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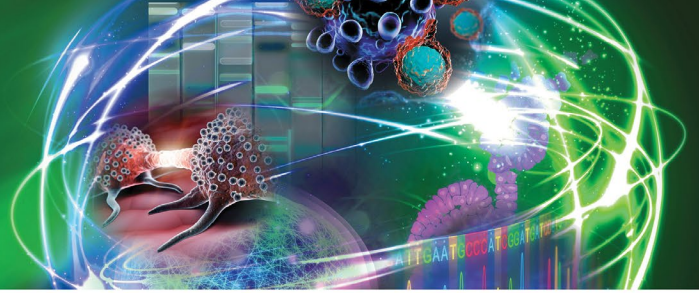

The Discovery of ARV-471, an Orally Bioavailable Estrogen Receptor Degrading PROTAC® for the Treatment of Patients with Breast Cancer

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Disclosure Information

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Lawrence Snyder

I have the following financial relationships to disclose:

Stockholder in: Arvinas Inc

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

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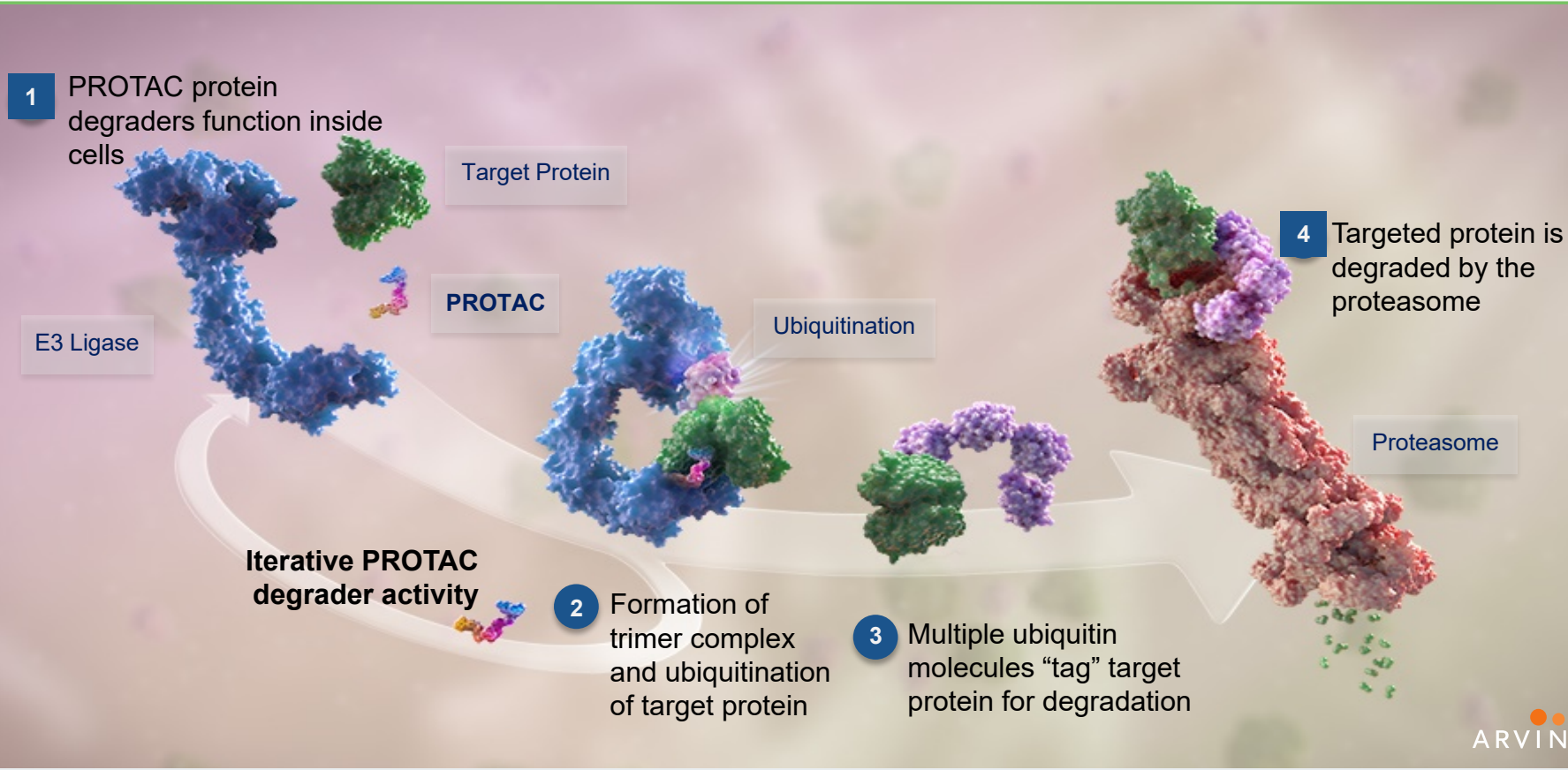

