TARGETED PROTEIN DEGRADATION

Progress on ASP3082, a first-in-class KRAS G12D selective protein degrader

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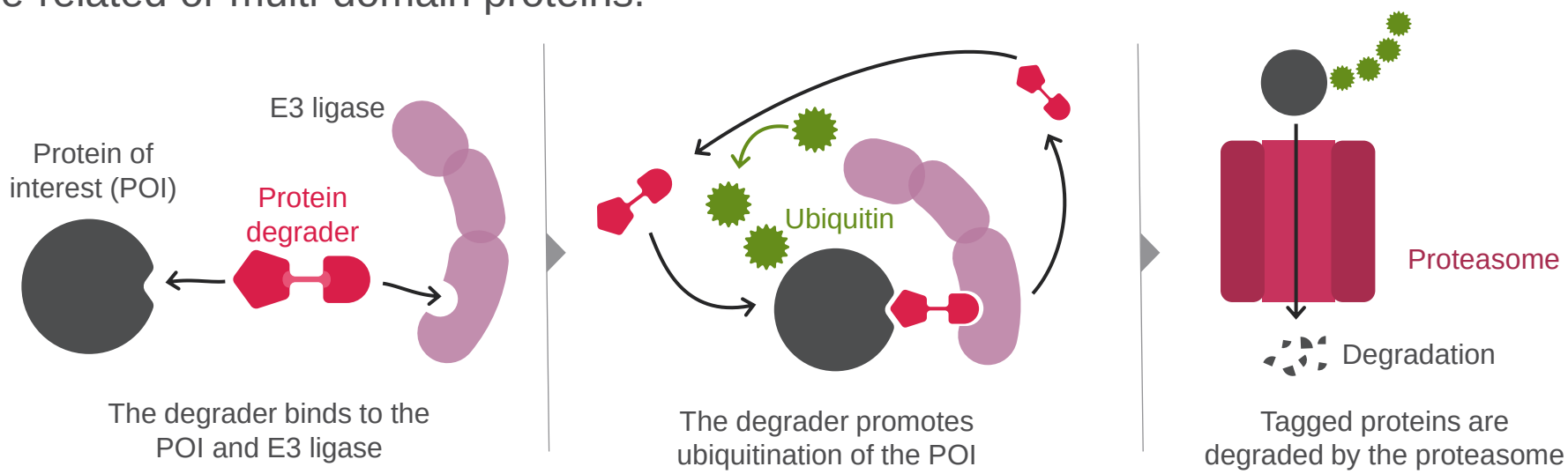
INTRODUCTION

Targeted protein degraders have the potential to overcome limitations of traditional small molecules and tackle “undruggable” targets

Historically, the efficacy of small molecule inhibitors has been limited by target selectivity, cell resistance and difficulty binding to disease-related or multi-domain proteins.[1]

Targeted protein degradation (TPD) works by harnessing the body’s natural protein waste disposal process – the ubiquitin-proteasome system to locate, break down and eliminate these targets.



The degrader binds to the POI and E3 ligase

The degrader promotes ubiquitination of the POI

Tagged proteins are degraded by the proteasome

ADVANTAGES OF PROTEIN DEGRADERS

1 TARGETING UNDRUGGABLES

2 PENETRATING BARRIERS

3 SPECIFICITY

1. Verdine, G.L. Drugging the "Undruggable". The Harvey Lectures. 2006;102:1-15.

TARGETED PROTEIN DEGRADATION STRATEGY

We aspire to evolve TPD into a key capability for Astellas and a major driver of our pipeline expansion

Our three-step strategic roadmap charts a clear path for continued innovation:

Step 1

Harvest KRAS hetero-bifunctional degrader pipeline

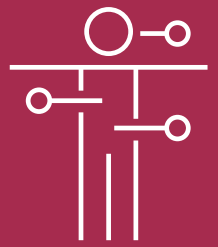
Establish hetero-bifunctional degrader platform

Step 2

Generate post-KRAS pipeline in oncology

Reinforce heterobifunctional degrader platform

Step 3



Expand into non-oncology field

Explore TPD beyond heterobifunctional degraders

TPD, Targeted Protein Degradation; KRAS, Kirsten rat sarcoma viral oncogene homolog.

Mutated KRAS is a historically “undruggable” target and KRAS G12D is the most common KRAS driver mutation[1]

Expression rate (%) of the G12D mutation:

Pancreatic ductal adenocarcinoma (PDAC)	Colorectal cancer (CRC)	Non-squamous non-small cell lung cancer (NSCLC)
		
~40%	**~15%**	**~5%**

While approved KRAS G12C inhibitors exist, therapies targeting KRAS G12D are still needed.

