600 milligrams so far.

The primary endpoints are safety related and in order to determine the maximum tolerated dose (MTD) and recommended dose, adverse events, including prespecified dose-limiting toxicity (DLT), are evaluated.

In addition, we also evaluated the therapeutic efficacy, pharmacokinetics, and target expression in tumors, meaning the amount of KRAS G12D mutation protein.

Our Phase 1 study population primarily had advanced pancreatic, colorectal and non-small cell lung cancer

Patient demographics and baseline characteristics

	ASP3082 monotherapy QW	
Characteristic	300–600mg (n = 48)	Overall (N = 111)
Median age, years (range)	66 (39–81)	64 (31–89)
Male, n (%)	30 (62.5)	62 (55.9)
Race, n (%)[a]		
White	21 (55.3)	64 (66.7)
Black or African American	2 (5.3)	8 (8.3)
Asian	15 (39.5)	23 (24.0)
ECOG PS, n (%)		
0	17 (35.4)	39 (35.1)
1	31 (64.6)	72 (64.9)
Tumor type, n (%)		
PDAC	31 (64.6)	74 (66.7)
NSCLC	15 (31.3)	19 (17.1)
CRC	1 (2.1)	16 (14.4)
Other[b]	1 (2.1)	2 (1.8)
Median number of prior lines of systemic anticancer therapy (range)	2 (1–5)	2 (1–7)

Data cutoff was 8 July 2024. [a]Percentages based on the number of patients with non-missing race information. One patient identified multiple races; 15 patients had missing race data. [b]Included 1 patient with gallbladder adenocarcinoma and 1 patient with small bowel cancer.
QW, once weekly; ECOG PS, Eastern Cooperative Oncology Group performance status; PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small cell lung cancer; CRC, colorectal cancer.

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Next slide, please. Page 13.

Study population characteristics generally reflected the demographics of cancer patients with KRAS G12D mutations, with the majority being PDAC and the rest mostly non-small cell lung cancer, NSCLC, or colorectal cancer, CRC.

Regarding other cancer types, one patient had bladder adenocarcinoma and another with a small bowel cancer. The median number of prior lines of systemic anticancer therapy was two, with a range of one to seven lines overall and one to five lines in the high-dose group.

ASP3082 safety profile in doses up to 600mg

Characteristic, n (%)	ASP3082 monotherapy QW			
	Any grade		Grade 3	
	300–600mg (n = 48)	Overall (N = 111)	300–600mg (n = 48)	Overall (N = 111)
TRAEs	43 (89.6)	83 (74.8)	5 (10.4)	7 (6.3)
TRAEs occurring in ≥ 5% of all patients				
Infusion-related reaction	17 (35.4)	21 (18.9)	0	0
Fatigue	6 (12.5)	20 (18.0)	1 (2.1)	1 (0.9)
Rash[a]	10 (20.8)	13 (11.7)	0	0
Urticaria	9 (18.8)	11 (9.9)	0	0
Nausea	5 (10.4)	10 (9.0)	0	0
Pruritus	6 (12.5)	9 (8.1)	0	0
AST increased	6 (12.5)	8 (7.2)	2 (4.2)	2 (1.8)
Vomiting	3 (6.3)	6 (5.4)	0	0

- No Gr4 or Gr5 TRAEs
- Three patients (2.7%) experienced a DLT and discontinued treatment: 2 patients at 450mg (Gr3 ALT increased; Gr3 ALT/AST increased) and 1 patient at 600mg (Gr3 cholangitis and neutrophil count decreased)

Safety evaluation included 111 patients who received ≥ 1 dose of 10–600mg ASP3082. Median duration of treatment with ASP3082 was 5.1 weeks (range: 0.1–59.4). No dose reductions were permitted during dose escalation. MTD has not yet been reached. [a]Included System Organ Class preferred terms of "rash" and "rash maculo-papular".
QW, once weekly; TRAE, treatment-related adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Gr, grade; DLT, dose-limiting toxicity.

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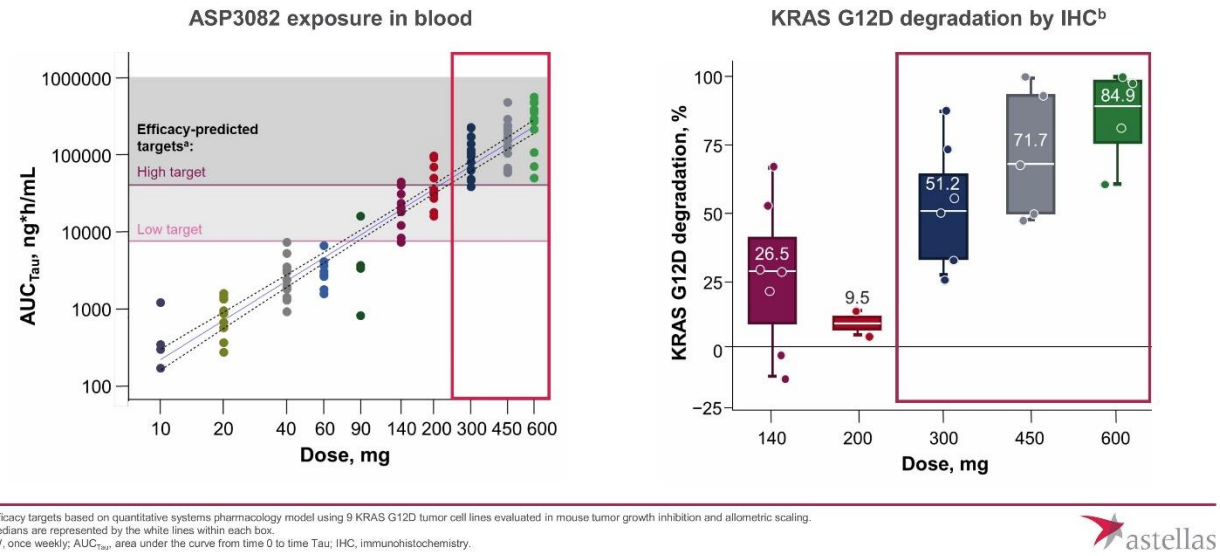
Next slide, please. On page 14, I will explain safety, the primary endpoint of the trial.

The rate of grade 3 adverse events was 6.3% overall in seven patients and 10.4% in the higher dose groups. That's a total of seven patients with a grade 3 event. No patients experienced a grade 4 adverse event or died due to an adverse event.

Three patients discontinued treatment because of DLT, or dose-limiting toxicity. Discontinuation was necessary as the study design did not allow for dose reductions. Two of those patients received the 450-milligram dose. One discontinued due to grade 3 increased ALT, and one due to grade 3 increased ALT and AST. These increases were transient and resolved when the drug was withdrawn.