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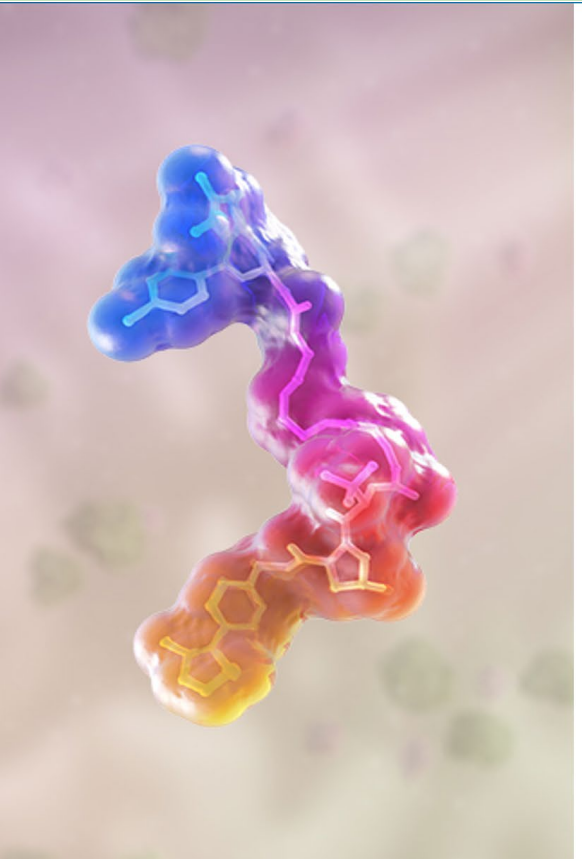
PROTAC® protein degraders combine the advantages of gene-based medicines and small molecule inhibitors



PROTAC protein degraders have distinct advantages over both small molecule inhibitors and gene-based medicines	PROTAC™ Protein Degraders	Small Molecule Inhibitors	Gene-Based Medicines
Eliminate pathogenic proteins	✓	✗	
Target scaffolding function	✓	✗	
Potential to treat "undruggable" proteins	✓	✗	
Iterative mechanism of action	✓	✗	✗
Broad tissue penetration	✓		✗
Orally bioavailable	✓		✗
Ease of manufacturing	✓		✗

Arvinas' pipeline encompasses a range of validated and undruggable targets in oncology, I-O, and neuroscience

