TARGETED PROTEIN DEGRADATION

R&D Meeting – December 9, 2022

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CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING INFORMATION

In this material, statements made with respect to current plans, estimates, strategies and beliefs and other statements that are not historical facts are forward-looking statements about the future performance of Astellas Pharma. These statements are based on management's current assumptions and beliefs in light of the information currently available to it and involve known and unknown risks and uncertainties. A number of factors could cause actual results to differ materially from those discussed in the forward-looking statements. Such factors include, but are not limited to: (i) changes in general economic conditions and in laws and regulations, relating to pharmaceutical markets, (ii) currency exchange rate fluctuations, (iii) delays in new product launches, (iv) the inability of Astellas to market existing and new products effectively, (v) the inability of Astellas to continue to effectively research and develop products accepted by customers in highly competitive markets, and (vi) infringements of Astellas' intellectual property rights by third parties.

Information about pharmaceutical products (including products currently in development) which is included in this material is not intended to constitute an advertisement or medical advice. Information about investigational compounds in development does not imply established safety or efficacy of the compounds; there is no guarantee investigational compounds will receive regulatory approval or become commercially available for the uses being investigated.

AGENDA

I

Introduction

Kenji Yasukawa, Ph.D.
President and Chief Executive Officer

II

Building Leadership in Targeted Protein Degradation

Masahiko Hayakawa, Ph.D.
Head of Targeted Protein Degradation

III

Closing

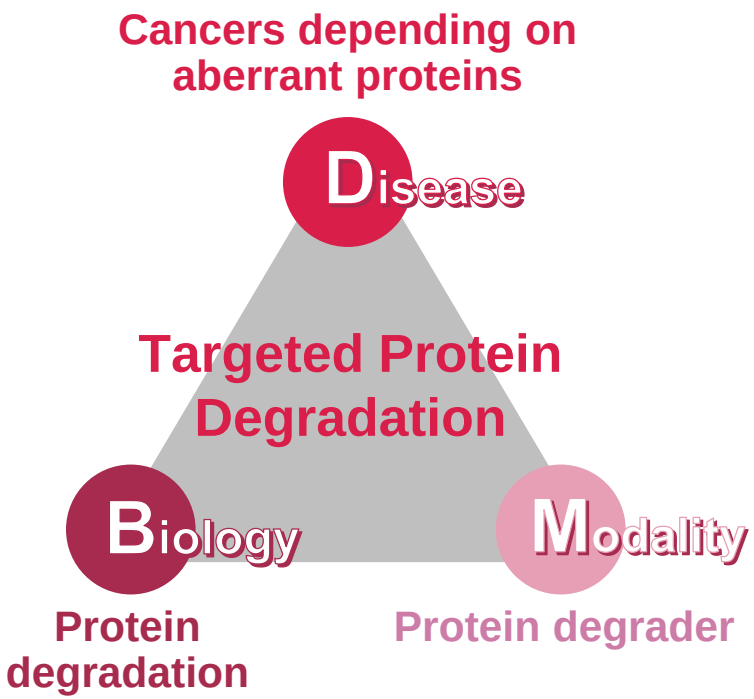
Yoshitsugu Shitaka, Ph.D.
Chief Scientific Officer

INTRODUCTION

Kenji Yasukawa, Ph.D.
President and Chief Executive Officer

NEW PRIMARY FOCUS – TARGETED PROTEIN DEGRADATION

Proactively invest resources to continuously create programs from the established competitive technology platform



Primary Focus Targeted Protein Degradation has been selected based on;

- Scientific validity:
  Established a technology platform for a new modality, protein degrader
- Feasibility:
  Leveraging proficient capabilities for medicinal chemistry and manufacturing of small molecules cultivated over the year, and development in oncology
- Identified lead program and potential follow-on programs:
  In addition to ASP3082, multiple follow-on programs are under investigation

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OVERVIEW OF TODAY'S PRESENTATION

BUILDING LEADERSHIP IN TARGETED PROTEIN DEGRADATION

Technology platform
allowing access to
undruggable targets

Product potential
of **ASP3082**

Capabilities to continuously
generate new programs

Expandability of
the Primary Focus

Masahiko Hayakawa, Ph.D.
Vice President
Head of Targeted Protein Degradation

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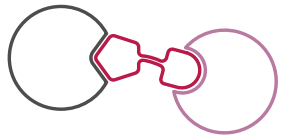
BUILDING LEADERSHIP IN TARGETED PROTEIN DEGRADATION

Masahiko Hayakawa, Ph.D.
Head of Targeted Protein Degradation

KEY POINTS

Technology platform
allowing access to
undruggable targets



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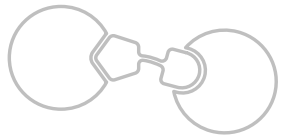

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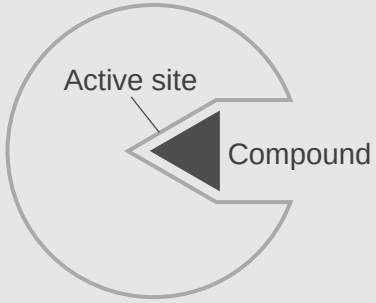
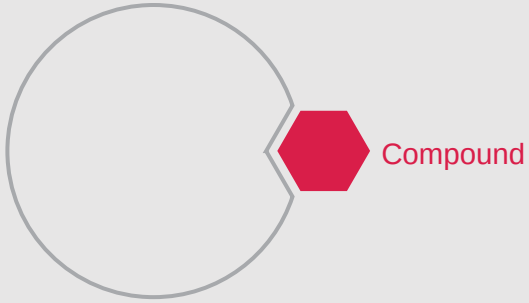
‘UNDRUGGABLE’ TARGETS

DRUGGABLE TARGET



Able to control its function through binding to active site, conformational change, etc.