There were no cases of high flow. One who received the 600-milligram dose discontinued due to grade 3 cholangitis and decreased neutrophil count. The most common adverse events were infusion site reactions, which did not reach grade 3.

ASP3082 exceeded target exposure in the body ≥ 300mg QW and KRAS G12D was degraded in a dose-dependent manner



[a]Efficacy targets based on quantitative systems pharmacology model using 9 KRAS G12D tumor cell lines evaluated in mouse tumor growth inhibition and allometric scaling.
[b]Medians are represented by the white lines within each box.
QW, once weekly; AUC_{Tau}, area under the curve from time 0 to time Tau; IHC, immunohistochemistry.

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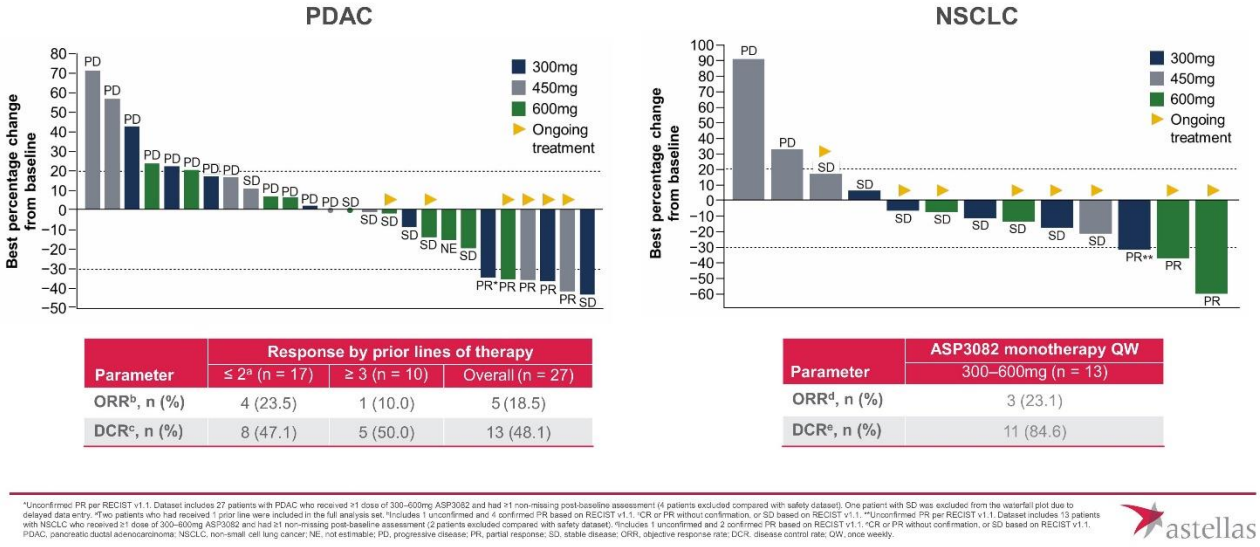
Next page, please. On page 15, I'd like to put the clinical data in context by looking at what ASP3082 does in the body.

The graph on the left shows drug exposure in the blood by area under the curve over the whole time period per dose level. You can see that the 300-milligram dose AUC demonstrated that the high target AUC was achieved in the majority of patients.

The graph on the right shows KRAS G12D mutant protein degradation levels at each dose. Dose-dependent G12D protein degradation was observed with increasing doses, especially in doses above 300 milligrams, which exceeded the high target AUC, as was shown by the PK analysis.

Based on these results, we want to focus on the patients who received 300 milligrams or more when we look at the efficacy endpoints.

Antitumor activity was observed in patients with PDAC and NSCLC receiving doses between 300–600mg



Parameter	Response by prior lines of therapy		
	≤ 2[a] (n = 17)	≥ 3 (n = 10)	Overall (n = 27)
ORR[b], n (%)	4 (23.5)	1 (10.0)	5 (18.5)
DCR[c], n (%)	8 (47.1)	5 (50.0)	13 (48.1)

Parameter	ASP3082 monotherapy QW
	300–600mg (n = 13)
ORR[d], n (%)	3 (23.1)
DCR[e], n (%)	11 (84.6)

*Unconfirmed PR per RECIST v1.1. Dataset includes 27 patients with PDAC who received ≥1 dose of 300–600mg ASP3082 and had ≥1 non-missing post-baseline assessment (4 patients excluded compared with safety dataset). One patient with SD was excluded from the waterfall plot due to delayed data entry. [a]Two patients who had received 1 prior line were included in the full analysis set. [b]Includes 1 unconfirmed and 4 confirmed PR based on RECIST v1.1. [c]CR or PR without confirmation, or SD based on RECIST v1.1. **Unconfirmed PR per RECIST v1.1. Dataset includes 13 patients with NSCLC who received ≥1 dose of 300–600mg ASP3082 and had ≥1 non-missing post-baseline assessment (2 patients excluded compared with safety dataset). [d]Includes 1 unconfirmed and 2 confirmed PR based on RECIST v1.1. [e]CR or PR without confirmation, or SD based on RECIST v1.1. PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small cell lung cancer; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease; ORR, objective response rate; DCR, disease control rate; QW, once weekly.

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Next page, please. On page 16, we have the waterfall plots for patients with PDAC and NSCLC who received 300-milligram to 600-milligram doses.

PDAC is shown on the left. You can see that there is some promising antitumor activity. It is important to note that this study enrolled a heavily pretreated population. ORR in PDAC was 18.5%, and the disease control rate, DCR, was 48.1%. In the patients who received one or two prior lines of therapy, the ORR was 23.5%, and DCR was 47.1%. In four out of five cases, their responses were confirmed per RECIST v1.1.

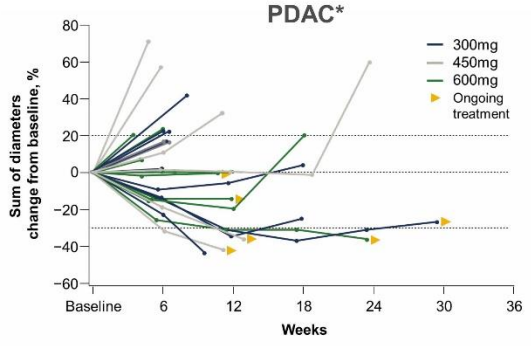
While the response rate in 10 patients with at least three prior lines of therapy or more was 10%, 50% achieved disease control. For your reference, ORR for third-line PDAC with chemotherapy is single digit in general. No true standard of care exists.

On the other hand, in the NSCLC group, 3 out of 13 patients, or 23.1%, achieved a response, and the majority, 11 out of 13, or 84.6%, achieved disease control.