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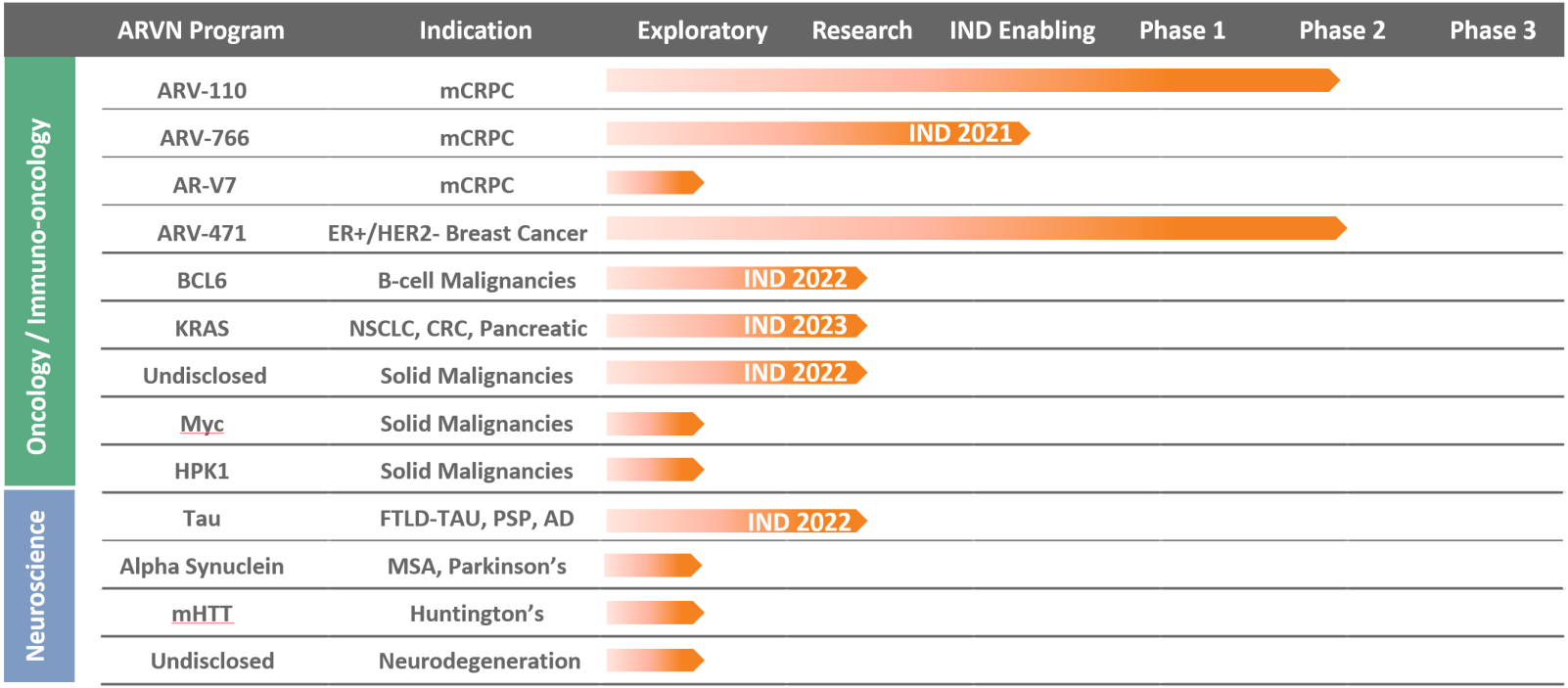

Note: Pipeline is non-exhaustive and IND dates are anticipated.
mCRPC, metastatic castration-resistant prostate cancer; ER+/HER2-, estrogen receptor+/human epidermal growth factor receptor 2-; NSCLC, non-small-cell lung carcinoma; CRC, colorectal cancer; FTLD-tau, frontotemporal lobar degeneration-tau; PSP, progressive supranuclear palsy; MSA, multiple systems atrophy

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Breast Cancer is the Second Leading Cause of Cancer Death in Women

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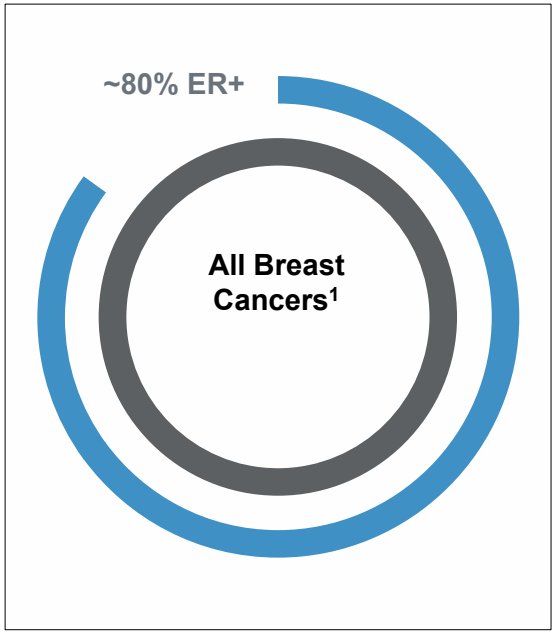
Breast cancer is the **second leading cause** of **cancer death in women**



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[2]
- Metastatic breast cancer accounts for ~6% of newly diagnosed cases[3]

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[4]

A superior ER degrader is needed

1 National Cancer Institute, Hormone Therapy for Breast Cancer 2. American Cancer Society; 3 Malmgren, J.A., Breast Cancer Res Treat (2018) 167:579–590; 4 Gutteridge et. Al., Breast Cancer Res Treat 2004;**88** suppl 1:S177;