UNDRUGGABLE TARGET



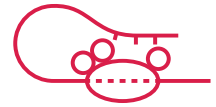
Not able to sufficiently control its function by just binding, due to lack of apparent active sites, etc., considered hard to be a target of drug

About 20% of disease-related proteins have an active binding site (or deep pocket) suitable for inhibition via small molecules [1]

The remaining 80% have shallow binding pockets traditionally considered undruggable [1]

Examples of undruggable targets include:

Small GTPase
(e.g. KRAS, NRAS)



Transcription factor
(e.g. c-Myc, β-catenin)

E3 ligase

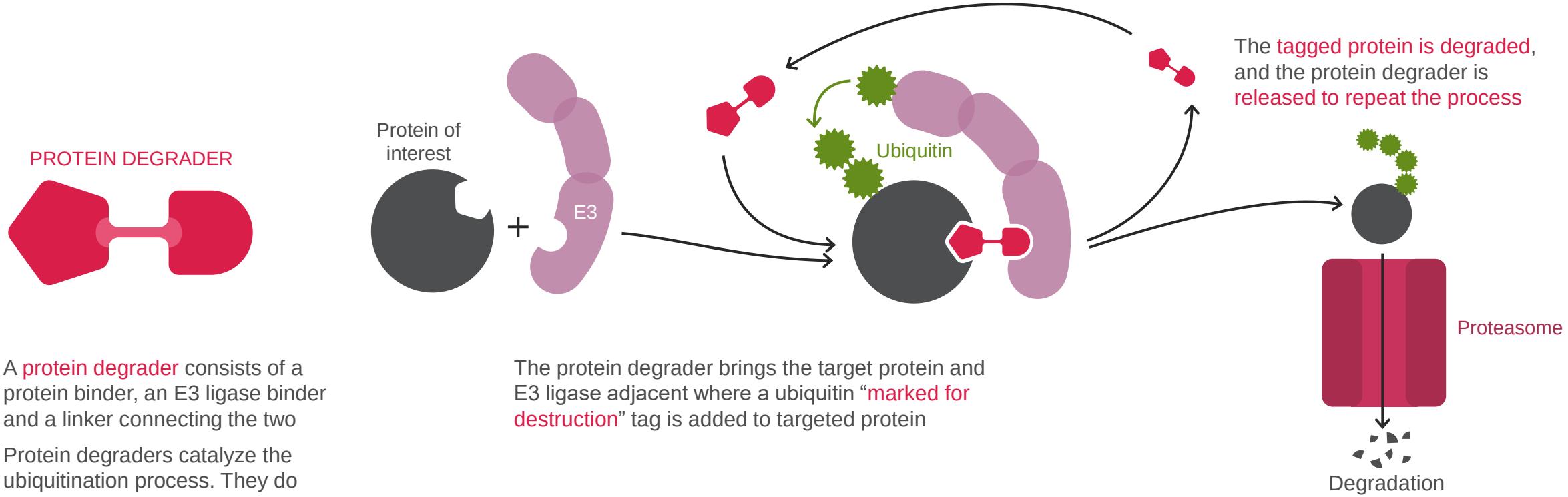
Scaffold protein

Adaptor protein

1. Verdine G.L. *Harvey Lect* 102:1-15 (2006)
GTP: guanosine triphosphate, KRAS: Kirsten rat sarcoma viral oncogene homologue, NRAS: Neuroblastoma rat sarcoma viral oncogene

PROTEIN DEGRADATION AS A KEY MODALITY TO ACCESS INTRACELLULAR UNDRUGGABLE TARGETS

A protein degrader works by hijacking the body's natural protein degradation process, the ubiquitin-proteasome system



A protein degrader consists of a protein binder, an E3 ligase binder and a linker connecting the two

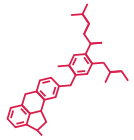
Protein degraders catalyze the ubiquitination process. They do not need potent binding affinity to the targeted protein

The protein degrader brings the target protein and E3 ligase adjacent where a ubiquitin "marked for destruction" tag is added to targeted protein

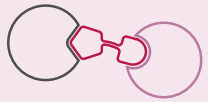
POTENTIAL BENEFITS OF PROTEIN DEGRADERS OVER OTHER MODALITIES

Molecular weight

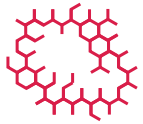
Intracellular target | Extracellular target



Covalent binding drugs
(e.g. small molecule cryptic pocket binder)

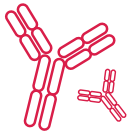


Protein degrader



Mid-size molecules
(e.g. cyclic peptides)

Oligonucleotide therapeutics
(e.g. siRNA)

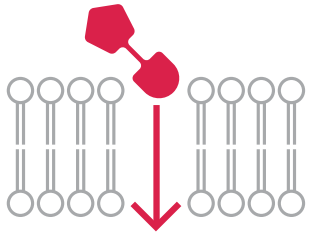


Protein-based drugs
(e.g. antibodies)

Advantages of protein degrader

Targeting undruggables

Up to 80% of proteins could be addressed by protein degraders since they do not need deep pockets (vs. conventional small molecules)



Penetrating barriers

Protein degraders can penetrate the cell membrane and blood brain barrier, and are likely to penetrate solid tumor better than some bigger modalities (vs. antibodies)