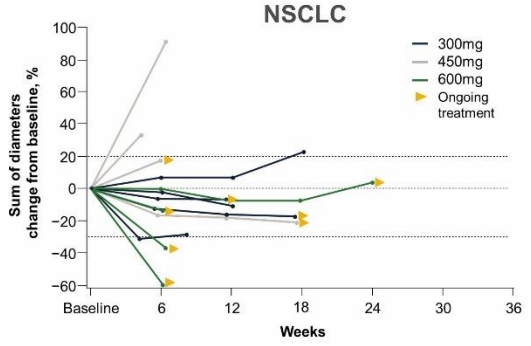
Treatment is ongoing in six patients with PDAC and the majority, 8 out of 13 patients with NSCLC.

Responses to ASP3082 over time in patients with PDAC and NSCLC

17



- At data cutoff, 6 of 27 (22.2%) patients remained on treatment
- DOR and PFS endpoints were not mature at data cutoff
- For 5 patients with PR, median time to response[a] was 2.6 months (range: 1.4–3.0 months)



- At data cutoff, 8 of 13 (61.5%) patients remained on treatment
- DOR and PFS endpoints were not mature at data cutoff
- For 3 patients with PR, median time to response[a] was 1.4 months (range: 1.0–1.5 months)

*Dataset includes 27 patients with PDAC who received ≥1 dose of 300–600mg ASP3082 and had ≥1 non-missing post-baseline assessment (4 patients excluded compared with safety dataset). One patient with SD was excluded from the spider plot due to delayed data entry. [a]Time to response was defined as time from the start of the study intervention until the date of best overall response without confirmation by investigators per RECIST v1.1. PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small cell lung cancer; DOR, duration of response; PFS, progression-free survival; PR, partial response.

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Next page, please. On page 17, I will explain these patients in more detail, including those who are still on treatment.

Duration of response (DOR), and progression-free survival (PFS), endpoint data were not mature in either group at this data cutoff. Nonetheless, we can see that the subset of patients is continuing on treatment for some time.

For patients who had a partial response (PR), median time to response was 2.6 months for the five cases in the PDAC group and 1.4 months for the three cases in the NSCLC group.

The results and safety profile of ASP3082 support further clinical investigation

18

Safety profile in doses up to 600 mg

Dose-dependent degradation of KRAS G12D mutant protein

Antitumor activity in patients with PDAC and NSCLC

NEXT STEPS

- Phase 1 study ongoing, as a single agent or in combination therapy regimens[1]
  - PDAC: 2L+ monotherapy, 1L combo w/ chemo
  - NSCLC: 2L+ monotherapy
  - CRC: 2L+ monotherapy, combo w/ cetuximab
- Proof of Concept (PoC) judgment anticipated for 1H CY2025

1. https://clinicaltrials.gov/study/NCT05382559.
KRAS, Kirsten rat sarcoma viral oncogene homolog; PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; CY, calendar year.

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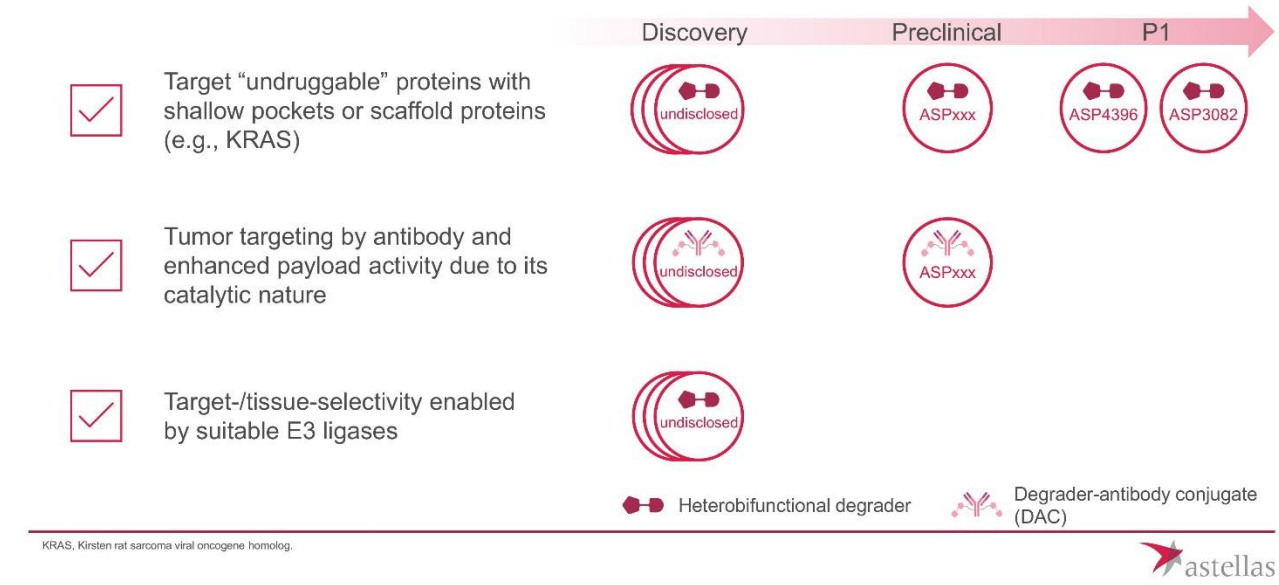
Next, page 18, which shows these results demonstrating the promise ASP3082 may hold for patients with KRAS G12D positive solid tumors.

In summary, we saw from the study data, a safety profile in doses up to 600 milligrams, dose-dependent degradation of the KRAS G12D mutant protein and antitumor activity in patients with PDAC and NSCLC. These results warrant further clinical investigation of ASP3082.

At present, Phase I study is ongoing, exploring ASP3082 as a single agent and in combination therapy regimens. We anticipate proof-of-concept judgment by 1H of calendar year 2025.