1. Lee JK et al. npj Precis Oncol. 2022;6:91;2

KRAS, Kirsten rat sarcoma viral oncogene homolog.

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There is high unmet need in cancers expressing KRAS G12D mutations – take PDAC as an example

PDAC is the 7th leading cause of cancer death in the world.[1]

<10-17% ORR associated with 2L+ treatments in studies.[2-10]

5-7 months median overall survival in 2L+.[2-10]

80% of 2L patients receiving irinotecan, 5-fluorouracil and leucovorin* in the NAPOLI-1 study experienced adverse events of at least grade 3.[11]

12.8% of 2L patients in the NAPOLI-1 study discontinued treatment for safety reasons.[11]

*This therapeutic combination is approved for use by the US FDA for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.[2]
Safety data are taken from the final analysis after all patients were no longer receiving study treatment.

1. Ushio, J. et al. Diagnostics (Basel). 2021;11:562. 2. Onivyde USPI. 3. Chiorean EG, et al. Clin Cancer Res 2021:27:6314–33. 4. Chung V, et al. JAMA Oncol 2017;3:516–22.
5. Hecht JR, et al. J Clin Oncol 2021;39:1108–18. 6. Hufman BM, et al. JAMA Network Open 2023;6:e2249720. 7. Hammel P, et al. ASCO GI 2022. 8. De La Fouchardière C, et al. J Clin Oncol 2024;42:1055–66.
9. Gupta A, et al. Frontiers Oncol 2023:28;13:1250136. 10. Enzler T, et al. Eur J Cancer 2024: 113950. 11. Wang-Gillam A, et al. Eur J Cancer 2019;108:78–87.
2L, second-line; PDAC, pancreatic ductal adenocarcinoma; ORR, objective response rate.

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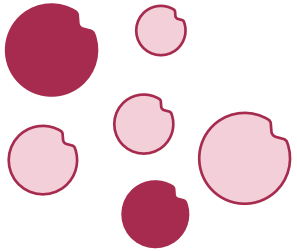
PROGRESS ON ASP3082

Our lead program, ASP3082, is the first protein degrader for mutated KRAS G12D to enter the clinic

Combining unique capabilities with speed and potency

ASP3082 is in Phase 1 trials for the treatment of solid tumors harboring the KRAS G12D mutation, having demonstrated a superior anti-tumor effect in preclinical studies when compared to conventional small molecule inhibitors.[1]

Preclinical studies showed that ASP3082:[1]



Potently and selectively degrades KRAS G12D proteins, inhibiting the downstream signaling that drives tumor growth.

Exhibited significant tumor growth inhibition with once-weekly intravenous administration in mice xenograft models.

If approved, ASP3082 could become a first-in-class therapy for cancers associated with the KRAS G12D mutation, providing a new treatment option for patients with hard-to-treat cancers.

1. Nagashima, T. et al. ASP3082, a first-in-class novel KRAS G12D degrader, exhibits remarkable anti-tumor activity in KRAS G12D-mutated cancer models. Presented at the 34th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Barcelona, Spain, 26–28 October (2022).
KRAS, Kirsten rat sarcoma viral oncogene homolog.