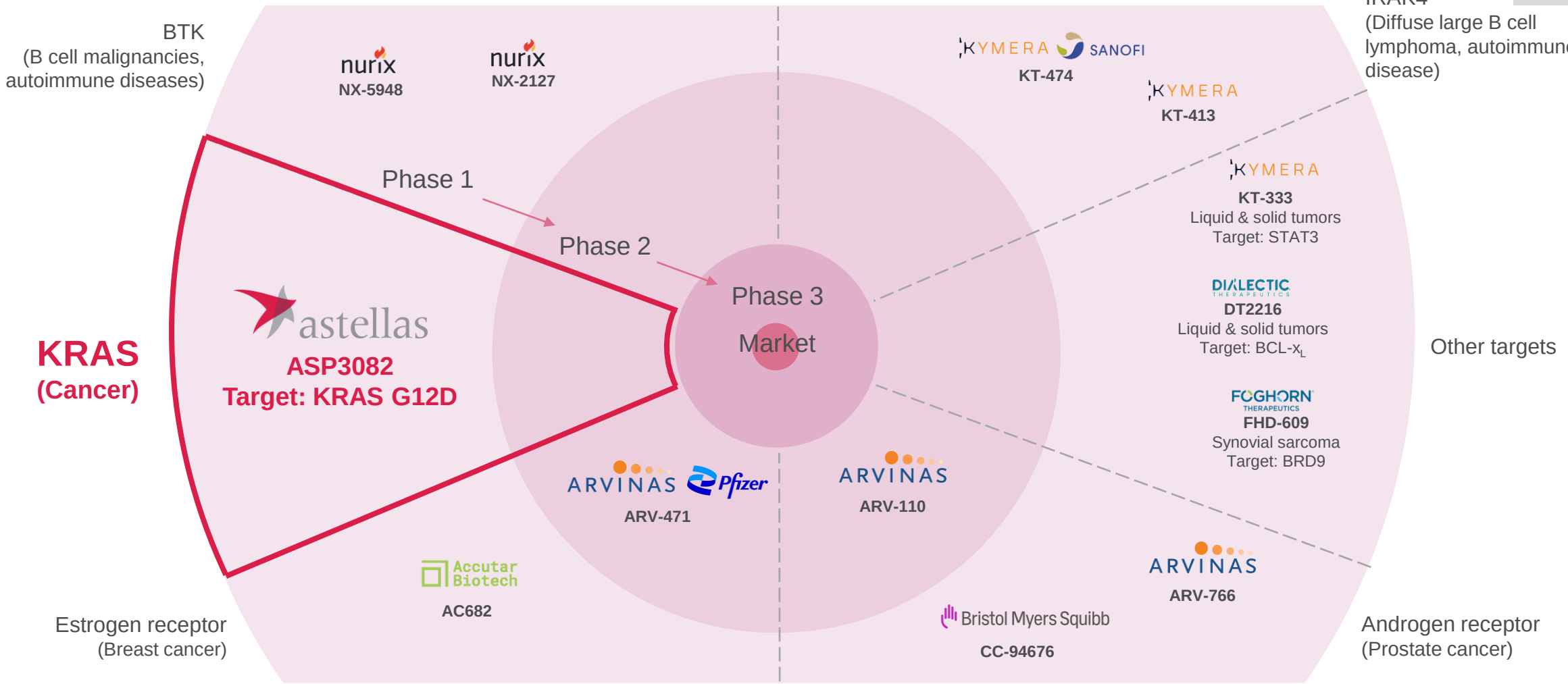
Specificity

Protein degraders are heterobifunctional molecules that can selectively degrade specific molecules by forming ternary complex (vs. conventional small molecules).

They can also act selectively on a specific organ by utilizing disease/tissue-specific E3 ligase (vs. cyclic peptides)

siRNA: small interfering ribonucleic acid

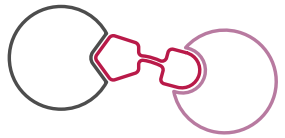
LANDSCAPE OF PROTEIN DEGRADERS



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

KEY POINTS

Technology platform
allowing access to
undruggable targets



Product potential
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Capabilities to continuously
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Expandability of
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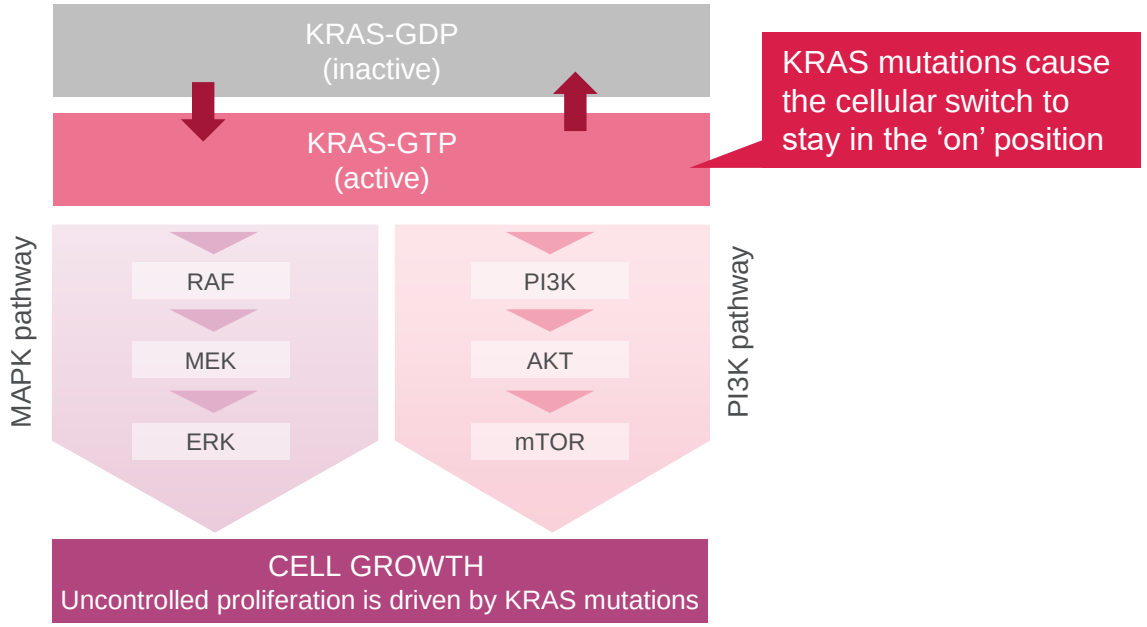
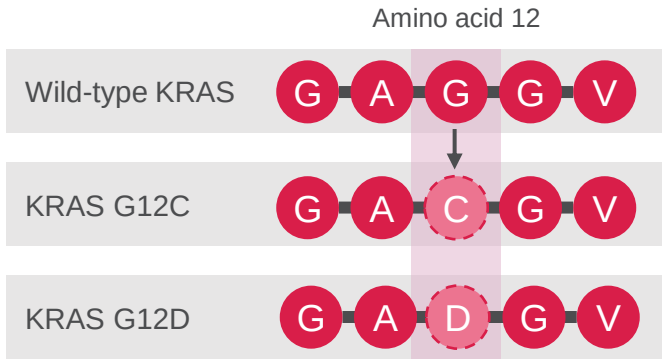
RAS MUTATIONS – A KEY DRIVER OF CANCER

RAS proteins are GTPases which regulate signaling pathways and other interactions

RAS mutations are key cancer drivers with KRAS, NRAS and HRAS most commonly involved