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

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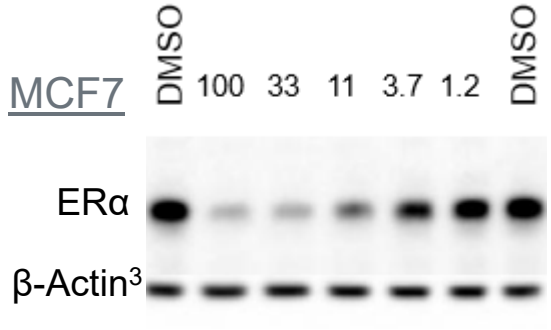
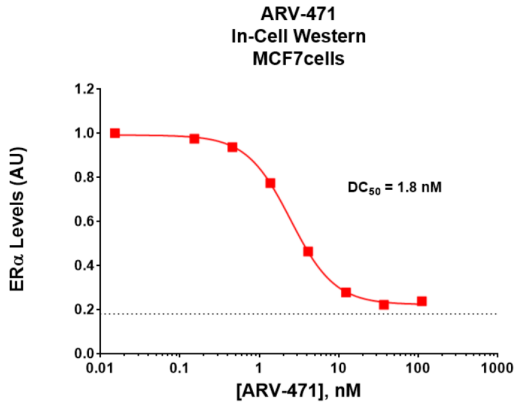
Orally bioavailable estrogen receptor-targeted PROTAC protein degrader

- 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[1]
- **DC_{50} = 1.8 nM** in MCF7 cells[2]





[1] Also tested: MB-134-VI, T47D, D538G, Y537S, ZR-75-1, BT474, CAMA-1
[2] DC_{50} = 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

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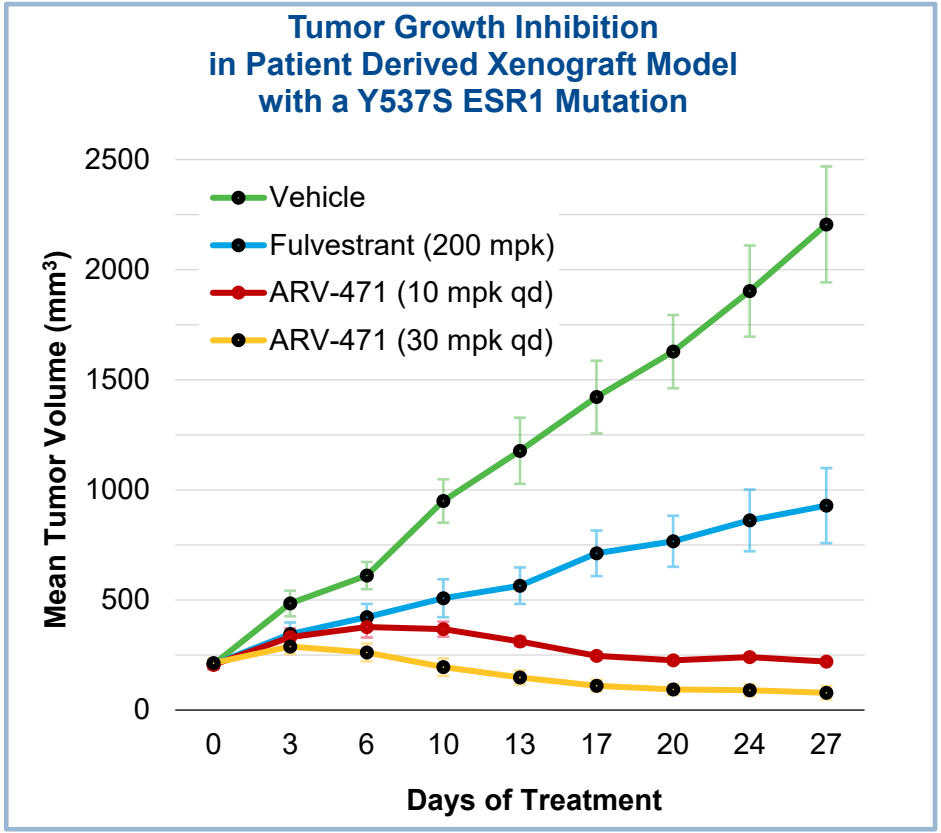
ARV-471 *In Vivo* Preclinical Development

- 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[1]
- 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