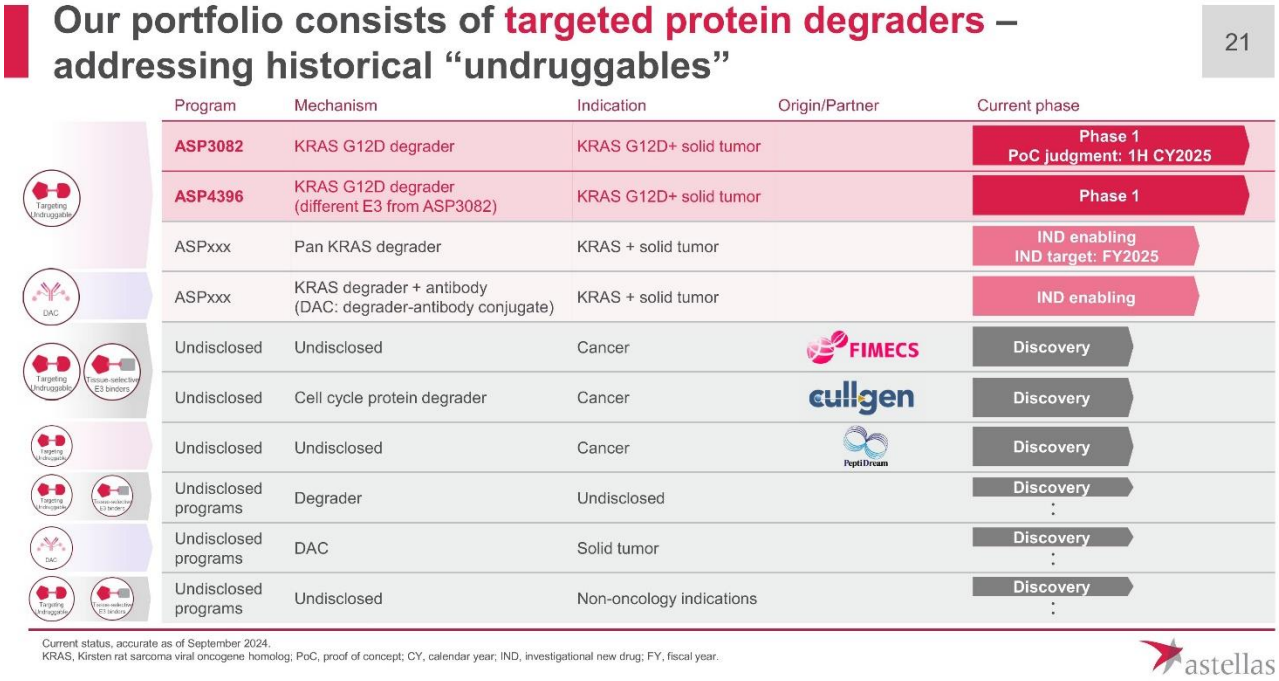
Next page, please. From here, I will explain the latest status of our TPD pipeline. Page 20.

In this primary focus, our robust early research pipeline leverages the advantages of protein degraders.

A number of our programs, including ASP3082 and ASP4396, reflect our capability to target undruggable proteins with shallow pockets, such as KRAS or scaffold proteins, which conventional inhibitors have difficulty to inhibit the functions completely.

We are also exploring targeting tumors through our DAC or degrader-antibody conjugate programs, leveraging the enhanced payload activity that stems from the catalytic nature of protein degraders.

Through our pipeline, we are also leveraging the target- and tissue-specific, tissue-selectivity made possible by the wide range of E3 ligases.



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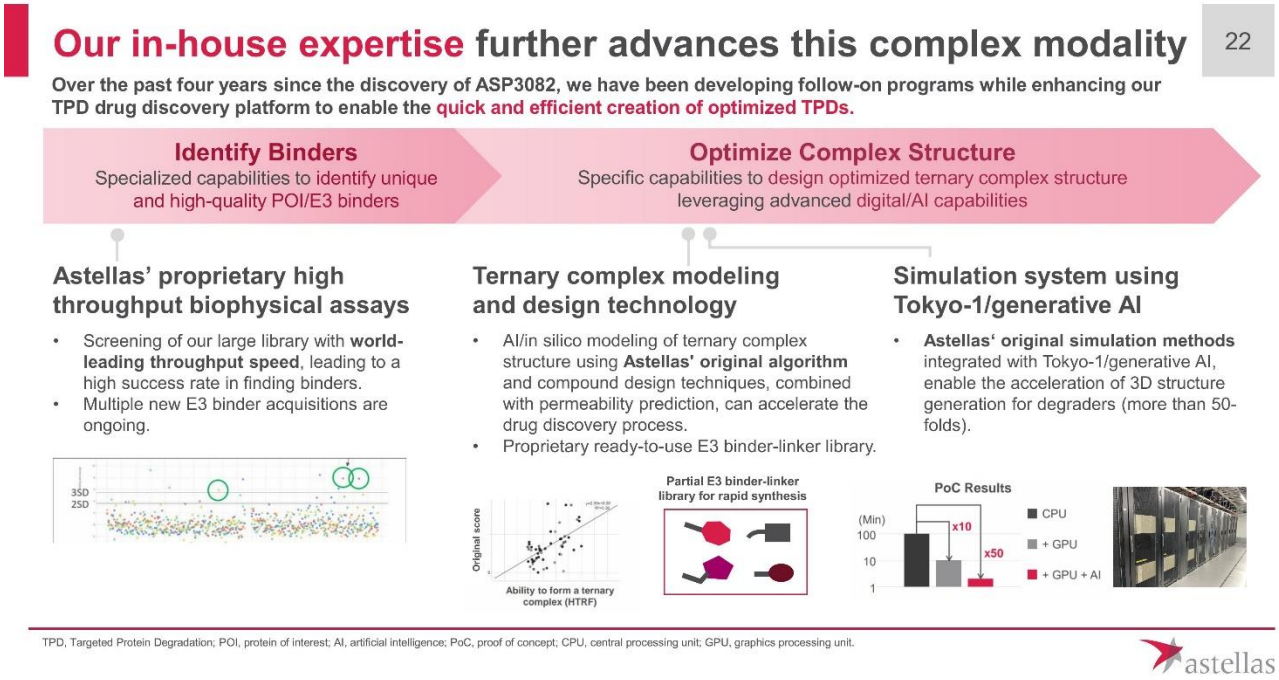
The speed with which we are now building follow-on programs and expanding our pipeline reflects the expertise and commitment Astellas Pharma brings to advancing TPD.

We have the in-house drug discovery capabilities to create optimal targeted protein degraders quickly and efficiently, including state-of-the-art modeling technology, highly efficient molecular synthesis technologies, robotics, and AI.

As I mentioned on the previous page, in terms of clinical stage assets, we also have ASP4396, which is also looking at degradation of the KRAS G12D mutant protein in solid tumors. We also have several assets in the preclinical or discovery phase, including some we are exploring in collaboration with our innovation partners.



