PROTAC Discovery Engine: Harnessing the power of oral blood brain barrier penetrant degraders and new E3 ligases
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 development and regulatory status of our product candidates, such as statements with respect to our lead product candidates, ARV-110, ARV-471 and ARV-766 and other candidates in our pipeline, and the timing of clinical trials and data from those trials and plans for registration for our product candidates, and our discovery programs that may lead to our development of additional product candidates, the potential utility of our technology and therapeutic potential of our product candidates, the potential commercialization of any of our product candidates, the potential benefits of our collaborative partnerships, and the Bayer joint venture, and the sufficiency of our cash resources. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. 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.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make as a result of various risks and uncertainties, including but not limited to: whether we will be able to successfully conduct Phase 1/2 clinical trials for ARV-110 and ARV-471, initiate and complete other clinical trials for our product candidates, and receive results from our clinical trials on our expected timelines, or at all, whether our cash resources will be sufficient to fund our foreseeable and unforeseeable operating expenses and capital expenditure requirements, each party’s ability to perform its obligations under our collaborations and/or the Bayer joint venture, our expected timeline and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, discussed in the “Risk Factors” section of the Company’s quarterly and annual reports on file with the Securities and Exchange Commission. The forward-looking statements contained in this presentation reflect our current views as of the date of this presentation with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law.

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PROTAC® protein degraders harness the ubiquitin-proteasome system to induce the degradation of disease-causing proteins.
**ARV-471 & ARV-110, our most advanced PROTACs: Proof-of-concept and opportunities to benefit patients in large areas of unmet need**

<table>
<thead>
<tr>
<th><strong>ARV-471</strong></th>
<th><strong>ARV-110</strong></th>
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<tbody>
<tr>
<td>Estrogen receptor-degrading PROTAC®</td>
<td>Androgen receptor-degrading PROTAC®</td>
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</table>

### Breast Cancer
- **ARV-471**
  - Potential best profile of any ER-targeting therapy:
    - Tolerability
    - ER degradation
    - Clinical benefit
  - Initiated Phase 2 VERITAC trial; while Phase 1 dose escalation continues
  - Potential future endocrine therapy of choice in both adjuvant and metastatic settings

### Prostate Cancer
- **ARV-110**
  - AR degradation and clear signals of efficacy observed in late-line mCRPC
  - Extensive molecular profiling of tumors to understand drivers of resistance
  - Initiated Phase 2 ARDENT trial; two potential paths to registration: 3L molecularly defined, and broader 1L/2L
  - >250k patients† per year with high unmet need

Data as presented 12/14/2020

† US incidence data from SEER database
AR, androgen receptor; ER, estrogen receptor
Arvinas’ pipeline encompasses a range of validated and undruggable targets in oncology, I-O, and neuroscience.

<table>
<thead>
<tr>
<th>ARVN Program</th>
<th>Indication</th>
<th>Exploratory</th>
<th>Research</th>
<th>IND Enabling</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tr>
<td>ARV-110</td>
<td>mCRPC</td>
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<td>ARV-471</td>
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<td>BCL6</td>
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<td>Undisclosed</td>
<td>Solid Malignancies</td>
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<td>Myc</td>
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<td>HPK1</td>
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Note: Pipeline is non-exhaustive and IND dates are anticipated.
mCRPC, metastatic castration-resistant prostate cancer; ER+/HER2-, estrogen receptor+/human epidermal growth factor receptor 2-; NSCLC, non-small-cell lung carcinoma; CRC, colorectal cancer; FTLD-tau, frontotemporal lobar degeneration-tau; PSP, progressive supranuclear palsy; MSA, multiple systems atrophy.
Arvinas’ breakthroughs are driven by our integrated PROTAC® Discovery Engine

**PROTAC Discovery Engine**

1. **Target/Ligase Selection & Ligand Identification**
   - E3 KnowledgeBase of novel E3 ligases
   - Advanced screening capabilities, including proprietary DNA-encoded libraries tailored for PROTAC development
   - Novel warheads for undruggable targets and new ligands for E3 ligases

2. **Rapid PROTAC Design**
   - Optimizing the Zone of Ubiquitination
   - Arvinas Next Generation Linker Evolution (ANGLE)
   - Predictive computational modeling
   - State-of-the-art proteomics capabilities

3. **Turning Degraders Into Drugs**
   - “Arvinas Rules” for drug-like properties, including blood-brain barrier penetration and oral bioavailability in humans
   - Deep knowledge of in vivo PK/PD and efficacy relationships

**Arvinas’ platform is built from nearly 20 years of experience, know-how, and IP**
Platform Validation: preclinical proof-of-concept – ternary complex

**ARV-471**: Induces proximity between CRBN E3 ligase & the estrogen receptor, leading to ER degradation

- The IC_{50-app} of ARV-471 is left-shifted when recombinant ER-LBD is included in a CRBN displacement assay, suggesting induced **ternary complex formation** between ER-LBD & CRBN

- The IC_{50-app} of lenalidomide remains unaffected by the presence or absence of ER-LBD
Platform Validation: preclinical proof-of-concept – *in vivo* degradation

**ARV-471**: Induces proximity between CRBN E3 ligase & the estrogen receptor, leading to ER degradation

- ARV-471 induces ER degradation in multiple ER+ breast cancer cell lines, including MCF-7 cells and ESR1-mutant lines
- Oral, daily dose of ARV-471 inhibited tumor growth by 99% at 10 mpk and 106% at 30 mpk in an ESR1 mutant PDX model, with superior tumor growth inhibition compared to fulvestrant

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1 also tested: MB-134-VI, T47D, D538G, Y537S, ZR-75-1, BT474 & CAMA-1
2 fulvestrant schedule: 2x weekly x2 / q7dx2
The Ultimate Platform Validation: PROTACs can be Drugs

**ARV-471**: ER Degradation & Confirmed RECIST Partial Response (cPR) in late-stage patients with extensive prior therapy

<table>
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<tr>
<th>Baseline</th>
<th>After treatment 60 mg ARV-471</th>
<th>Baseline CT Scan</th>
<th>After 4 Cycles</th>
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† Includes one selective ERα covalent antagonist.