Multiple types of KRAS mutations are known



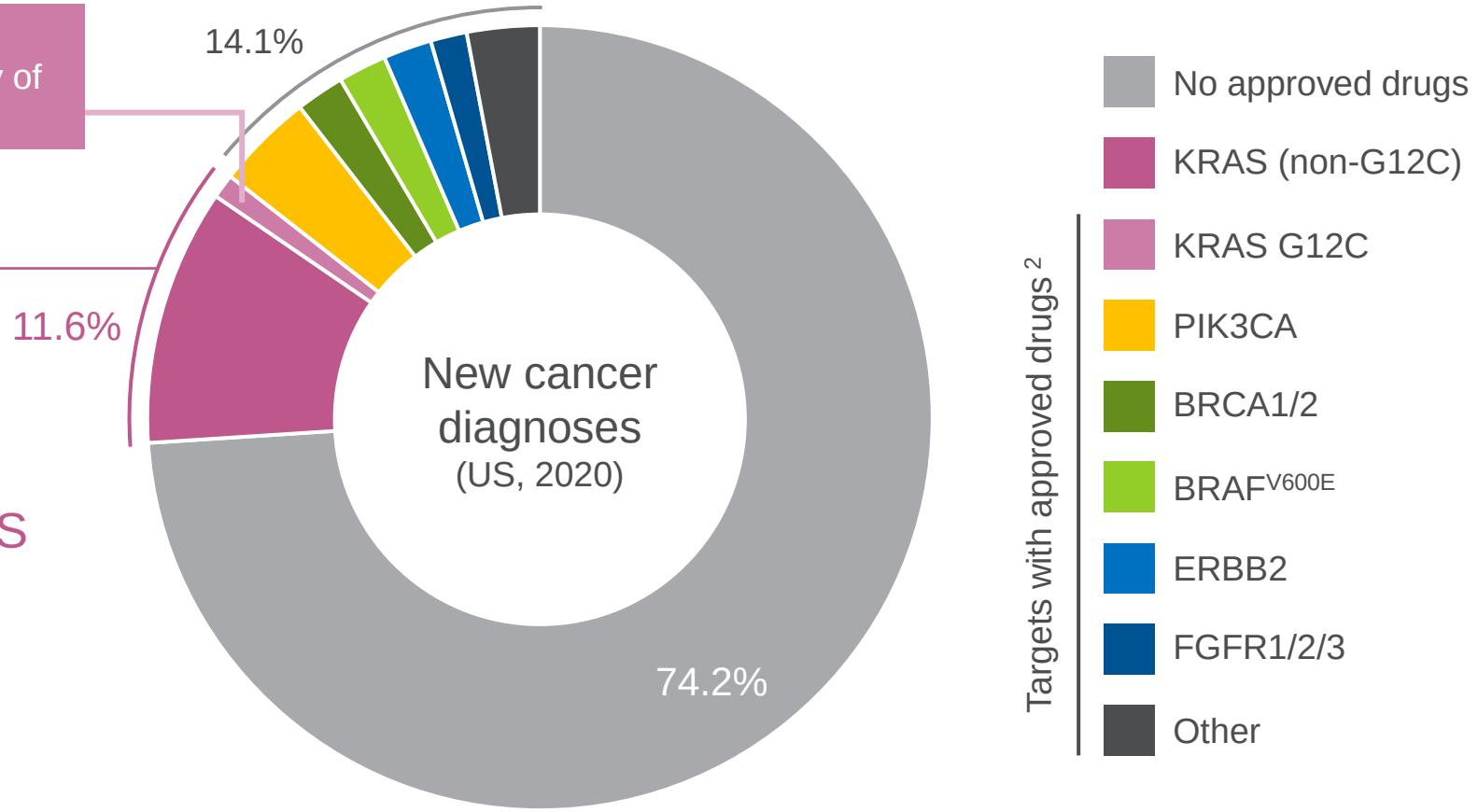


'G12C' or 'G12D' indicates that the 12th amino acid is replaced from G (glycine) to C (cysteine) or D (aspartic acid), respectively

RAS: rat sarcoma virus, KRAS: Kirsten rat sarcoma viral oncogene homologue, NRAS: Neuroblastoma rat sarcoma viral oncogene, HRAS: Harvey rat sarcoma viral oncogene, GDP: guanosine diphosphate, GTP: guanosine triphosphate, MAPK: mitogen-activated protein kinase, RAF: rapidly accelerated fibrosarcoma, MEK: mitogen-activated protein kinase kinase, ERK: extracellular signal-regulated protein kinase, PI3K: phosphatidylinositol 3-kinase, AKT: protein Kinase B, mTOR: mammalian target of rapamycin

TARGETING KRAS MUTATIONS IS ONE OF THE GREAT FRONTIERS IN ADDRESSING UNMET MEDICAL NEEDS IN CANCER

KRAS G12C inhibitor demonstrated the validity of targeting KRAS mutation



210,000 (11.6%) of new cancer diagnoses in the US harbor KRAS alterations/ mutations [1]

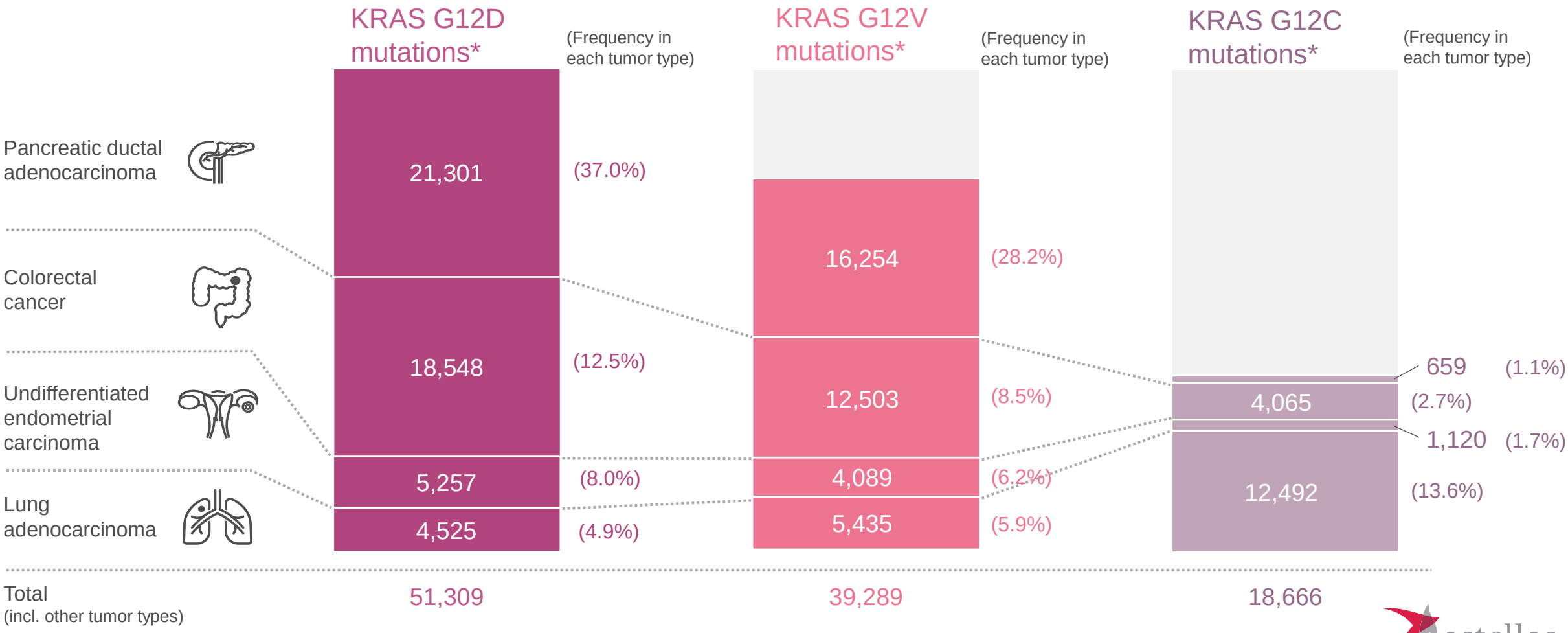
There remain great unmet medical needs in other (non-G12C) KRAS mutations