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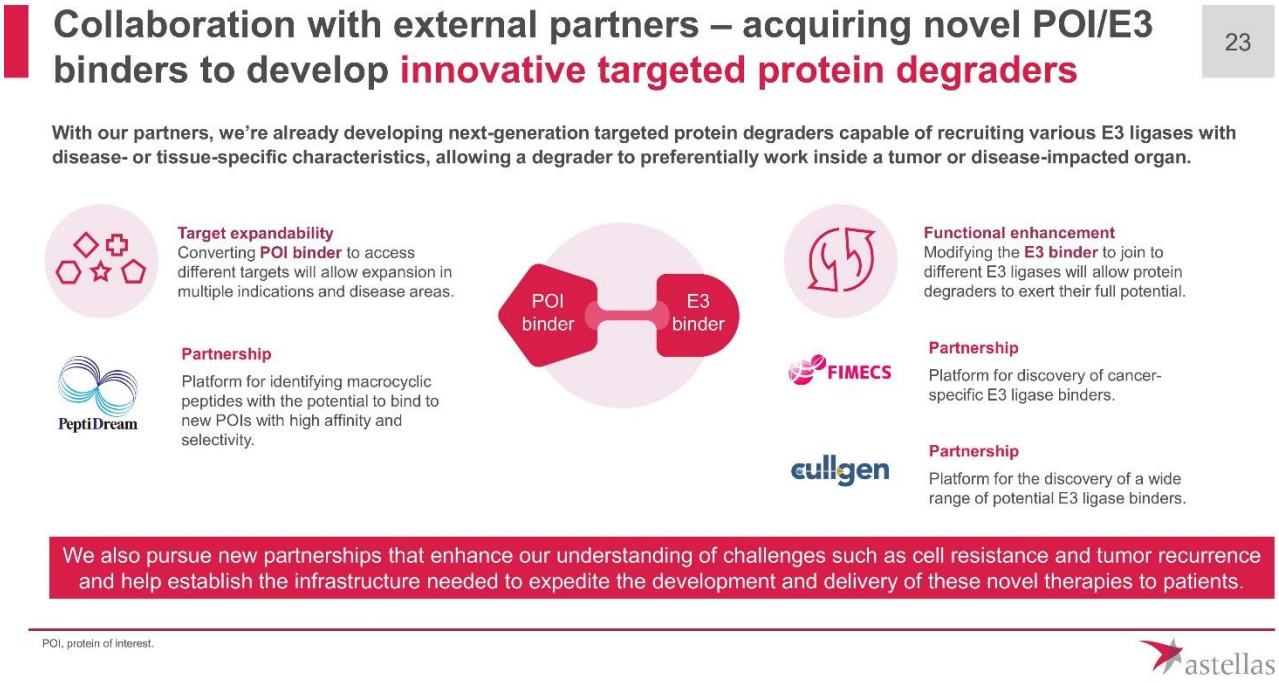
Our capabilities are helping us to move quickly and efficiently to optimize TPDs and rapidly create new candidates. Through our partnerships and team of in-house experts, we can leverage our combined specialized capabilities to identify unique and high-quality constituents for each part of a degrader.

We can also mix and match different proteins of interest and E3 ligase binders connected by the linker to design optimal TPD compounds with the potential to treat a wide range of diseases with high efficacy, specificity, and duration of action.

Astellas Pharma's advanced AI simulation technology, Tokyo-1, robotics capabilities, will enable us to automate the rapid modeling and simulation of TPDs.



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To accelerate progress of TPDs, Astellas Pharma builds win-win partnerships with like-minded organizations that complement our areas of expertise.

In TPD, our specific areas of partnering interest are proprietary protein of interest binders for historical undruggables, proprietary E3 ligase binders that are tissue or tumor-specific or allow for longer action, molecular design technology for degraders, including molecular glues, and antibody degrader conjugate or peptide degrader conjugate platforms.

We are also pursuing new partnerships to help overcome challenges, such as cell and tumor resistance, and to help establish the infrastructure needed to expedite these novel therapies to patients.

Next page, please.

For all of us at Astellas Pharma, it's about the patients we could help. The most important is our contribution to patients. We believe that pioneering developments in TPD could reshape and redefine what's possible in treating some of the world's most devastating diseases.

That's why we are committed to making the strategic investments needed in TPD to accelerate our ambitious work and unlock the transformative value of TPD for patients and their families who urgently need our help and new treatments.

That's all for me. Thank you very much for your attention.

Question & Answer

Ikeda [M]: Thank you very much. Now, we would like to entertain your questions.

First question, Citigroup Securities, Mr. Yamaguchi, please.

Yamaguchi [M]: Can you hear me?

Ikeda [M]: Yes, we can.

Yamaguchi [Q]: Thank you very much. Yamaguchi from Citi. I have a couple of questions.

First of all, ASP3082, PFS, DOR, the data have yet to be available at the time of the ESMO. PFS, two months that might be considered quite interesting if it is two months, and looking at the current one, tow months, that means up until eight weeks and PDAC also showing that level of the data.

Currently, again, the data is not available, so it might be difficult for you to make a comment, but roughly speaking, what would be the PFS in the case of PDAC? Could it be expected if you're looking at the discharge?

Sakata [A]: Thank you for your question.

With regard to the analysis, again, we haven't had the results yet, so difficult to answer, but from our perspective, as for the current situation of this Phase I study, we are quite positive.

So, Ahsan, about the interpretation of the currently available data, could you make some comments, if you have any?

Arozullah [A]*: Thank you, Chinatsu, and thank you for the question. This is Ahsan Arozullah. I'm the Head of Oncology Development here at Astellas Pharma.

Regarding the question of duration of therapy, duration of response, and PFS, we are not currently able to provide an accurate estimate of that time frame. What we can share, as shown on the slide currently, is that we still have several patients that have ongoing treatment, particularly in PDAC as well as with lung cancer, and in these patients, we are very encouraged that they are continuing on treatment. As that data matures at these dose levels as well as at higher dose levels, we will bring that data forward as quickly as possible.

Yamaguchi [Q]: Thank you. I would like to go to the next question. Yes, please. The coming a pipeline, I think you have several, like, next generation on the pipeline and DAC that is a conjugate with antibody is also available. What's your expectation level of this modality? Of course, you haven't done anything, so you don't know, but you have the anti-body and also this drug and such. So, in order to enhance your portfolio, what would you do on DAC?

Sakata [A]: Thank you for the question.

Making use of the technology of the DAC, the tumor targeting and also protein degrader efficient delivery will be achieved. That leads to the enhanced efficacy. That is what we are expecting.

Hayakawa-san, would you please make additional comment on this?

Hayakawa [A]: I'm Hayakawa, in charge of the research side. Thank you very much for your question.

Just as Sakata explained to you, ADC is a platform that we are expecting a lot from. Safety and efficacy are both quite expected or promising. As for the safety, the degrader is attached onto the antibody, so delivery would acquire the select ability. Depending on the antigen selection, delivery select ability would be possible, and payload, usually for ADC, chemo agent is utilized.

So, from the perspective of toxicity, degrader is an extremely high safety program that we can make. That is also promising. As for the efficacy, the selection of antigen and also degrader combination, so just like the case of the combination, although here, we use just one drug, but that level of efficacy can be expected.

Also, as I already explained, degrader basically tends to be the larger molecules compared to the conventional inhibitor. Of course, it goes through the membrane, but if it is compared, that part might be the weakness, but it will be on the antibody and get into the cells. Therefore, that hurdle can be removed. Once it goes into the cancer cells, then in a catalytic manner, degrader would work. So just with one molecule, multiple targets can be degraded. That's what I think, and by binding this to the antibody, half-life can be extended. Patients' burden can be reduced and also the number of dosing can be reduced. That's what we can expect.

Yamaguchi [Q]: Thank you very much.

