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
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
OVERVIEW OF TODAY’S PRESENTATION

BUILDING LEADERSHIP IN TARGETED PROTEIN DEGRADATION

Technology platform
allowing access to undruggable targets

Capabilities to continuously generate new programs

Product potential of ASP3082

Expandability of the Primary Focus

Masahiko Hayakawa, Ph.D.
Vice President
Head of Targeted Protein Degradation
BUILDING LEADERSHIP IN TARGETED PROTEIN DEGRADATION

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

Technology platform allowing access to undruggable targets

Capabilities to continuously generate new programs

Product potential of ASP3082

Expandability of the Primary Focus
KEY POINTS

Technology platform allowing access to undruggable targets

Capabilities to continuously generate new programs

Product potential of ASP3082

Expandability of the Primary Focus
‘UNDRUGGABLE’ TARGETS

About 20% of disease-related proteins have an active binding site (or deep pocket) suitable for inhibition via small molecules. The remaining 80% have shallow binding pockets traditionally considered undruggable.

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

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GTP: guanosine triphosphate, KRAS: Kirsten rat sarcoma viral oncogene homologue, NRAS: Neuroblastoma rat sarcoma viral oncogene
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.

The tagged protein is degraded, and the protein degrader is released to repeat the process.
POTENTIAL BENEFITS OF PROTEIN DEGRADERS OVER OTHER MODALITIES

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).

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)

Molecular weight

Intracellular target

Extracellular target

siRNA: small interfering ribonucleic acid
LANDSCAPE OF PROTEIN DEGRADERS

**BTK**
- **Target**: B cell lymphoma-extra large (BCL-xL)
- **Phase**: Phase 2

**KRAS**
- **Target**: KRAS G12D
- **Phase**: Phase 1

**IRAK4**
- **Target**: Interleukin-1 receptor-associated kinase 4
- **Phase**: Phase 3

**ARV-110**
- **Target**: Estrogen receptor
- **Phase**: Market

**ARV-471**
- **Target**: Estrogen receptor
- **Phase**: Market

**ARV-766**
- **Target**: Androgen receptor
- **Phase**: Market

**Other targets**
- 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-xL: B cell lymphoma-extra large
- BRD9: Bromodomain-containing protein 9


**Technology platform**
- CC-94676

**Technology companies**
- Astellas
- Arvinas
- Pfizer
- Bristol Myers Squibb
KEY POINTS

Technology platform allowing access to undruggable targets

Capabilities to continuously generate new programs

Product potential of ASP3082

Expandability of the Primary Focus
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.
TARGETING KRAS MUTATIONS IS ONE OF THE GREAT FRONTIERS IN ADDRESSING UNMET MEDICAL NEEDS IN CANCER

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

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


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

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>KRAS G12D mutations* (Frequency in each tumor type)</th>
<th>KRAS G12V mutations* (Frequency in each tumor type)</th>
<th>KRAS G12C mutations* (Frequency in each tumor type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic ductal adenocarcinoma</td>
<td>21,301 (37.0%)</td>
<td>16,254 (28.2%)</td>
<td>4,065 (2.7%)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>18,548 (12.5%)</td>
<td>12,503 (8.5%)</td>
<td>1,120 (1.7%)</td>
</tr>
<tr>
<td>Undifferentiated endometrial carcinoma</td>
<td>5,257 (8.0%)</td>
<td>4,089 (6.2%)</td>
<td>12,492 (13.6%)</td>
</tr>
<tr>
<td>Lung adenocarcinoma</td>
<td>4,525 (4.9%)</td>
<td>5,435 (5.9%)</td>
<td>659 (1.1%)</td>
</tr>
<tr>
<td>Total (incl. other tumor types)</td>
<td>51,309</td>
<td>39,289</td>
<td>18,666</td>
</tr>
</tbody>
</table>

*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.
ASP3082 demonstrates superior anti-tumor efficacy vs inhibitors in preclinical studies.

Xenograft mice bearing human pancreatic cancer with KRAS G12D mutation.

**PK-59 cell** (KRAS G12D positive)

**Tumor cell implantation**

**KRAS Inhibitor (PO)**

**KRAS Degrader (IV)**

ASP3082

**Vehicles**

**Inhibitors**

@30 mg/kg PO twice a day

**Degrader (ASP3082)**

@30 mg/kg IV twice a week

Tumor cell implantation

**Days**

0 5 10 15

**Tumor volume (mm³)**

0 500 1000 1500

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

Technology platform allowing access to undruggable targets

Capabilities to continuously generate new programs

Product potential of ASP3082

Expandability of the Primary Focus
**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.

<table>
<thead>
<tr>
<th>2010s</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Started KRAS mutant inhibitor research</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identified proprietary KRAS mutant binders based on Astellas’ historical small molecule capabilities</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Started protein degrader research</td>
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<td></td>
</tr>
<tr>
<td>Developed differentiated capabilities based on multiple technologies for protein degrader drug discovery</td>
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</tr>
</tbody>
</table>

- **Aug 2020** Identified ASP3082
- **Mar 2020** Started KRAS G12D degrader research
- **Jan 2021** Selected ASP3082 as a drug candidate
- **Jun 2022** First subject first treatment
- **Jan 2022** IND submission

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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

**Challenge**

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

**POI binders**
- KRAS mutants
- Other targets

**E3 binders**
- Multiple E3 binders

**Proprietary POI and E3 binders**

**Combined multiple technologies**
- Expert chemists
- Robotics
- AI algorithms

**Efficacy**

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

**Capabilities**
- State-of-the-art modeling technology
- Highly effective molecular synthesis
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.
KEY POINTS

Technology platform allowing access to undruggable targets

Capabilities to continuously generate new programs

Product potential of ASP3082

Expandability of the Primary Focus
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

POI binder: proprietary binders for historical undruggables

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

Partnership with FIMECS provides access to RaPPIDS™ which enables:
- Synthesis platform for efficient protein degraders
- Discovery of cancer-specific E3 ligase binders

POI binder for multiple diseases

Next-generation protein degrader

POI: protein of interest, RaPPIDS: Rapid Protein Proteolysis Inducer Discovery System
OVERALL STRATEGY FOR PRIMARY FOCUS TARGETED PROTEIN DEGRADATION

1\textsuperscript{ST} WAVE

Mutated KRAS

ASP3082
pan KRAS degrader

2\textsuperscript{ND} WAVE

Other oncology targets

Next-generation protein degrader

3\textsuperscript{RD} WAVE

Non-oncology target (e.g. immunology)

Next-generation protein degrader

KRAS: Kirsten rat sarcoma viral oncogene homologue
OUR PORTFOLIO CONSISTS OF **DIFFERENTIATED DEGRADERS AND THEIR BACKUPS – ALL ADDRESSING HISTORICAL UNDRUGGABLES**

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

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

<table>
<thead>
<tr>
<th>Primary Focus Candidate</th>
<th>Primary Focus</th>
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Research Organization

Venture Unit
Tumor-directed Inhibition

Research Engine
Targeted Protein Degradation

Goal

<table>
<thead>
<tr>
<th>Lead Program Creation</th>
<th>Drug Candidate Creation and Program Expansion</th>
</tr>
</thead>
</table>

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