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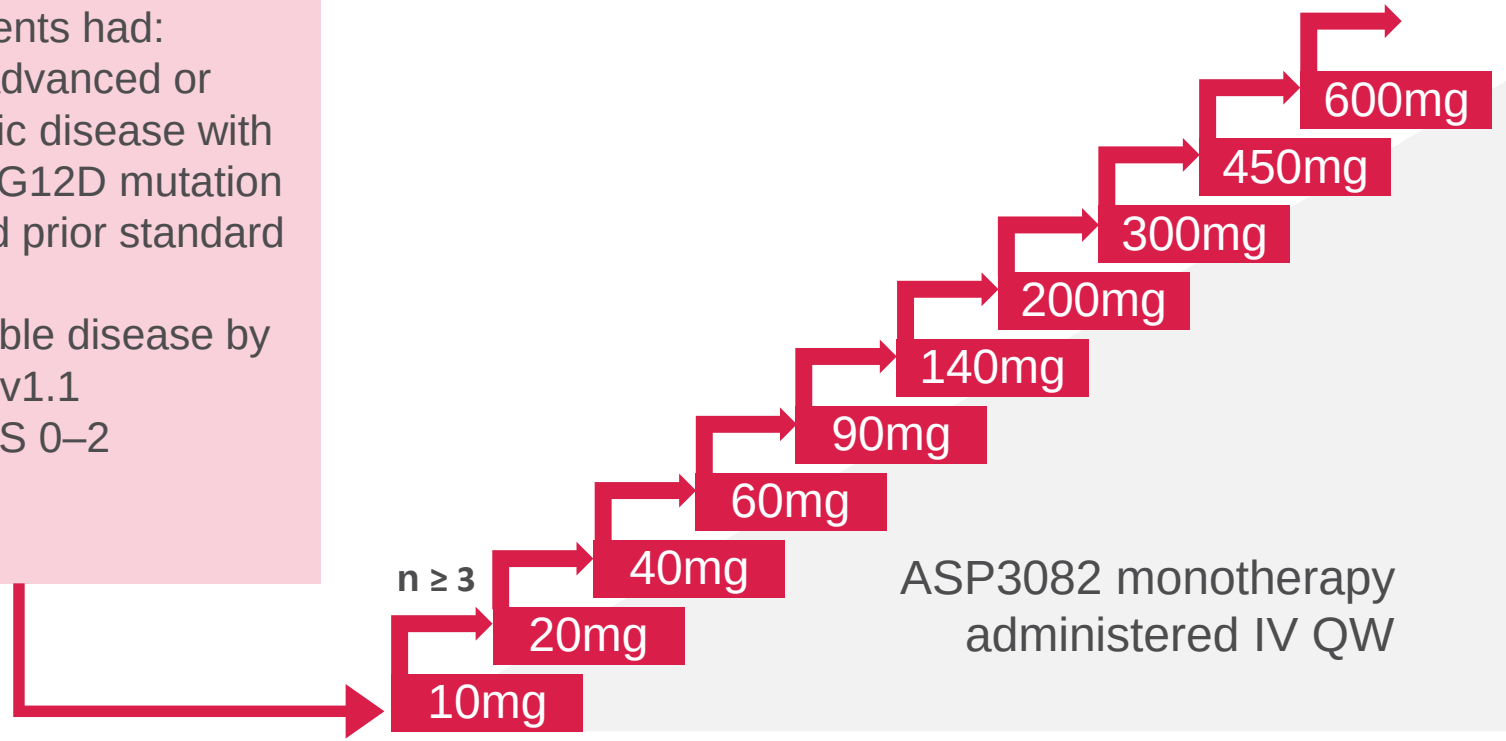
Phase 1 study design of ASP3082

Key Eligibility Criteria

Eligible patients had:

- Locally advanced or metastatic disease with a KRAS G12D mutation
- Received prior standard therapy
- Measurable disease by RECIST v1.1
- ECOG PS 0–2

Dose Escalation



Key Endpoints

Primary endpoints:

- DLT, AE
- MTD, RP2D

Secondary endpoints:

- ORR, DCR
- PK, KRAS G12D levels in tumors

Dose Expansion

https://clinicaltrials.gov/study/NCT05382559

KRAS, Kirsten rat sarcoma viral oncogene homolog; RECIST, response evaluation criteria in solid tumors; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; QW, once weekly; DLT, dose-limiting toxicity; AE, adverse event; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; ORR, objective response rate; DCR, disease control rate; PK, pharmacokinetics.