Next, Mr. Wakao from JPMorgan Securities, please.

Wakao [M]: Thank you very much. Wakao from JPMorgan. Can you hear me?

Ikeda [M]: Yes.

Wakao [Q]: Thank you. It's very interesting. I have a few questions to you.

First, antitumor activity, dose dependency was evaluated in terms of the antitumor activity and the recommended dose, any possibility that you would go beyond 600 milligrams? What is the definition of POC?

As for dose dependency, G12D degradation is being seen, according to my understanding, but antitumor activity, the sample size is still small, so it's very difficult to see antitumor activity. How do you evaluate this? Based on this data, you may be able to go higher than 600 milligrams. I'd like to know that.

Also, POC, you go to the dose expansion cohort, if you have good data, is that what you define as POC? I'd like to confirm.

Sakata [A]: Thank you for your question.

Yes. As you said, regarding dose dependency at each dose, the sample size is small, so as of now, we cannot say there is a clear dose dependency; however, in the dose expansion cohort, we'd like to check it.

As to your second question, dose higher than 600 milligrams, dose escalation is still ongoing, and we are currently studying doses higher than 600 milligrams as well. So, once the data is available, we'd like to share this in the future.

As for the POC criteria, which is your last question, as you suggested, in the dose expansion cohort, we'd like to continue the study to further explore the efficacy. Once we obtain sufficient data, we would carefully evaluate the data in totality to judge POC.

Ahsan, anything to add from your side?

Arozullah [A]*: What I can share is that we have been able to dose higher than 600 milligrams, and so we are continuing to increase the dose. Appreciating that what we have been able to demonstrate to date is that at the 600-milligram dose, we see significant degradation of the target protein, which is very encouraging from a pharmacological perspective. And we hope to be able to continue to expand and extend the dose to higher doses to see if we can even increase the degradation to a higher extent. So, that is our current status within the study right now, dosing patients at doses higher than 600 milligrams.

Wakao [Q]: Thank you very much.

Then, as of now, you're still in the dose escalation phase, and next year, by the end of June, the dose will be determined, and you would achieve the results of the dose expansion cohort. Is my understanding correct?

Sakata [A]: Yes, your understanding is correct.

Wakao [Q]: Understood.

Next, regarding the targeted protein degraders, you entered the clinic, and you have data. You have the clinical data, and you are ahead in development, including other modalities. There are competitors, so I'd like to know the situation in terms of the competition. RMC-6236 by Revolution Medicines, I'd like to know your competitive edge. You may not have that much data. It may be difficult to compare, but 3082 vis-a-vis 6236 by Revolution Medicines, do you see any superiority or competitive edge with 6236 by Revolution Medicines, how to win the competition? I'd like to hear your view on your strategy.

Sakata [A]: Thank you for your question. ASP3082 and RMC-6236 pan-KRAS inhibitor from Revolution Medicines. I think your question is about the differentiation between those two.

I believe you already have understanding, and ASP3082 is targeting KRAS G12D mutation. It is specifically a degrader. This is heterobifunctional. RMC-6236 is a noncovalent pan-RAS inhibitor. The clinical data by Revolution Medicines and our clinical data based upon those results, ASP3082 and RMC-6236 safety profile shows the differences. As has been introduced within the presentation, ASP3082 shows the favorable safety profile, and in the future, when it is combined with other drug in the combination therapy, this drug is expected to be quite promising. From other clinical data, we could say in that way. Also, on top of that, theoretically, degrader and inhibitor, so the resistance-related mechanism is likely to be different. That's what we are expecting. So, with a degrader, the longer efficacy period or the response period might be able to gain. That is also what we are expecting. That is something we would like to confirm within the dose expansion study.

Wakao [Q]: Thank you very much. So, if we're focusing on G12D and protein degrader capabilities higher than 6236, the data focusing on G12D, do you know that kind of data?

Sakata [A]: Well, first of all, RMC-6236, this is an inhibitor, so this does not degrade protein. That's what I think. But the G12D mutation focusing analysis, well, actually, we do not analyze other companies' data, so currently, there is no comparison, just focusing on that aspect. What we are doing is the overall analysis based upon the information disclosed by Revolution Medicines. That's also our intention to do for the future as well.

Wakao [Q]: Thank you very much, and one last question from me.

As one of the characteristics of 3082 is the favorable good safety profile, this is one of the characteristics that can be expected on to other TPD as well?

Sakata [A]: Thank you for the question.

So, we, yes, came up with such a favorable safety profile for 3082. Of course, it depends on the targeting protein because on-target toxicity would happen. So, I think the result depends on the targeting protein, but PROTAC itself derived toxicity, that concern is greatly eliminated. That's what I think.

Wakao [M]: I understand. Thank you very much. That's all.

Ikeda [M]: Thank you.

Next question, BofA Securities, Mr. Mamegano.

Mamegano [Q]: Mamegano, thank you very much. Thank you for the clear explanation. I also have a couple of questions.

First of all, the administration, this is once-weekly administration, I believe. According to PK data, AUC alone is available. There is no T half data. But for the dosage and administration, once-weekly administration is going to be continued as a development or twice weekly or once biweekly or three weeks, one time per three weeks, that will be also considered? Also, in the future, do you think that this could be possible to be developed as the oral therapy as well?

Sakata [A]: Thank you very much for the question.

Well, the dosage and administration system, yes, once-weekly IV is what it is. The coming development plan will be decided based upon the available data, and the same is applied to the study design that requires further discussion. But basically, the once-weekly IV is what we would like to stick onto for the upcoming development. Having said that, of course, we consider about the convenience of the patients, and based upon the data, Q2 weeks, Q3 weeks could be available or possible. We would like to continue the development of that as well.

Regarding the second question about the formulation, as of now, ASP3082 to be given orally, converting this to an oral drug, we are not planning such a formulation. In principle, it's going to be an injectable. We'd like to continue development with, in principle. But like the administration, given the convenience for the patients, if there is going to be an appropriate formulation, we could identify, we'd like to continue studying those possibilities.

Mamegano [Q]: Thank you very much.

Regarding 3082 and its data, the safety profile was very good. It's maybe easy to consider combinations, so we have high expectations. But on the other hand, sorry for a mean question, the target rather than the compound, if it's an inhibitor for the driver gene, EGFR activation mutation genes, inhibitors seem to be more efficacious. This time, KRAS mutation, when you check the cancer, it's seen at a high frequency, but is that related to the actual incidence of cancer? And its contribution to cancer asset compared to other driver genes, it may not be so strong. So, I think it may be related to the efficacy. Any insights you may have?

Sakata [A]: Thank you for your question. It's a very difficult question.

KRAS G12C inhibitors, Revolution Medicines, RMC-6236, looking at their results, this is my personal opinion, but I don't think there is such a big gap and variance. So, this is within the range of expectations in terms of the efficacy in our opinion, but the sample size is still small, and we will have a dose expansion part we are going to implement. And how the efficacy is going to change, please watch carefully.

