The Discovery of ARV-471, an Orally Bioavailable Estrogen Receptor Degrading PROTAC® for the Treatment of Patients with Breast Cancer

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PROTAC® protein degraders harness the UPS to induce the degradation of disease-causing proteins.

1. PROTAC protein degraders function inside cells.
2. Formation of trimer complex and ubiquitination of target protein.
3. Multiple ubiquitin molecules “tag” target protein for degradation.
4. Targeted protein is degraded by the proteasome.

**Diagram:**
- **E3 Ligase**
- **PROTAC**
- **Target Protein**
- **Ubiquitination**
- **Proteasome**

**Iterative PROTAC degrader activity.**
PROTAC® protein degraders combine the advantages of gene-based medicines and small molecule inhibitors

<table>
<thead>
<tr>
<th>PROTAC protein degraders have distinct advantages over both small molecule inhibitors and gene-based medicines</th>
<th>PROTAC™ Protein Degraders</th>
<th>Small Molecule Inhibitors</th>
<th>Gene-Based Medicines</th>
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<tbody>
<tr>
<td>Eliminate pathogenic proteins</td>
<td>✓</td>
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<tr>
<td>Target scaffolding function</td>
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<td>Potential to treat “undruggable” proteins</td>
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<td>Iterative mechanism of action</td>
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<td>Broad tissue penetration</td>
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<td>Orally bioavailable</td>
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<td>Ease of manufacturing</td>
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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>
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<th>Phase 1</th>
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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.
Breast cancer is the second leading cause of cancer death in women

Types of Breast Cancer
- Breast cancer is the second most common cancer in women
- ~268,000 women are expected to be diagnosed with invasive breast cancer in the US in 2019
- Metastatic breast cancer accounts for ~6% of newly diagnosed cases

Targeted Approaches to Treat ER+ Breast Cancer
- Fulvestrant has validated the value of ER degradation
- After 6 months of fulvestrant treatment, up to 50% of ER baseline levels remain

A superior ER degrader is needed

ARV-471 is a Potent Degrader of ER in multiple cell lines

Orally bioavailable estrogen receptor-targeted PROTAC protein degrader

- ARV-471 is in development for the treatment of women with ER+ locally advanced or metastatic breast cancer
- Potential as both a single agent and in combination with CDK4/6 inhibitors

ARV-471 Degrades ER in ER+ Breast Cancer Cell Lines

- ARV-471 induces ER degradation in multiple ER+ breast cancer cell lines, including MCF-7 cells and ESR1-mutant lines
- $\text{DC}_{50} = 1.8 \text{ nM}$ in MCF7 cells

1 Also tested: MB-134-VI, T47D, D538G, Y537S, ZR-75-1, BT474, CAMA-1
2 $\text{DC}_{50} = \text{Half-maximal degradation concentration}$
3 Beta-actin is a protein ARV-471 and fulvestrant are not targeted to degrade, and is included as a loading control
ARV-471 Exhibits Superior TGI vs Fulvestrant in a Y537S (ER Gene Mutation) PDX Model

**ARV-471 In Vivo Preclinical Development**

- 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 (at right)
- Superior inhibitor of tumor growth compared to fulvestrant
- In corresponding quantitative western blots, ER is reduced by 79% and 88% in the 10 mpk and 30 mpk arms, respectively, vs. 63% for fulvestrant

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1 Fulvestrant schedule: 2x weekly x2 / q7dx2
In Combination with Palbociclib, ARV-471 Exhibits Superior Tumor Shrinkage Versus Fulvestrant

ARV-471 In Vivo Preclinical Development

- Achieved significant tumor shrinkage in combination with palbociclib (131% TGI)
  - In all 10 mice in experiment, tumors reduced by >80%
- Superior tumor shrinkage (in combination with palbociclib) compared to fulvestrant (108% TGI)

-Palbociclib arm: 60 mpk po qd; 94% TGI
-Fulvestrant + Palbociclib arm: Fulvestrant 200 mpk sc biwx 2, qwx 3 + palbociclib 60 mpk po qd; 108% TGI
-ARV-471 + Palbociclib arm: ARV-471 30 mpk po qd + palbociclib 60 mpk po qd; 131% TGI

ARV-471’s PK is dose proportional; exposures far exceed preclinical efficacy thresholds

The orange line represents the efficacious exposure for tumor regression in preclinical models.

† AUC_{24}=5717 ng*h/mL for preclinical effective exposure in preclinical model (mice@30mpk). AUC, area under the curve; SE, standard error

Effective half-life (T_{1/2}) \approx 28 hours

Data as presented 12/14/2020
ER degradation observed in patient tumor biopsies

**Red**: Estrogen receptor

**Blue**: Nuclei

**Green**: Tumor (cytokeratin)

*Baseline* vs *After treatment with 60 mg ARV-471*

Method: ER immunoreactivity analyzed by quantitative immunofluorescence (QIF) using the automated quantitative analysis (AQUA) method
ARV-471 demonstrates promising anti-tumor activity in late line patients

Antitumor Activity in Eligible Patients (N=14)†

<table>
<thead>
<tr>
<th>Best Percentage Target Lesion Diameter From Baseline</th>
<th>CDK4/6 inhibitor</th>
<th>Fulvestrant</th>
<th>Investigational SERD</th>
<th>Chemotherapy</th>
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<tr>
<td>0%</td>
<td>SD</td>
<td>SD</td>
<td>PD</td>
<td>PD</td>
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<tr>
<td>-5%</td>
<td>SD (uPR)</td>
<td>SD (uPR)</td>
<td>PR</td>
<td>SD</td>
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</table>

† 7 patients out of 21 are excluded from graph due to no measurable disease at baseline (n=4), discontinuation of treatment without post-treatment target lesion measurements (n=2), and discontinuation after 2 doses due to non-compliance (n=1).
Confirmed RECIST Partial Response in a patient with extensive prior therapy and an ESR1 mutation at 120 mg

**Extensive prior therapy**
- CDK4/6 inhibitor: Palbociclib
- Endocrine therapies: 6 Agents
  - Aromatase inhibitors x 3
  - Tamoxifen
  - Investigational SERDs X 2
- Other targeted agents: Everolimus
- Chemotherapy: 2 Regimens
  - 1 neoadjuvant + 1 metastatic

**ESR1 mutations**
- D538G

Baseline CT Scan

After 4 Cycles

*51% reduction in target lesions (RECIST partial response)*
Medicinal Chemistry Driven Evolution Leading to ARV-471

**Early Discovery Efforts**
- Multiple E3 recruiting ligands
- Multiple ER binders

1. Encouraging DC\textsubscript{50}
   - In vivo exposure

2. GSPT1 degrader

3: \( R = H \)
   - In vivo activity MCF7 xenograft
   - Metabolism suboptimal

4: \( R = \text{CF}_3 \)
   - Good PO exposure in dog

5. Dose escalation
   - In vivo efficacy suitable for DRF

ARV-471
Drug Discovery and Development is a Team Sport