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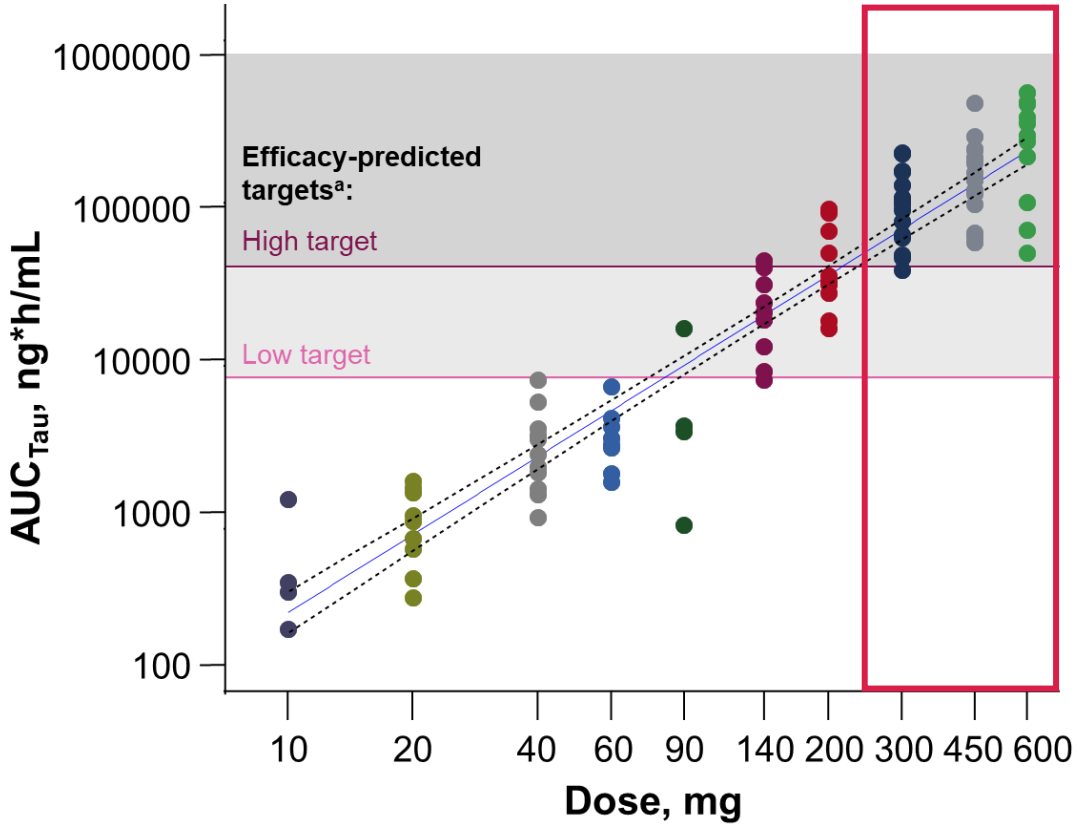
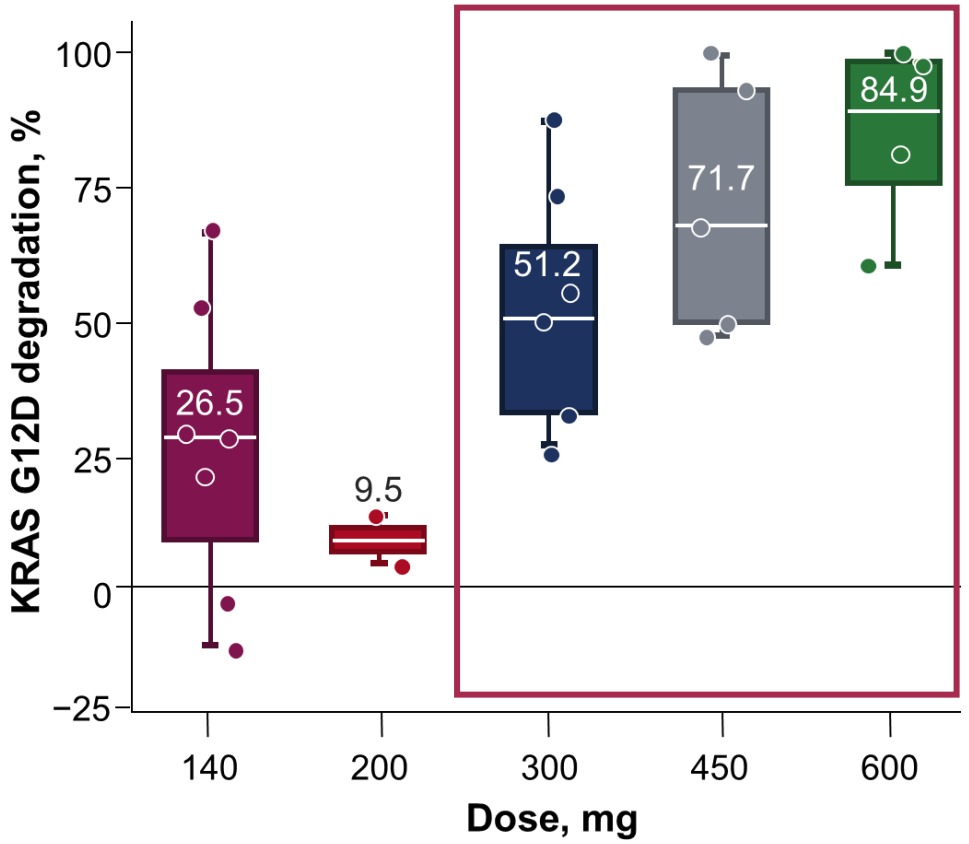
ASP3082 exceeded target exposure in the body ≥ 300mg QW and KRAS G12D was degraded in a dose-dependent manner