Mamegano [M]: Understood, thank you very much. So KRAS as a driver gene is functioning as well with this much efficacy as a drug, it can be helpful. That's how I understood. Thank you very much.

Ikeda [M]: Thank you very much.

Morgan Stanley MUFG Securities, Mr. Muraoka, please.

Muraoka [Q]: Hello, Muraoka from Morgan Stanley. Thank you for your time and the presentation.

It may be too early to discuss this, but there was a mention of resistance. Compared to inhibitors, your drug may not develop resistance very much, but as of now, you're still in Phase I. Any signs of resistance when looking at the data in patients, no such sign? It's not going to be a drug which would develop resistance. G12C is more likely to have resistance. So, can I expect such a profile?

Sakata [A]: Thank you for your question.

Yes, you're right. As of now, we cannot conclude yet that there could be no resistance. The observation period is still short, and the sample size is small. Degraders with less resistance, it's difficult to conclude that way as of now. But regarding the resistance, when more data becomes available, we would proceed with analysis. What's the difference in the mechanism of resistance compared to inhibitors, translational science research through that, we'd like to look into this.

Muraoka [Q]: Thank you very much.

I didn't go to ESMO, so I didn't see your presentation at the venue, but according to the presentation today, PDAC and NSCLC data was shared. What about CRC? You didn't show the clinical data in CRC. Did you find any promising data in CRC as well or there was a difference?

Sakata [A]: Thank you for your question.

Regarding safety analysis, PDAC, NSCLC, CRC for all these three cancer types in a mixed manner, the analysis was conducted. But high dose that we expect the efficacy in 300-milligram to 600-milligram range, we have just one CRC patient, so it's currently unanalyzable. Therefore, for your efficacy analysis, it was excluded.

Muraoka [Q]: Thank you.

Last question is ASP4396 following ASP3082. Looking at page 21, E3 is different. That's what is said. What is improved there is just a difference of E3 when it comes to the ASP4396, or there is something else, meaning that ASP3082 has some more potential to be improved in such and such. In that perspective, is there anything that you can share with us?

Sakata [A]: Thank you for your question.

As of now, for ASP4396, data is not disclosed. So, which specifically is different in what extent is, rather, we would like to refrain from telling you about that. This compound, just like ASP3082 is targeting KRAS G12D mutation, so ASP4396 is a successor of ASP3082 in conducting a Phase I study, and character might be different.

Muraoka [Q]: Thank you.

For example, E3 capacity of the degradation, if that is higher, or is 300 milligrams to 600 milligrams, but you might be able to reduce the dose if the ALT data are available, but in those perspectives as well, you might

be able to improve the safety further. That is, though, my imagination. Is that something also you are assuming? Or do you think that could happen?

Sakata [A]: Well, again, data is not disclosed yet, so it's difficult to make a comment, but we are expecting that the good profile difference would appear. That in our mind, we are continuing clinical phase. When the result is available to be disclosed, then we would like to share that with you.

Muraoka [M]: Thank you. That's all.

Ikeda [M]: Thank you very much.

Next, Mizuho Securities, Mr. Tsuzuki, please.

Tsuzuki [Q]: Thank you for the presentation.

In my understanding, with regard to the addition from ESMO, safety is high, combination is possible, the dose might be expanded further and also drug resistance. Well, other protein degraders are not showing any resistance, so that's very good information for me.

Now, the question is about ORR. So, ORR high characteristics, although the number of the subject sample size is limited, but is there any observation about that? Again, the sample size is limited. Is it possible for you to make some comment about this ORR high people?

Sakata [M]: Thank you for the question. Well, your question is, is there any difference in a high dose?

Tsuzuki [Q]: No, the characteristics of those with a responder. It's very difficult for pancreatic cancer. Now, you're trying to expand the dose, but at this moment, you already achieved 20% of ORR. Therefore, the question is about the characteristics of the patients who are showing you such a high level of response.

Sakata [A]: The characteristics of the responders so far, some common characteristics. That's what we don't know from my side.

But Ahsan, is it possible for you to make some comment on this?

Arozullah [A]*: Yes. Thank you for the question.

This is a question that we're very interested in exploring further in understanding whether there is some additional targeting or identification of patients who are responding to ASP3082. We're currently doing a lot of additional translational-type analysis of these patients. We've successfully been able to achieve biopsies, post-treatment biopsies, in many of these subjects, and one of the things that we're particularly interested in is whether there are any co-mutations, additional mutations that may exist in these patients that may predict response. At this time, we do not have any confirmatory or conclusive data to be able to identify these responders ahead of treatment, but that is something that is of great interest to us.

Tsuzuki [Q]: It was very clear. Thank you very much. One additional question.

As Muraoka-san asked the question earlier, for ASP4396, what could be the potential differences in characteristics? You can expand the dose for ASP3082 with good data. E3 ligase is going to be different between the two compounds of your company. Anything you can still comment on this?

You are also considering DAC as well of target and effect. To avoid that, you are considering DAC. Could you comment further on ASP4396?

Sakata [A]: Thank you for your question.

You have high expectations, so we are very grateful. ASP4396, once data becomes available, we'd like to share that with you. So, in the near future, we hope to present. So, I hope that you can look forward to such an occasion.

Thank you very much.

Ikeda [M]: Thank you very much.

Next, Daiwa Securities, Mr. Hashiguchi, please.

Hashiguchi [Q]: Hashiguchi speaking. Thank you very much.

First, ASP3082 development is going forward. Monotherapy dose expansion in parallel in the near future, exploratory study in combination therapies would be started according to your plan, or POC would be determined in monotherapy, and then you would consider combination therapies. What is the schedule?

Sakata [A]: Thank you for your question.

ASP3082, right now, monotherapy assessment is ongoing. In addition, combination therapy Phase I expansion cohort is already ongoing. So, we'd like to develop better dosage and administration.

Ahsan, anything to add regarding the future development outlook?

Arozullah [A]*: Thank you, Chinatsu.

From a patient perspective, we do appreciate that treatment for pancreatic cancer, in particular, is very challenging, and we do see the greatest potential value that we could bring to these patients would be if we could combine ASP3082 with standard of care treatment in the first line to really improve upon that standard of care. With that in mind, we have already initiated those combination therapy regimen cohorts, and as you noted, we have not necessarily waited just for a proof of concept with the monotherapy, but with the adequate response data that we've observed so far, we have begun to move forward into combination therapy.

Hashiguchi [Q]: Thank you very much. One more question. TPD pipeline as a whole, I have a question to you.