[1] Fulvestrant schedule: 2x weekly x2 / q7dx2

In Combination with Palbociclib, ARV-471 Exhibits Superior Tumor Shrinkage Versus Fulvestrant

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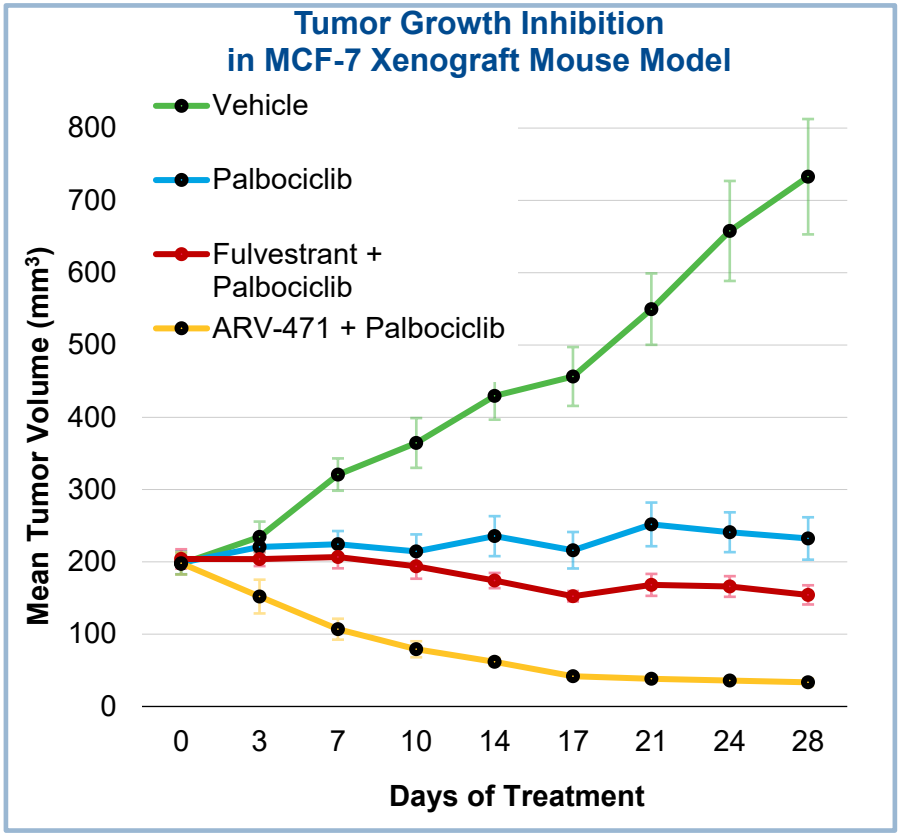
ARV-471 *In Vivo* Preclinical Development

- 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

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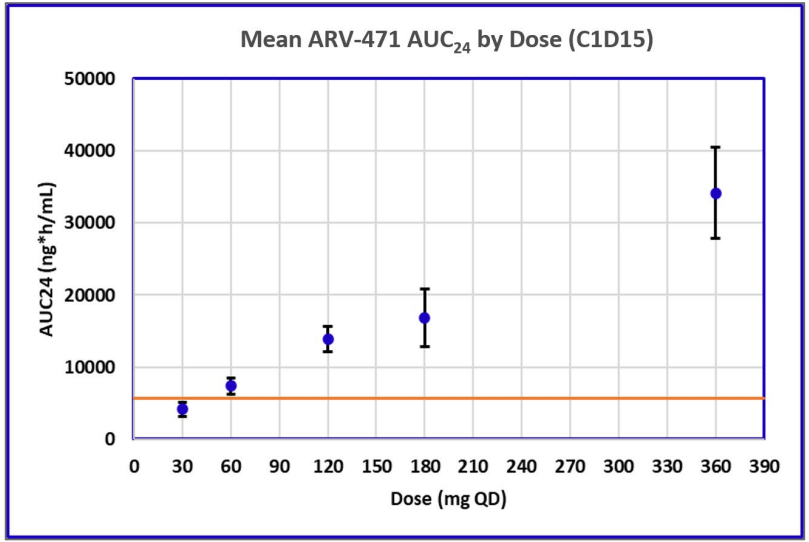

