Protein Degradation Therapeutics: PROTAC®
Drug Discovery at Arvinas
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Safe harbor and forward-looking statements

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including statements regarding the potential for PROTAC® protein degraders and whether our PROTAC® degraders eliminating the androgen receptor, or AR, may surpass the benefits of AR inhibitors and the extent to which an AR-targeting PROTAC® degrader may address the unmet needs of patients with prostate cancer across multiple stages of disease; and timings with respect to any of our clinical trials. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

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Arvinas: Advancing a new therapeutic modality to patients

**ARVINAS**

- Founded in 2013 by the original PROTAC pioneer
- Protein degradation platform with clinical proof of concept

**400+ team members**

**PROTEIN DEGRADATION**

- PROTAC® protein degraders **eliminate** vs. inhibit disease-causing proteins
- Combines the **power of genetic knockdown** technology with the **benefits of small-molecule** therapeutics
- Consistent ability to create PROTAC® degraders with drug-like properties and signals of clinical efficacy and tolerability

**PIPELINE**

Clear efficacy signals in patients with difficult-to-treat breast and prostate cancers

- **1 Program in Phase 3**
- **2 Programs in Phase 2**
- **20+ Pipeline Programs** in oncology and neuroscience

**PARTNERED FOR SUCCESS**

in drug discovery, development, and commercialization

- **ARV-471**
- **ARV-766**
- **ARV-110**
- Pfizer
- Genentech
- Insilico Medicine
- GNS
- PHOREMOST
- Bayer
- Cerbios-Pharma
PROTAC® protein degraders combine the benefits of small molecules and gene-based knockdown technologies

Arvinas’ proteolysis-targeting chimera (PROTAC®) degraders can:

• Eliminate (rather than inhibit) disease-causing proteins
• Disrupt scaffolding functions of target proteins
• Bind and degrade classically “undruggable” proteins
• Act iteratively (catalytically)
• Be delivered orally and achieve broad tissue distribution, including across the blood-brain-barrier
Potential advantages of PROTAC® protein degraders over inhibitors

**Overcome Target Protein Overexpression**

*PROTAC® degraders can disable this common tumor resistance mechanism*

- Lapatinib alone results in HER2-overexpression, but a PROTAC created with lapatinib as the “warhead” degrades natural and overexpressed HER2
- HER2 degraded despite increased RNA levels

**Selectively Eliminate Mutated Proteins**

*PROTAC® degraders can differentiate between mutant and wild type proteins*

- The three mutants of BRAF shown (V600E, K601E, G466V) differ from the wild type by a single point mutation, but are degraded by a BRAF-targeted PROTAC that spares the wild type

1 hMito is a protein not targeted to degrade (loading control)
Weak or promiscuous ligands can be converted into potent and selective PROTAC® degraders

When developed into PROTAC® degraders, weak binders can become potent degraders

- Foretinib is a relatively weak binder to p38a
- PROTAC 1 is a foretinib-based PROTAC degrader with a p38a binding affinity of 11 mM
- Despite its 11 mM binding affinity, PROTAC 1 has a DC$_{50}$ of 210 nM
  - Based on experience, optimization of potency better than 210 nM is likely

When developed into PROTAC degraders, promiscuous ligands can become selective degraders

- Foretinib binds to 133 protein kinases (left panel)
- In cells treated with a foretinib-based PROTAC degrader, only a small subset of cellular proteins are degraded (blue-shaded quadrant of the right panel)

A PROTAC degrader based on foretinib has a nanomolar DC$_{50}$ despite a 11 mM binding affinity

DC$_{50}$ = 210 nM

Binds 133 Kinases

Degrades <10 Proteins
Heterobifunctional PROTAC® protein degraders pose unique challenges for drug design and development

1. Complex Formation: Recognizing disease causing protein of interest
2. Protein Tagging: Tagging of target protein for degradation
3. Protein Destruction: Target protein is degraded by the proteasome

**PROTAC®**
- High specificity without the requirement for strong binding

**Inhibitor**

<table>
<thead>
<tr>
<th>Potency</th>
<th>ADME/PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligand binding (x2)</td>
<td>Oral availability: Usually within Ro5 space</td>
</tr>
<tr>
<td>POI off-targets + E3 neomorphs</td>
<td>Pharmacology of inhibition</td>
</tr>
<tr>
<td>Ternary complex (linker length/exit vector)</td>
<td></td>
</tr>
</tbody>
</table>