In 2022, you had an explanatory meeting. Compared to that schedule back then, ASP3082 and pan-KRAS are slightly behind schedule, it seems. In the previous meeting, without partner, you were promoting the programs in solid tumors on your own, you were at the stage to optimize the programs, but looking at the current pipeline, I couldn't find anything which corresponds to that. What are the factors behind for the situation of your portfolio? I appreciate your comments.

Sakata [A]: Thank you for your question.

As you said, ASP3082 timeline, dose escalation, depending on number of doses, it can be subject to change in oncology studies. This could happen. So, also for ASP3082, we are aiming for higher doses because of the better safety than expected. So, we are going to higher doses. There is a need to evaluate higher doses. That's why it may look as if it's behind the schedule.

As for the pipeline, we are hoping to proceed with all the pipeline compounds as scheduled. We are doing our best. But internally, the best compound we'd like to deliver to patients, so we are doing optimization activities to move forward our portfolio right now for the pipeline.

Hashiguchi [Q]: Thank you very much.

The best compound would be identified, and in that process, TPD project specific difficulties exist in your opinion? Or in the conventional drug discovery methodology, the difficulty of R&D in preclinical and drug discovery stages is not very different. What are your feelings right now?

Sakata [M]: Thank you for your question. Hayakawa is going to answer that question.

Hayakawa [A]: Thank you for your question.

TPD, conventional molecules, the difference between those two are that, well, the compounds are relatively bigger, so it is difficult to pursue the drug-like aspect. So, from that perspective of drug-likeness, and there is a certain level of efficiency on us, so we can overcome the issue of new targets. If those were to be selected, then our learnings and also applications might be incorporated so that we could do some trials and errors. But, overall, we are working in a very speedy manner. If you look at this display of the pipeline, you might wonder about the speed delay, but we are not observing this as a delay compared to the original plan.

Hashiguchi [M]: I understand. Thank you very much.

Ikeda [M]: Thank you.

Next, JPMorgan Asset Management, Mr. Sawada, please.

Sawada [M]: JPMorgan Asset Management, Sawada is my name. Can you hear me?

Ikeda [M]: Yes.

Sawada [Q]: My questions might be something more basic.

First of all, KRAS G12D positive, G12D positive, that means the cancer cells of that particular patient, each one of the cancer cells expresses G12D, KRAS G12D, or there are some cancer cells not expressing G12D. With this perspective, do you have any insight or information? Also, the ubiquitin system of cancer cells, that is highly maintained in extended time.

This is the first question for me.

Sakata [A]: Thank you for your question.

KRAS G12D mutation, basically, when you test this mutation, basically, all the cancer cells of the particular patient have the G12D mutation, but when it comes to the level of the protein expression, that differs depending on the patient.

Regarding the ubiquitin system, this is an indispensable system for the body, so it will not be eliminated so soon or dysregulated. It's not something like that. This is the more scientific perspective.

So, Hayakawa-san, if you have any additional comment, could you mention some?

Hayakawa [A]: What Sakata said quite is right. This selection of E3 is quite important, and we're very particular about that. Something existing in cancers and that kind of E3 is what we are selecting.

Sawada [Q]: Okay, and expansion cohort, combination with cetuximab is also available. When a KRAS mutation exists, cetuximab cannot be used. So here, with the good efficacy is shown, I think it will be meaningful, meaning that there, the value of this drug is going to be quite clear. So, in that perspective, any

data with the combination with the cetuximab cohort? When do you think it would be possible to disclose that kind of information?

Sakata [A]: Thank you for your question.

Combination with cetuximab, that cohort study is currently ongoing. So, once the data matured, then we would like to report that to you. As for the specific timing, as of now, we cannot tell. So, once we start to see the timing, then we'll share that with you.

Sawada [Q]: But at least that study is currently ongoing?

Sakata [A]: Yes.

Sawada [Q]: Last question, that is about the comparison with the competitors. Bristol Myers, who are themselves a leader in this segment, DAC is also something that they are trying to do. But what about the comparison with them? Are there any factors that you could say you are the leader in this segment? Could you make some comments on this perspective?

Sakata [A]: Thank you for your question.

For us, we have the capabilities, which are one of the best to create protein degraders in the world. We are confident, so we think we are also TPD leaders. We'd like to promote R&D activities going forward, particularly in areas we are good at.

Hayakawa would like to comment.

Hayakawa [A]: We are very confident. In the small molecule drug discovery in the past, we have a long history, and binders are derived from there and PROTAC, which can be used for TPDs instead of functional assays as constituents or components. We have appropriate assay systems, which are abundant in our company.

Once again, we have the capabilities to design. We are very confident about it. Ternary complex-based design is our strength, and to further reinforce this, AI robotics and expertise are fused and combined. We started to work on this ahead of others, so sustainable competitive edge can be maintained.

Ikeda [M]: Thank you very much. There are many people who are still raising their hands, but time is approaching the end. We'd like to take questions from the last person before we close.

AllianceBernstein, Ms. Sogi, please.

Sogi [Q]: Good morning. Thank you for taking my questions. Regarding the future development, I have questions to you.

You have not made any announcement yet, but I'd like to understand the future possibilities. KRAS G12D drugs are not available right now. Phase II monotherapy, single arm, for example, to get accelerated approval, then going to a confirmatory study, or you may do these in parallel. You may not have decided on a strategy, but the fastest scenario may be considered.

Sakata [A]: Thank you for your question.

Regarding the future development approach, ongoing Phase I study results would be checked. And then, we would like to determine our future development policy.

Ahsan, any additional comments from your side?

Arozullah [A]*: It is important to appreciate in pancreatic cancer that the overall survival is very low. So, the distinction between first line, second line, and third line are very short time frames. And so, when we think about our future development, we really are focused on what will maximize the benefit of this drug potentially for patients. And so, that very well could be in the first-line space because the time is so limited for patients to benefit from the drug. So, as you mentioned, we have not determined our development strategy. We will go where our evidence points us but really with an interest to really serve the patients in the best way possible.

Sogi [Q]: Thank you very much. One more question. I have a question about DAC.

ASP3082 protein degraders, in that case, KRAS and E3 ligase binding is seen. If there's going to be an antibody here, the antibody itself or cancer cells, protein degraders are delivered by the antibody. It's not the role to be played by the antibody. If you consider the overall molecule, everybody requires targets on the cell surface. Also, inside a driver mutation, target proteins exist inside. There are two targets for such a product for DAC. DAC is not the concept?

Sakata [A]: Thank you for your question.

We are doing research for DAC programs right now. We are pursuing both possibilities: antibody-based cancer targeting and also delivery efficiency. There's going to be two actions in DAC we'd like to generate, so we are working on both.

Thank you very much.

Ikeda [M]: Thank you very much. There are still others who are waiting to ask questions. The IR team would follow up on you, so please contact us. Thank you very much.

The time has come, so we'd like to close this meeting today. Once again, thank you very much for joining us this morning.

Thank you very much.

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