ASP3082 exposure in blood



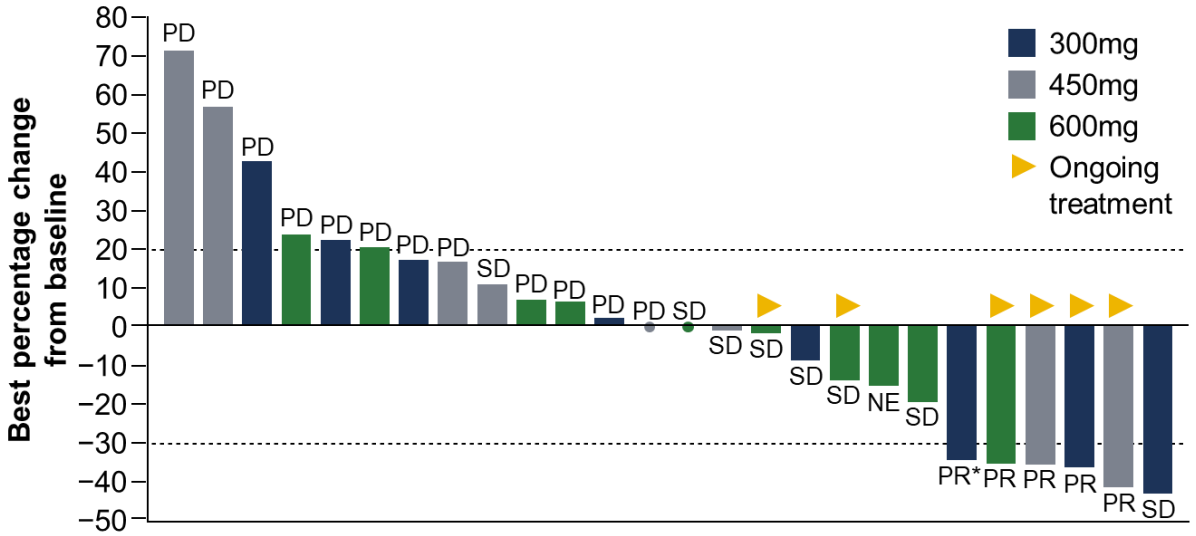
KRAS G12D degradation by IHC[b]



[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.

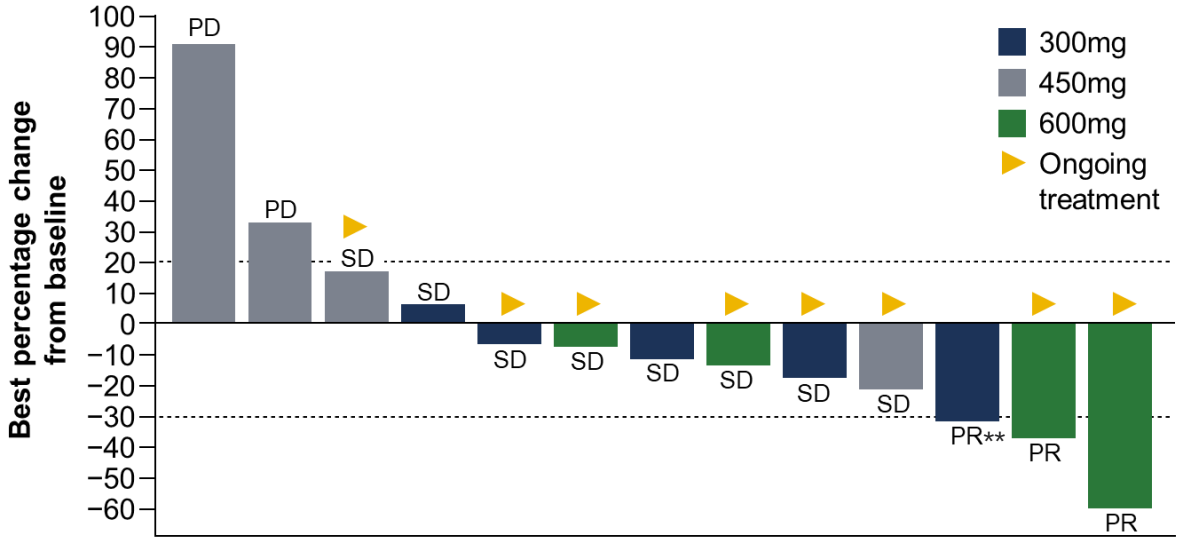
Antitumor activity was observed in patients with PDAC and NSCLC receiving doses between 300–600mg

PDAC



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)