**Oral availability:**
- Usually within Ro5 space
- Pharmacology of inhibition
Considerations on why to Make a Molecule (or PROTAC)

- Improve potency – usually the easiest part
- Improve in vitro ADME – not usually informative for PROTACs
- Improve in vivo pharmacokinetics – multifactorial analysis
  - permeability, metabolism, efflux.....
- Improve in vivo pharmacodynamics and activity – relationship of plasma protein binding, exposure and potency
- Synthetic accessibility – balance resources

ADME: Absorption, Distribution, Metabolism, Excretion
Considerations on how to Make a Molecule (or PROTAC)

- How can it be broken down into synthetically accessible fragments?
- What fragments can be bought?
- What reagents can be bought?
- How should the fragments be assembled?
- What known chemical reactions can be used?
- Does a new chemical reaction need to be researched/invented?
- Are there any related molecules that have already been made?
Arvinas’ PROTAC® degraders eliminate the androgen receptor (AR), potentially surpassing the benefits of AR inhibitors

An AR-targeting PROTAC degrader may address the unmet needs of patients with prostate cancer across multiple stages of disease

AR is a critical target in prostate cancer, but tumors develop resistance to standard-of-care AR inhibitors

Arvinas has two oral AR-targeting PROTAC degraders in Phase 2 studies:

• Bavdegalutamide (ARV-110)
• ARV-766

Activity in late-line settings suggests potential for even stronger benefit in earlier-line, less-pretreated patients

1 in 8 U.S. men will be diagnosed with prostate cancer during their lifetime

Prostate cancer is the 2nd leading cause of cancer death for men in the U.S.

AR, androgen receptor

1 ACS: https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html, accessed 2/22/22;
2 American Cancer Society
Evolution of AR-degrading PROTACs leading to ARV-110

Early discovery efforts
-Multiple E3 recruiting ligands
-Multiple AR binders

**1**
Potent degradation
Encouraging %F
High CI

**14**
Possible candidate
In vivo potency suboptimal
Crystallized to high melting solid

**15**
Good in vitro degradation potency
Possible autoinduction signal
AR ligand by itself agonist
In vivo potency superseded by **16**

**16**
Possible candidate
Dose escalation exposure suboptimal

Bavdegalutamide
(ARV-110)
Bavdegalutamide (ARV-110) retrosynthesis

Bavdegalutamide (ARV-110) + Intermediate-1 = Intermediate-2

Intermediate-3 + Intermediate-3 = Second generation

Intermediate-3 + Intermediate-3 = Fifth generation

John Grosso, Max Reeve, Herman Chen
Intermediate 2: Second generation

1. Cl17\[\text{N} \rightarrow \text{Boc}\text{H} \text{Cl}\[\text{N} \rightarrow \text{Boc}\text{H}\]
   \(\text{NaH, DMA, 45 °C}\)

2. Cl19\[\text{N} \rightarrow \text{Cl}\[\text{N} \rightarrow \text{Cl}\]
   \(\text{AcCl, MeOH, rt}\)

3. Intermediate-3

4. Cl20\[\text{N} \rightarrow \text{OH}\]
   \(\text{TEA, T3P, EtOAc}\)

5. HO21\[\text{N} \rightarrow \text{OH}\]
   \(\text{DIPEA, DMA, 90-100 °C}\)

6. Intermediate-2

7. TEMPO/NaOCl
   \(\text{DCM}\)
Intermediate 2: Fifth generation

24

\[ \text{HO-} \text{C-} \text{C-} \text{OH} \text{EtOH} \text{H}_2\text{N}^+ \text{NH}_2 \rightarrow \text{HO-} \text{C-} \text{N-} \text{OH} \text{AcOH} \rightarrow \text{HO-} \text{C-} \text{N-} \text{OH} \text{POCl}_3 \]

MeOH HCl

25

26 R = H

27 R = Me

20

28

\[ \text{NH-} \text{CH}_2 \text{CH}_2 \text{OH} \text{DIPEA} \rightarrow \text{RO-} \text{C-} \text{N-} \text{OH} \]