CDK: cyclin-dependent kinases; ESR1 mutation-D538G

Data as presented 12/14/2020

51% reduction in target lesions (RECIST partial response)
PROTAC® heterobifunctional degrader molecules create a strong opportunity in neuroscience compared to other modalities.

PROTAC® degraders may overcome the limitations of other platforms.

**PROTAC Potential**
- Reduce intra- and extracellular pathologic protein
- Discriminate between wild type and pathologic protein
- Oral administration with BBB biodistribution

**ASO**
- Requires intrathecal dosing
- Does not discriminate wt from pathologic protein

**Ab**
- Blocks only extracellular pathologic protein
- IV dosing results in only 0.5% in CSF
tau PROTAC small molecules can degrade P301L insoluble aggregates

In vitro insoluble tau PROTAC degradation

In vivo insoluble tau PROTAC degradation

Reduced Seed Potential Ex vivo brain extracts

PK-PD

Dose (mg/kg)

Insoluble PHF1 Tau (%Veh)

Brain exposure (nM)

Tg2508 24h post single PROTAC IV dose

Tg2508 brain extracts 24h post single IV dose

Cortex – Vehicle
Cortex – PROTAC A – 24 hours
Cortex – PROTAC B – 24 hours
P301L\(^5\), No PFF seeds\(^2\)

**

* on mechanism

![Image 46x70 to 221x280]

![Image 482x69 to 692x221]
PROTAC targets mutant and spares WT to tackle genetically defined disease target in CNS

Fit with Neuroscience Strategy

Core Strategy
- Precision Medicine
- Genetic/Proteinopathy
- Target root cause
- PROTAC differentiator
- Biomarker PoC

PROTAC selectively degrades mutant and spares WT protein

Other CNS Diseases

Genetic Neuromuscular

WT DC$_{50}$ >5µM
Mutant protein DC$_{50}$ = 23nM
PROTACs degrade a scaffolding target dose-dependently in brain 24h following single oral administration.

*Target involved in pathologic protein clearance*
Employing E3 ligases for PROTACs
Arvinas’ PROTAC® Discovery Engine – Unlocking E3 ligases

**Rationally designed degraders – PROTACs, etc**

- Ability to target multiple therapeutic areas
- Versatility in pathway coverage (can target multiple signaling nodes)
- Large potential in chemical space
- Advantage of the power of the tenets of PROTACs

**What is a good E3 of choice? What makes a good PROTAC E3 to develop?**

**600+ E3 ligases in humans → how best to sample this ligase ocean?**
Our E3 KnowledgeBASE: understanding E3 ligase tumor enrichment

- Classifying E3 ligases based on essentiality, tumor- & tissue distribution
  - Non-enriched, ubiquitously expressed (e.g. CRBN)
  - Enriched, pan-cancer, essential
  - Enriched, cancer-specific
Our E3 KnowledgeBASE: understanding ligase attributes for ligase selection

- Tissue distribution
- Tumor enrichment
- Tumor essentiality
- Structural enablement
- Mechanistic understanding
- Line-of-sight to PROTAC

600+ human E3 ligases

High value E3s for PROTAC development

Ligase selection → Deep understanding of ligase mechanisms → E3 Ligand ID & optimization → Conversion to PROTAC
From ligase-to-PROTAC at Arvinas: endogenous substrate degradation

Validating a CRL-based ligase for endogenous substrate degradation

Deep understanding of ligase mechanisms
From ligase-to-PROTAC at Arvinas: structure-binding relationship to evolve ligase ligands

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Structural & mechanistic understanding of ligase:substrate relationships leads to rapid lead discovery & hit evolution

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potency evolution

E3 ligand ID & optimization

ARVN ligand: E3 ligase co-crystal structure(s)
From ligase-to-PROTAC at Arvinas: untapped E3 hijacked for PROTAC degradation

Rational design of PROTACs against a new E3 compare favorably to a CRBN PROTAC

Conversion to tool PROTAC & PoC degradation

Degradation Evolution
HiBiT-Brd4 degradation (6hr / prostate cancer cells)

*specificity also showed by KD of E3 (data not shown)
Putting it all together: one ligase-to-PROTAC campaign at Arvinas

The list of ligases exploited for tool PROTAC (& molecular glue!) degraders keeps growing at incredible pace:

- CRBN, VHL, IAPs, MDM2, DCAF15
- DCAF16, RNF114, RNF4
- KEAP1, AhR, DDB1
- DCAF11, FEM1B ...

...we are very much looking forward to seeing these potentially translate into in vivo active & clinical degrader molecules over the coming years to benefit patients!
Acknowledgements – the entire Arvinas Team

Thank you!