NSCLC



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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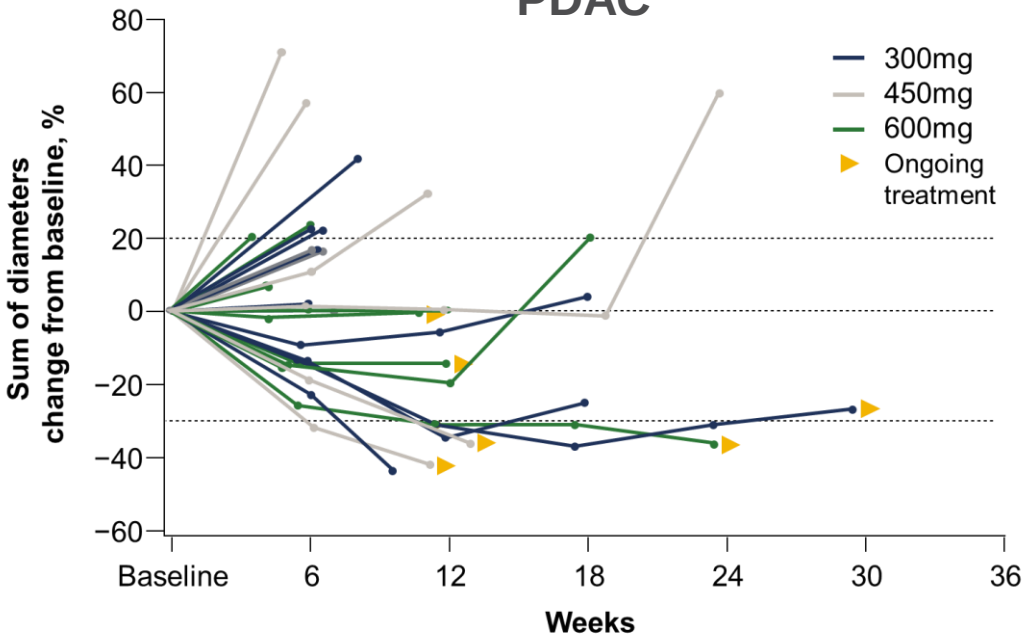
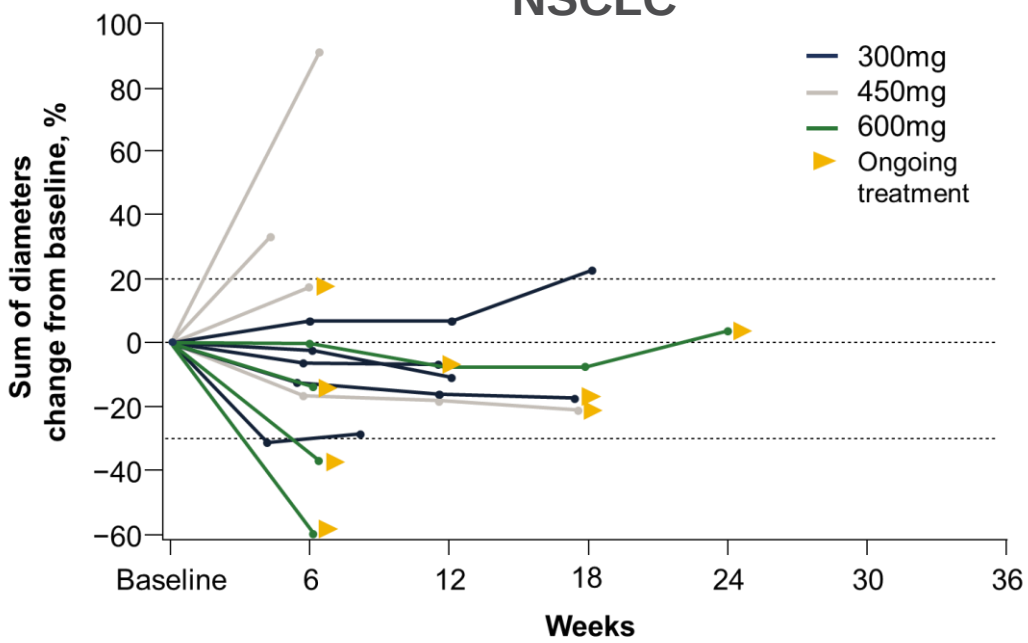
Responses to ASP3082 over time in patients with PDAC and NSCLC

PDAC*



- 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)

NSCLC



- 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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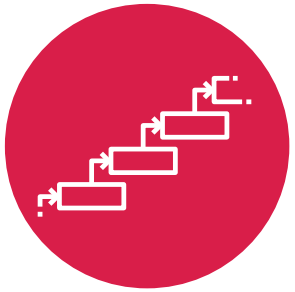
The results and safety profile of ASP3082 support further clinical investigation