1.8 M new cancer patients/year in US [3]

1. Hofmann M.H. *Cancer Discov* 12:924-37 (2022). 2. Precision medicine drugs approved by FDA (Food and Drug Administration). 3. American Cancer Society. Cancer Facts & Figures (2020).
KRAS: Kirsten rat sarcoma viral oncogene homologue, PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, BRCA: breast cancer gene, BRAF: v-raf murine sarcoma viral oncogene homolog B1, ERBB2: Erb-B2 receptor tyrosine kinase 2, FGFR: fibroblast growth factor receptor

TARGETING MAJOR KRAS MUTATIONS CAN HAVE A SIGNIFICANT IMPACT ON UNMET MEDICAL NEEDS

The most prominent KRAS mutations are G12D, G12V, and G12C



*Estimated new diagnoses/patients per year in US

Ref. Hofmann M.H. *Cancer Discov* 12:924-37 (2022)
KRAS: Kirsten rat sarcoma viral oncogene homologue

KRAS G12D IS ONE OF THE MOST IMPORTANT AND CHALLENGING MUTATIONS

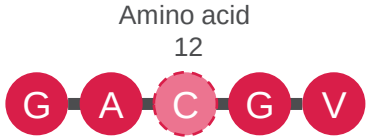
Inhibiting KRAS is difficult because the pocket to which the inhibitor binds is “shallow”, calling for novel therapeutic approaches

KRAS G12C has been successfully targeted, but KRAS G12D has proven to be more challenging

- The recently launched KRAS G12C inhibitor exploits a cysteine residue that makes irreversible covalent binding possible
- Other KRAS mutations including G12D has no cysteine residue, and even if it binds, it is easily released

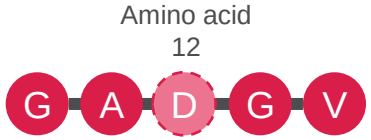
ASP3082 binds to KRAS G12D and E3 ligase, bringing them adjacent to each other, and catalyzes the degradation via the ubiquitin-proteasome system

KRAS **G12C** mutation

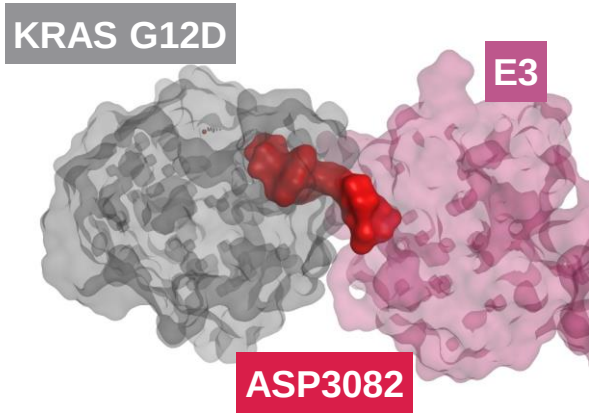


Mutation to cysteine: compounds can be covalently bound

KRAS **G12D** mutation



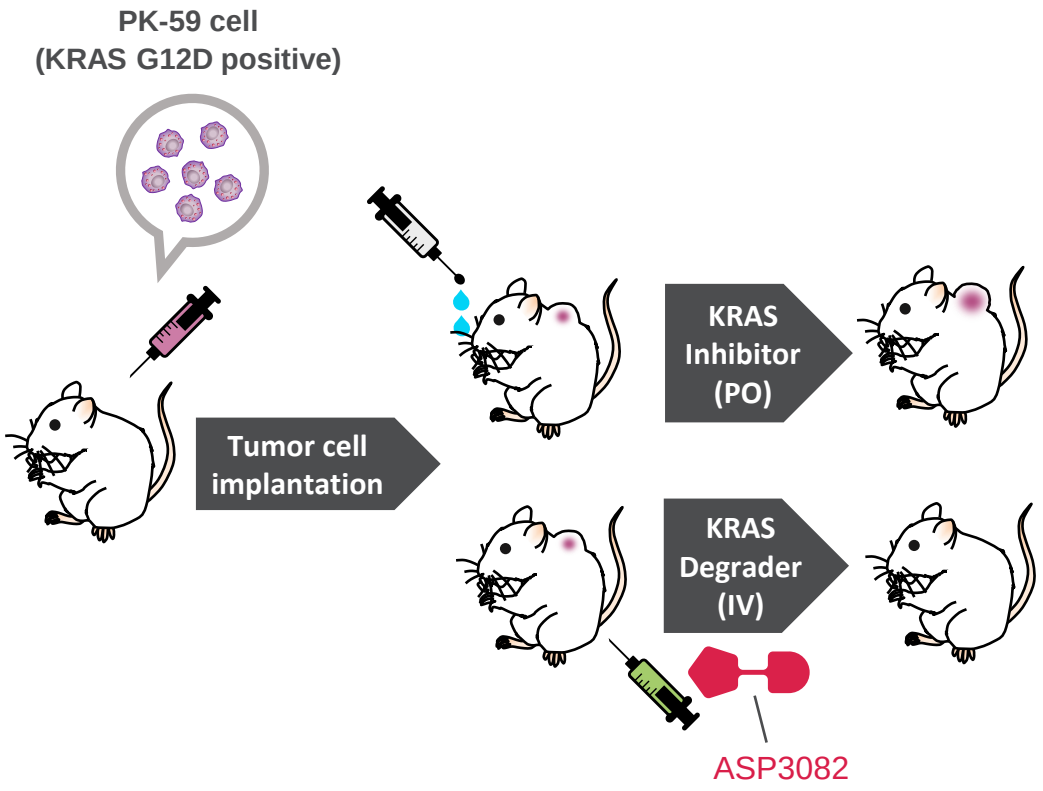
Mutation to aspartic acid: difficult to achieve strong binding