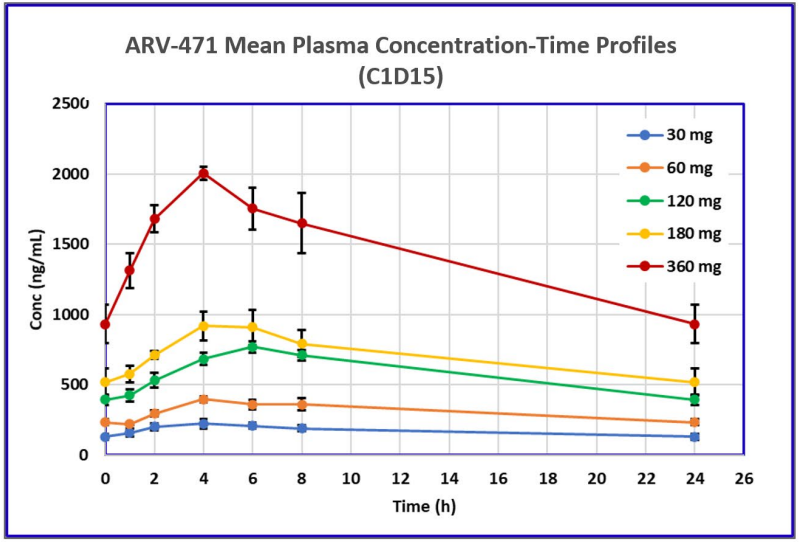

The orange line represents the efficacious exposure for tumor regression in preclinical models †

Effective half-life ($T_{1/2}$) ≈ 28 hours

Data as presented 12/14/2020

† AUC24=5717 ng*h/mL for preclinical effective exposure in preclinical model (mice@30mpk).
AUC, area under the curve; SE, standard error

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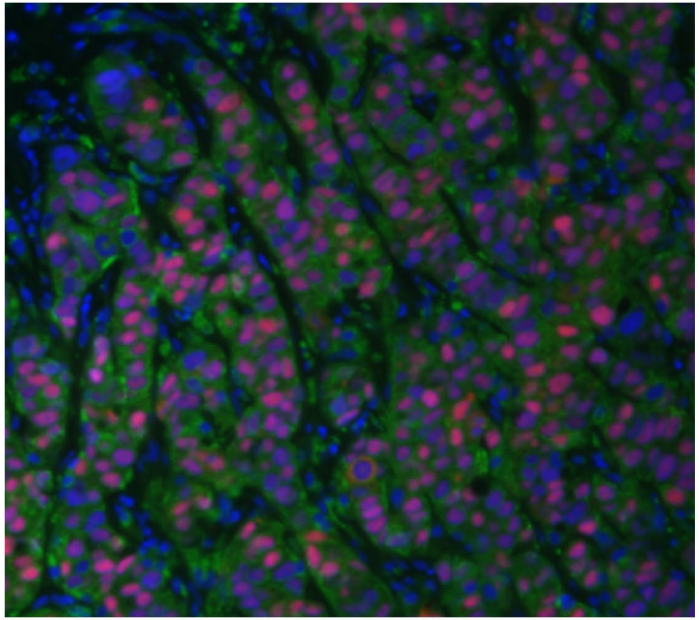
ER degradation observed in patient tumor biopsies

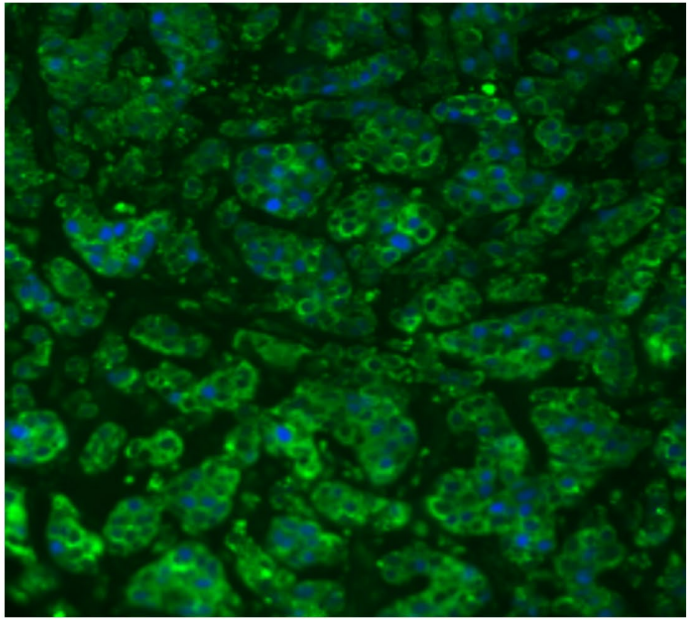
Red: Estrogen receptor

Blue: Nuclei

Green: Tumor (cytokeratin)