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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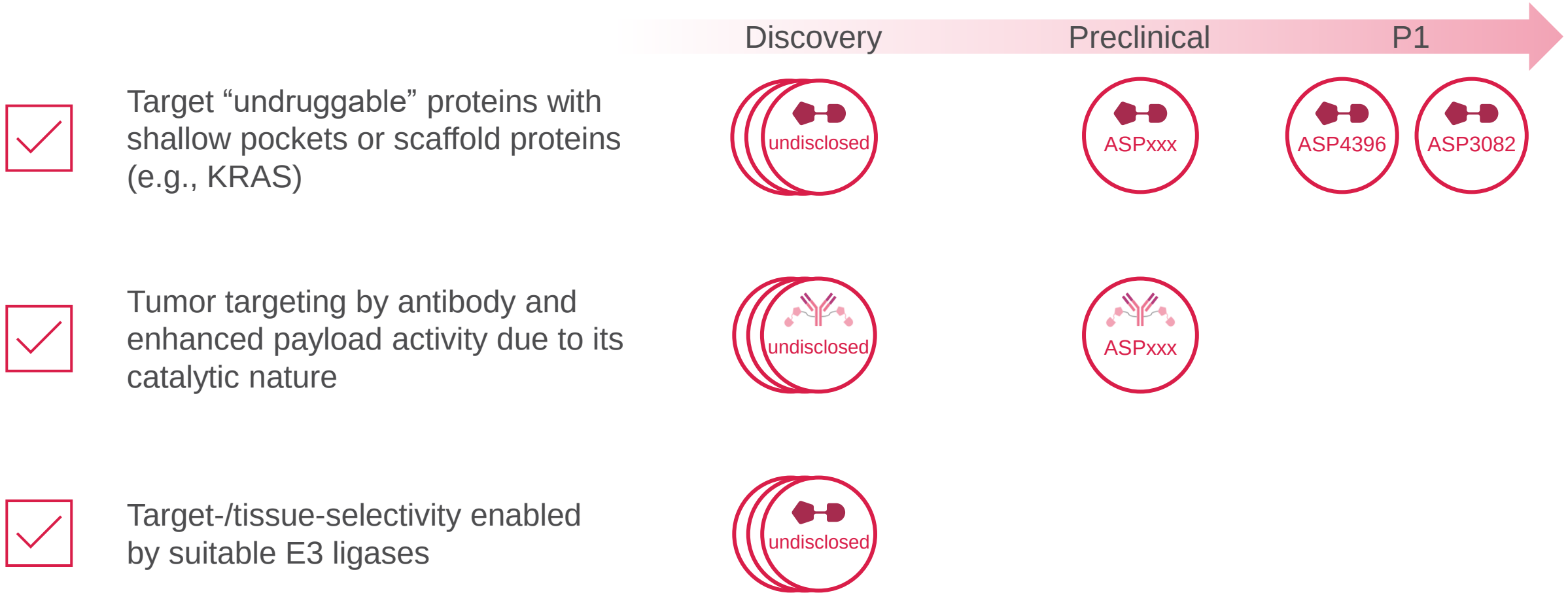
PIPELINE UPDATE

Robust early research pipeline leveraging advantages of protein degraders



KRAS, Kirsten rat sarcoma viral oncogene homolog.

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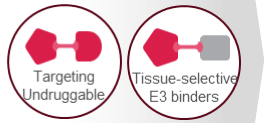
Our portfolio consists of targeted protein degraders – addressing historical “undruggables”

	Program	Mechanism	Indication	Origin/Partner	Current phase
	**ASP3082**	KRAS G12D degrader	KRAS G12D+ solid tumor		**Phase 1 PoC judgment: 1H CY2025**
	ASP4396	KRAS G12D degrader (different E3 from ASP3082)	KRAS G12D+ solid tumor		**Phase 1**
	ASPxxx	Pan KRAS degrader	KRAS + solid tumor		**IND enabling IND target: FY2025**
	ASPxxx	KRAS degrader + antibody (DAC: degrader-antibody conjugate)	KRAS + solid tumor		**IND enabling**
	Undisclosed	Undisclosed	Cancer	FIMECS	**Discovery**
	Undisclosed	Cell cycle protein degrader	Cancer	cullgen	**Discovery**
	Undisclosed	Undisclosed	Cancer	PeptiDream	**Discovery**
	Undisclosed programs	Degrader	Undisclosed		**Discovery**
	Undisclosed programs	DAC	Solid tumor		**Discovery**
	Undisclosed programs	Undisclosed	Non-oncology indications		**Discovery**

Current status, accurate as of September 2024.
KRAS, Kirsten rat sarcoma viral oncogene homolog; PoC, proof of concept; CY, calendar year; IND, investigational new drug; FY, fiscal year.