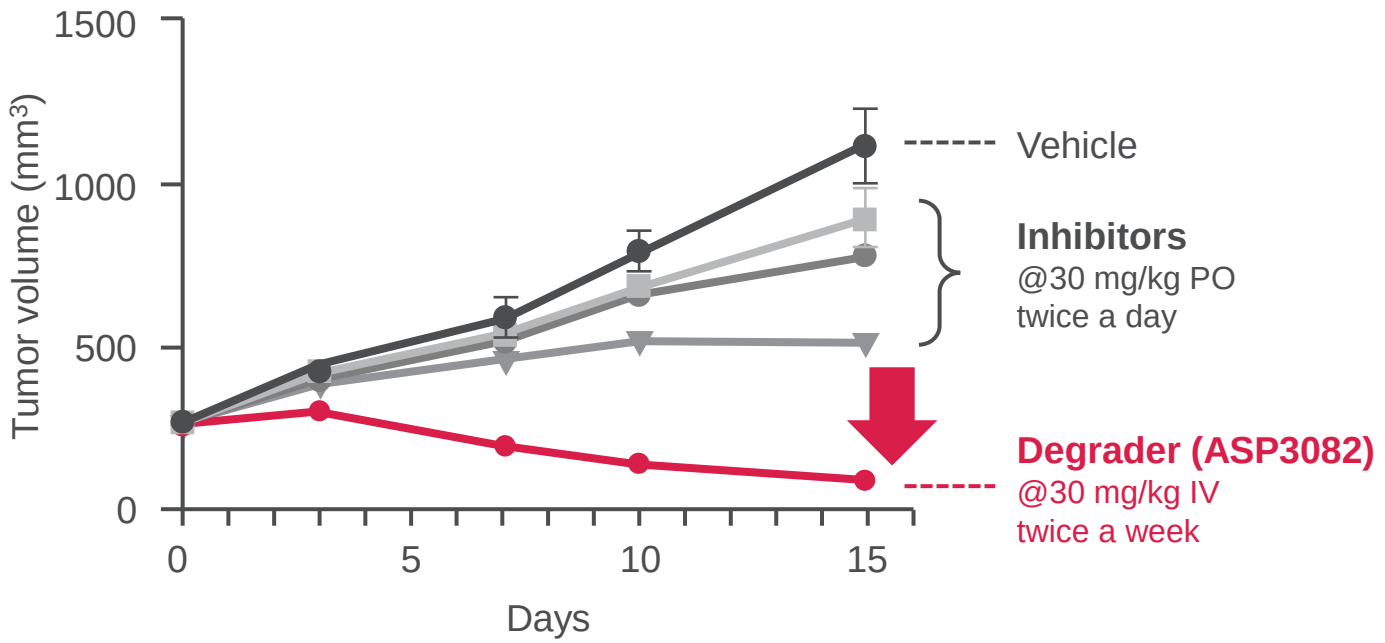


KRAS: Kirsten rat sarcoma viral oncogene homologue

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

Xenograft mice bearing human pancreatic cancer with KRAS G12D mutation

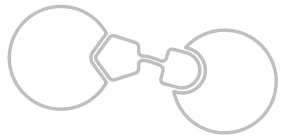




KRAS: Kirsten rat sarcoma viral oncogene homologue, PO: oral administration, IV: intravenous administration

KEY POINTS

Technology platform
allowing access to
undruggable targets



Product potential
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Capabilities to continuously
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Expandability of
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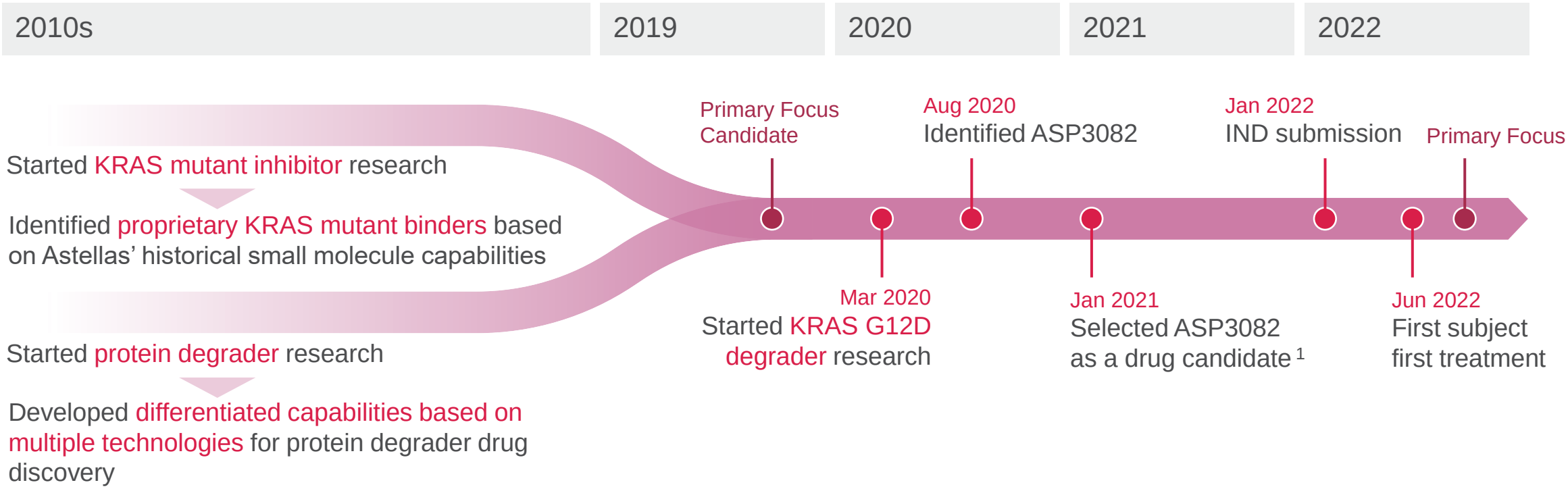
HISTORY OF IN-HOUSE CHALLENGE IN TARGETED PROTEIN DEGRADATION TO ADDRESS KRAS G12D

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

THE COMBINATION OF UNIQUE BINDERS AND PROTEIN DEGRADER CAPABILITY SETS US APART IN CHALLENGING UNDRUGGABLE TARGETS USING PROTEIN DEGRADATION