Baseline



After treatment with 60 mg ARV-471

Method: ER immunoreactivity analyzed by quantitative immunofluorescence (QIF) using the automated quantitative analysis (AQUA) method

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ARV-471 demonstrates promising anti-tumor activity in late line patients

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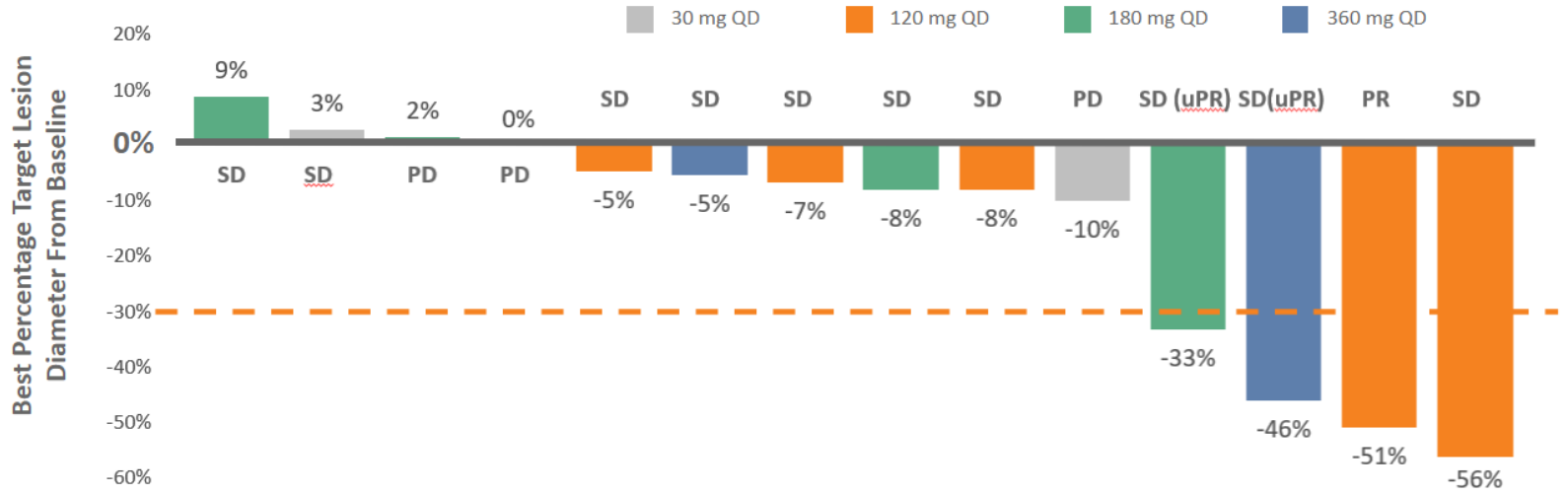
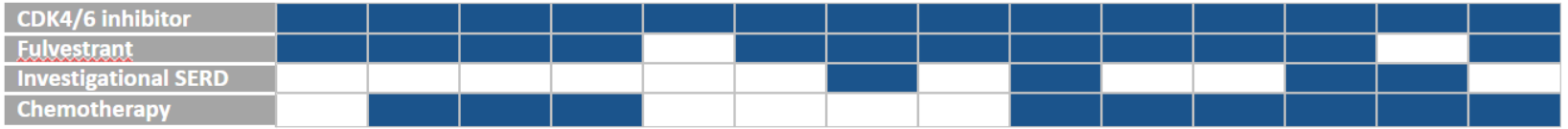
Antitumor Activity in Eligible Patients (N=14)†

Data as presented 12/14/2020





† 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).