Our in-house expertise further advances this complex modality

Over the past four years since the discovery of ASP3082, we have been developing follow-on programs while enhancing our TPD drug discovery platform to enable the quick and efficient creation of optimized TPDs.

Identify Binders

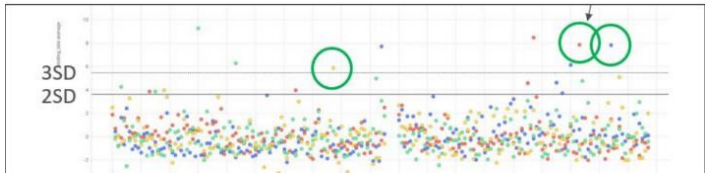
Specialized capabilities to identify unique and high-quality POI/E3 binders

Optimize Complex Structure

Specific capabilities to design optimized ternary complex structure leveraging advanced digital/AI capabilities

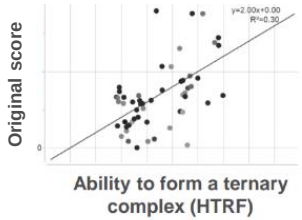
Astellas' proprietary high throughput biophysical assays

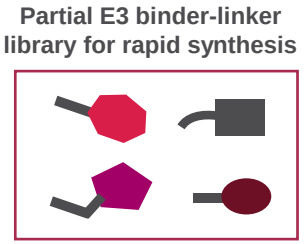
- Screening of our large library with **world-leading throughput speed**, leading to a high success rate in finding binders.
- Multiple new E3 binder acquisitions are ongoing.



Ternary complex modeling and design technology

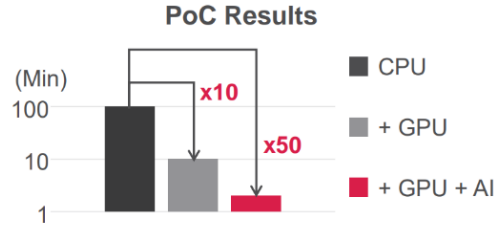
- AI/in silico modeling of ternary complex structure using **Astellas' original algorithm** and compound design techniques, combined with permeability prediction, can accelerate the drug discovery process.
- Proprietary ready-to-use E3 binder-linker library.





Simulation system using Tokyo-1/generative AI

- **Astellas' original simulation methods** integrated with Tokyo-1/generative AI, enable the acceleration of 3D structure generation for degraders (more than 50-folds).



TPD, Targeted Protein Degradation; POI, protein of interest; AI, artificial intelligence; PoC, proof of concept; CPU, central processing unit; GPU, graphics processing unit.

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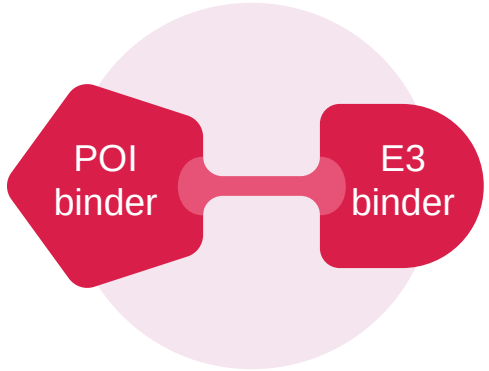
Collaboration with external partners – acquiring novel POI/E3 binders to develop innovative targeted protein degraders

With our partners, we're already developing next-generation targeted protein degraders capable of recruiting various E3 ligases with disease- or tissue-specific characteristics, allowing a degrader to preferentially work inside a tumor or disease-impacted organ.

Target expandability
Converting **POI binder** to access different targets will allow expansion in multiple indications and disease areas.



Functional enhancement
Modifying the **E3 binder** to join to different E3 ligases will allow protein degraders to exert their full potential.

PeptiDream

Partnership

Platform for identifying macrocyclic peptides with the potential to bind to new POIs with high affinity and selectivity.

FIMECS

Partnership

Platform for discovery of cancer-specific E3 ligase binders.

cullgen

Partnership

Platform for the discovery of a wide range of potential E3 ligase binders.

We also pursue new partnerships that enhance our understanding of challenges such as cell resistance and tumor recurrence and help establish the infrastructure needed to expedite the development and delivery of these novel therapies to patients.

POI, protein of interest.

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At Astellas, we believe the TPD modality could transform the treatment landscape for some of the world's most devastating diseases.

We are making strategic investments in TPD to accelerate our research and development, bringing together the right expertise and capabilities to realize the platform's therapeutic potential.

Q&A