Proprietary POI and E3 binders

POI binders

- KRAS mutants
- Other targets

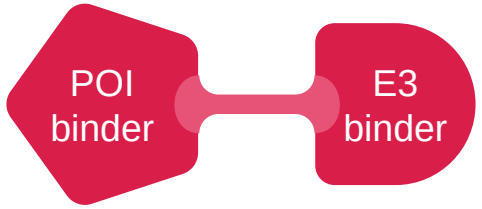
E3 binders

- Multiple E3 binders

Challenge

BINDING

Technical difficulty in creating a compound that specifically binds to undruggable targets



Challenge

EFFICACY

Even if a binder can be created, the inhibition of function is challenging

Combined multiple technologies

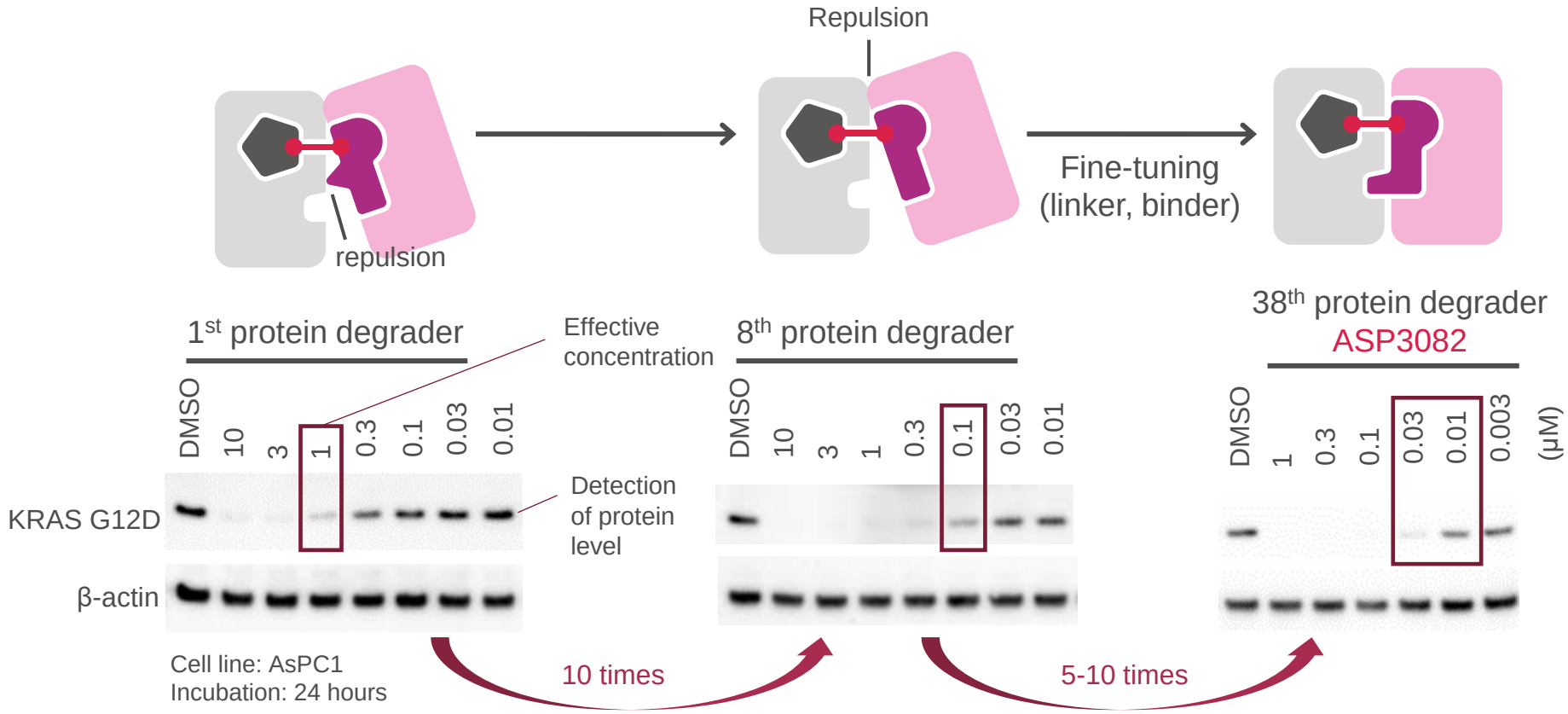
- Expert chemists
- Robotics
- AI algorithms

- State-of-the-art modeling technology
- Highly effective molecular synthesis

POI: protein of interest, KRAS: Kirsten rat sarcoma viral oncogene homologue, AI: artificial intelligence

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

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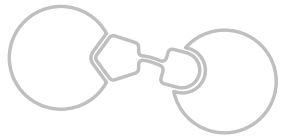