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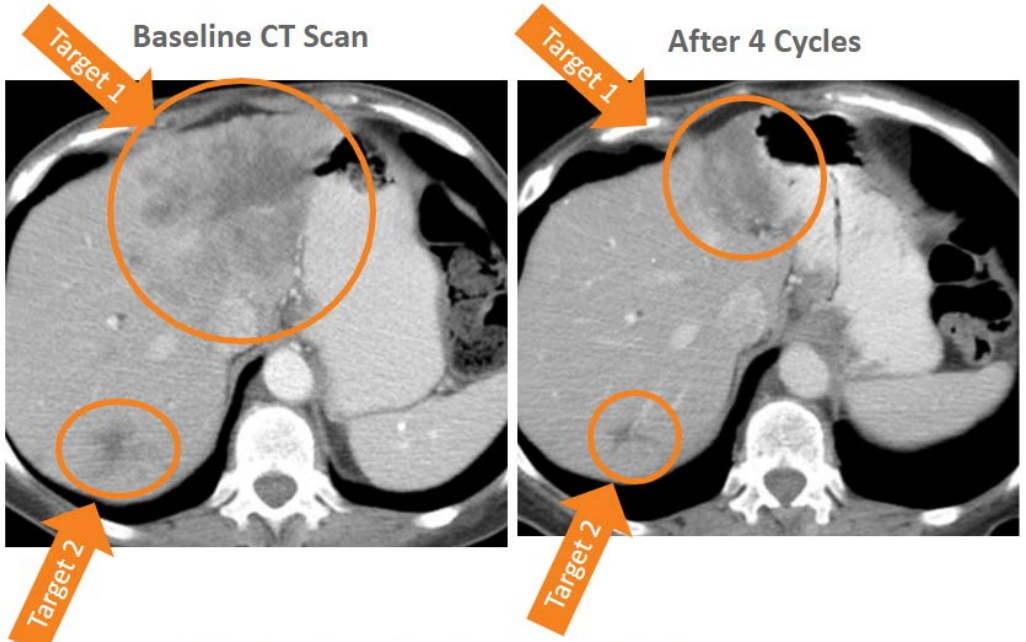
Confirmed RECIST Partial Response in a patient with extensive prior therapy and an ESR1 mutation at 120 mg

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

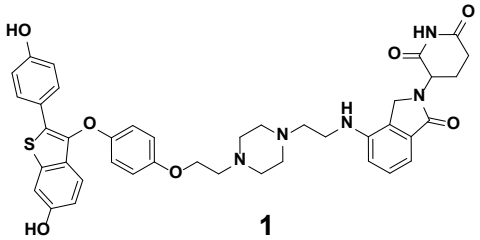
- D538G



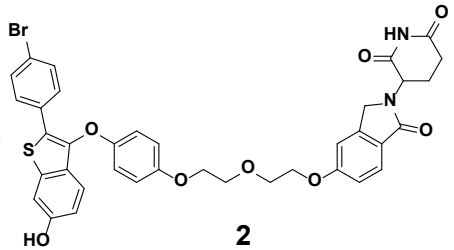
51% reduction in target lesions (RECIST partial response)

Medicinal Chemistry Driven Evolution Leading to ARV-471

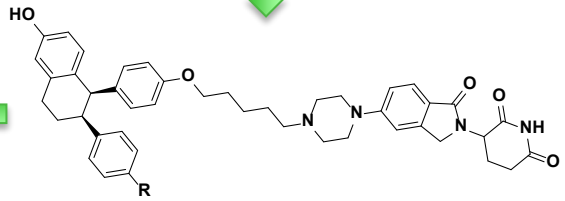
Early Discovery Efforts
Multiple E3 recruiting ligands
Multiple ER binders



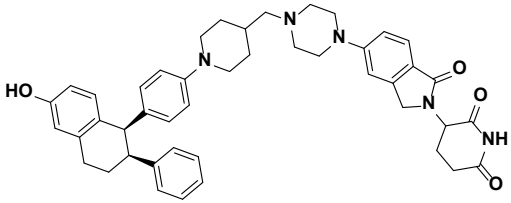
1
Encouraging DC_{50}
In vivo exposure



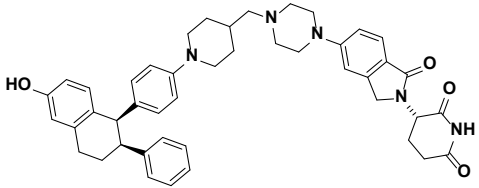
2
GSPT1 degrader



3: R = H
In vivo activity MCF7 xenograft
Metabolism suboptimal
4: R = 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