NaOH LiOH

29 R = Me

30 R = H

Intermediate-3

31

\[ \text{Cl-CH} = \text{CH}_2 \text{O-} \text{C-} \text{C-} \text{NH}_2 \text{HCl} \]

DMAc DIPEA HOPO EDCI

23

24

\[ \text{HO-} \text{C-} \text{C-} \text{OH} \text{EtOH} \text{H}_2\text{N}^+ \text{NH}_2 \rightarrow \text{HO-} \text{C-} \text{N-} \text{OH} \text{AcOH} \rightarrow \text{HO-} \text{C-} \text{N-} \text{OH} \text{POCl}_3 \]

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DMAc DIPEA HOPO EDCI

23

Intermediate-2

TEMPO

\[ \text{NaOCl} \]

DCM/H$_2$O, 20 °C

Intermediate-2

\[ \text{HO-} \text{C-} \text{C-} \text{OH} \text{EtOH} \text{H}_2\text{N}^+ \text{NH}_2 \rightarrow \text{HO-} \text{C-} \text{N-} \text{OH} \text{AcOH} \rightarrow \text{HO-} \text{C-} \text{N-} \text{OH} \text{POCl}_3 \]

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DMAc DIPEA HOPO EDCI

23

Intermediate-2

TEMPO

\[ \text{NaOCl} \]

DCM/H$_2$O, 20 °C

Intermediate-2
Intermediate 1 and final steps

17 + 18 \rightarrow \text{Reflex, AcOH/}AcO^- 

19 \rightarrow 7 \rightarrow \text{Boc} \text{NH} \rightarrow \text{HCl}

\text{Cl}_3\text{NH} \rightarrow \text{Intermediate-2} \rightarrow \text{NaHB(OAc)}_3\text{NMM DMA, 0 °C}

\text{Bavdegulutamide}
Bavdegalutamide (ARV-110) is shown to robustly and selectively degrade AR

- Assessed ARV-110 selectivity by proteomics
- After 8 hours of treatment of VCaP cells with 10 nM ARV-110 in vitro, AR was the only degraded protein among the nearly 4,000 proteins measured
  - 85% $D_{\text{max}}$\(^2\) (DC50 = 1 nM in VCaP cells)
  - p-value: 3x10\(^{-9}\)

1 VCaP, Vertebral Cancer of the Prostate
2 $D_{\text{max}}$, maximal degradation
Bavdegalutamide (ARV-110) is shown to inhibit tumor growth in an in vivo model of acquired enzalutamide resistance

- In vivo mouse xenograft model of acquired enzalutamide resistance developed at Arvinas
- In this model, VCaP tumors acquired resistance to enzalutamide after being continuously propagated in castrated, enzalutamide treated mice for ~3 years
- Daily and orally delivered ARV-110 significantly inhibited tumor growth (at right)
  - 10 mpk ARV-110: 70% tumor growth inhibition
# Bavdegulutamide (ARV-110) in the Clinic

## Androgen Receptor (AR) Franchise Clinical Trials

<table>
<thead>
<tr>
<th>Post-NHA</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bavdegulutamide pivotal Phase 3 trial</td>
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<td>Anticipated 2H23</td>
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<td>Bavdegulutamide/abiraterone combo Phase 1B</td>
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<td>Ongoing</td>
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<td>ARV-766 Phase 2 dose expansion</td>
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<td>Ongoing</td>
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<tr>
<td>ARV-766 Phase 1 dose escalation</td>
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<td>Data expected 2Q23</td>
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</table>

| Pre-NHA | Phase 1B/2 | | | Expect to begin in 2023 |

**NHA**, novel hormonal agent
Summary

- PROTAC® protein degraders provide advantages over inhibitors, and also pose unique design challenges, which Arvinas has pioneered overcoming in placing three compounds to date in human clinical trials.
- Significant oral availability across multiple preclinical species in the AR degrader program provided confidence in pushing the first PROTAC®, bavdegalutamide, to the clinic.
- Process route developed to provide highly pure bavdegalutamide on kilogram scale to enable multiple clinical trials globally.
Thank You