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PROTEIN DEGRADERS HAVE VAST PLATFORM POTENTIAL IN CANCER AND BEYOND

Target expandability

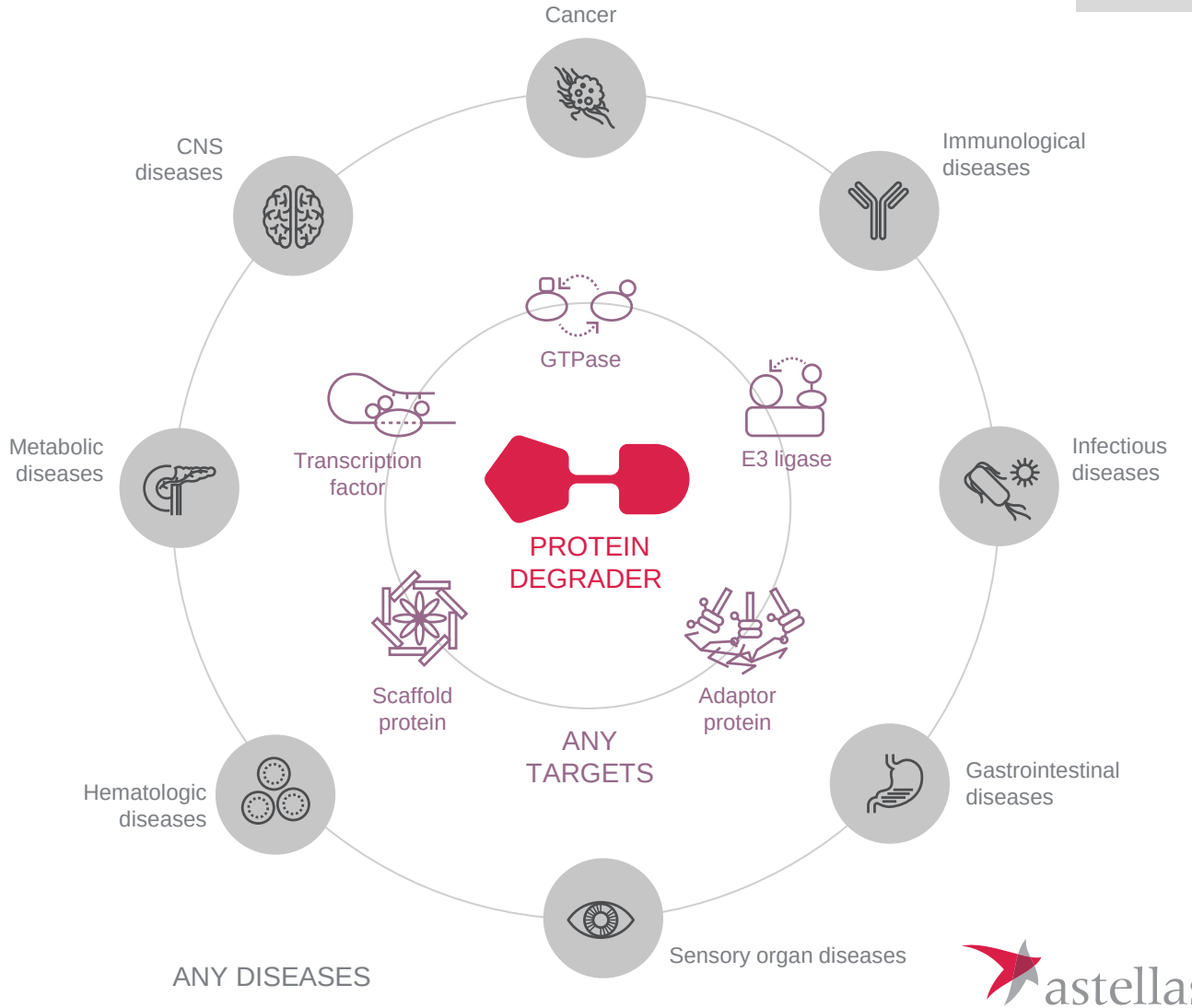
Converting **POI binder** to access different targets will allow expansion in multiple indications and disease areas

Functional enhancement

Converting **E3 binder** to access different E3 ligases will allow protein degraders to exert their full potential

Partnering

We will continue to actively acquire **external capabilities** to integrate with our **in-house expertise**



POI: protein of interest, CNS: central nervous system, GTP: guanosine triphosphate

ACCELERATING OUR PROGRESS THROUGH COLLABORATIONS WITH INNOVATIVE PARTNERS

Target expandability

POI binder: proprietary binders for historical undruggables

+ New partner

POI binder for multiple diseases

Functional enhancement

Partnership with FIMECS provides access to RaPPIDS™ which enables:

- Synthesis platform for efficient protein degraders
- Discovery of cancer-specific E3 ligase binders

FIMECS

E3 binder: for specificity, longer-action, and patentability

+ New partner

Next-generation protein degrader

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POI: protein of interest, RaPPIDS: Rapid Protein Proteolysis Inducer Discovery System

OVERALL STRATEGY FOR PRIMARY FOCUS TARGETED PROTEIN DEGRADATION

1ST WAVE	2ND WAVE	3RD WAVE
Mutated KRAS	**Other oncology targets**	**Non-oncology target (e.g. immunology)**
×	×	×
ASP3082 pan KRAS degrader	**Next-generation protein degrader**	**Next-generation protein degrader**

KRAS: Kirsten rat sarcoma viral oncogene homologue

OUR PORTFOLIO CONSISTS OF DIFFERENTIATED DEGRADERS AND THEIR BACKUPS – ALL ADDRESSING HISTORICAL UNDRUGGABLES

Program	Target protein	Target disease	Hit Identifying	Lead Optimizing	IND Enabling	Phase 1	Next milestone	Partner
ASP3082	KRAS G12D	KRAS G12D+ solid tumor					Completion of dose escalation part (Mono): FY23	
ASP3082 Back-up	KRAS G12D	KRAS G12D+ solid tumor						
pan KRAS degrader	pan KRAS	KRAS mutation+ solid tumor					IND: FY23	
pan KRAS Back-up	pan KRAS	KRAS mutation+ solid tumor						
Undisclosed Program	Undisclosed	Solid tumor						
Collaboration Program	Undisclosed	Cancer						FIMECS
Collaboration Program	Undisclosed	Cancer						FIMECS
Discovery Programs	Undisclosed	Non-oncology diseases						

KRAS: Kirsten rat sarcoma viral oncogene homologue, IND: Investigational New Drug

CLOSING

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Yoshitsugu Shitaka, Ph.D.
Chief Scientific Officer

ACHIEVEMENT FROM NEW RESEARCH ORGANIZATION STRUCTURE

MODIFIED ORGANIZATION STRUCTURE FROM FUNCTION-LED/ HIERARCHICAL TO OBJECTIVE-BASED/AGILE

Assigned top-talented researchers by objective-based

ON-SITE DECISION-MAKING

Optimal and quick decision-making by experts in the laboratory rather than top-down

CULTURAL AND BEHAVIORAL TRANSFORMATION

In a flat organization, researchers' original ideas and ambitious plans are shared without fear and reflected in the research plan

Mindset change spills over from Research to Manufacturing and Development Divisions, resulting in entry into clinical trial in record time

TIMELY INVESTMENT DECISIONS BY TOP RESEARCH EXECUTIVES

Visualization of investment effects in each objective enables enhancement of achievement-based investment in a timely manner

CREATION OF A NEW PRIMARY FOCUS AND ACCELERATION OF ORGANIZATIONAL GROWTH

IND for lead program ASP3082 (world's first to target KRAS G12D), leading to robust follow-on pipeline and selection as the Primary Focus at a time that secured competitive advantage

Strategic stage	Primary Focus Candidate	Primary Focus
Research Organization	Venture Unit Tumor-directed Inhibition	Accelerate → Research Engine Targeted Protein Degradation Enhance driving-force
Goal	Lead Program Creation	Drug Candidate Creation and Program Expansion

Research organization grows and becomes independent from Venture Unit to Research Engine, with a more significant delegation of authority

Proactively invest in the Primary Focus to maintain growth momentum and continue to create programs

IND: Investigational New Drug, KRAS: Kirsten rat sarcoma viral oncogene homologue

ON THE FOREFRONT OF HEALTHCARE CHANGE