ARVINAS

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.

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 and complete development for bavdegalutamide (ARV-110) and ARV-766, including whether we initiate and complete clinical trials for our product candidates and receive results from our clinical trials on our expected timelines, or at all; whether our cash and cash equivalent resources will be sufficient to fund our foreseeable and unforeseeable operating expenses and capital expenditure requirements; 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 our quarterly and annual reports on file with the U.S. 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. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this presentation.

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Arvinas: Advancing a new therapeutic modality to patients

ARVINAS

400+ team members

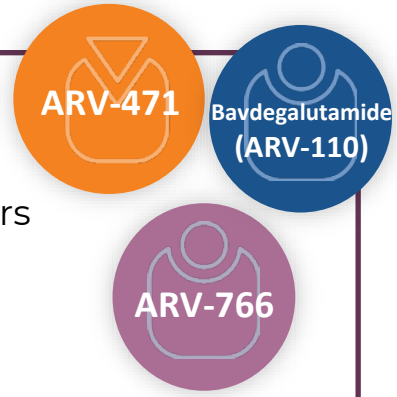
- Founded in 2013 by the original PROTAC pioneer
- Protein degradation platform with clinical proof of concept

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



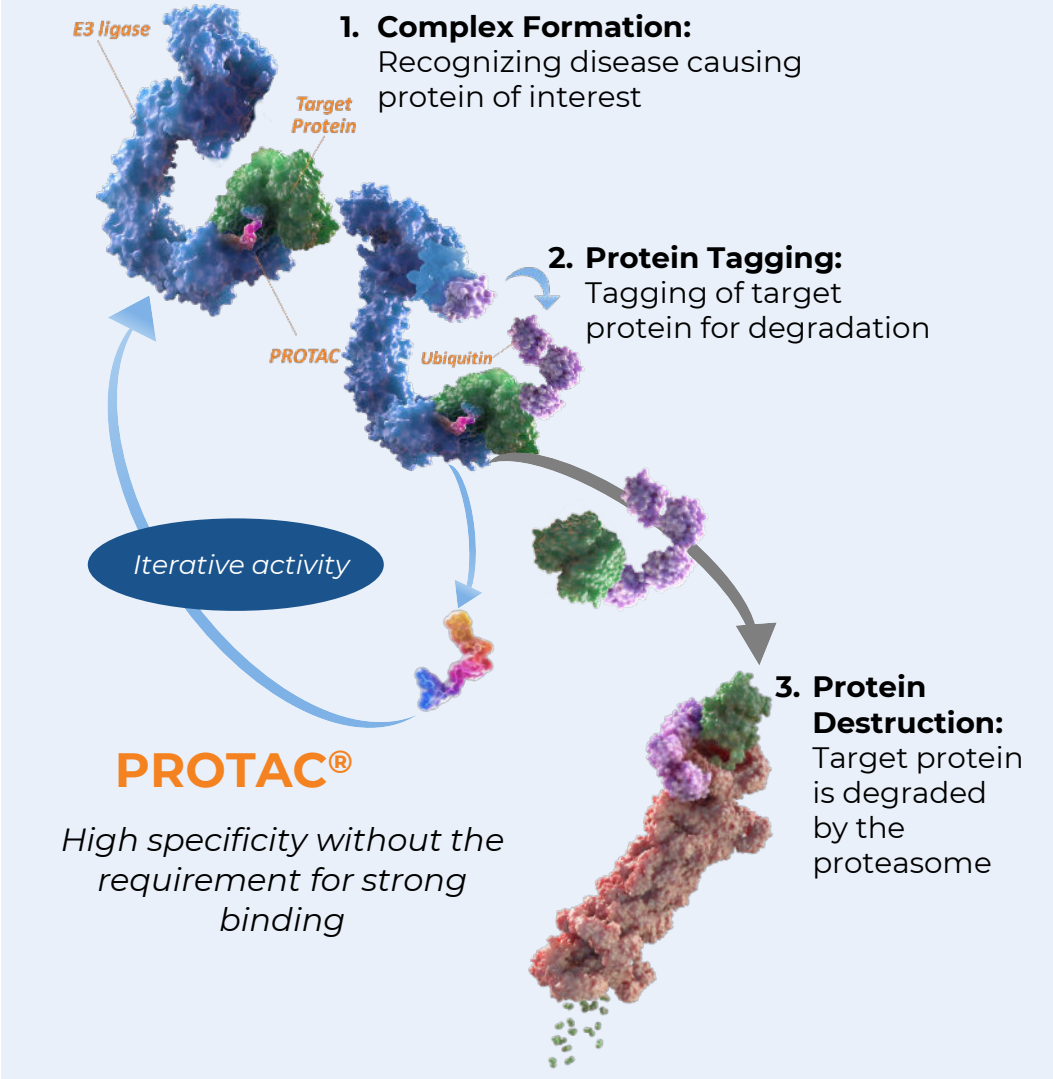
- **1 Program in Phase 3**
- **2 Programs in Phase 2**
- **20+ Pipeline Programs** in oncology and neuroscience

PARTNERED FOR SUCCESS

in drug discovery, development, and commercialization

Pfizer
Genentech
A Member of the Roche Group
Insilico Medicine
Gerthbio
BAYER
GNS
PHOREMOST

PROTAC® protein degraders combine the benefits of small molecules and gene-based knockdown technologies



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

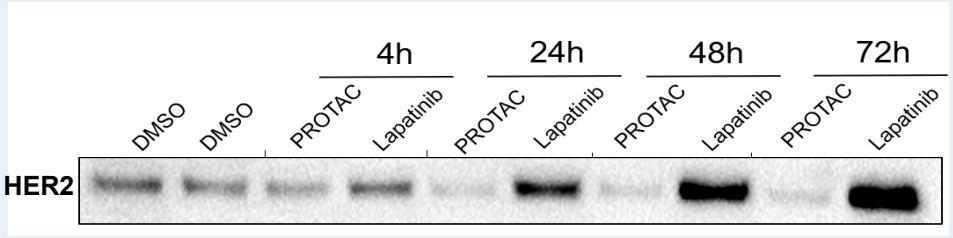
- Eliminate (rather than inhibit) disease-causing proteins
- Disrupt scaffolding functions of target proteins
- Bind and degrade classically "undruggable" proteins
- Act iteratively (catalytically)
- Be delivered orally and achieve broad tissue distribution, including across the blood-brain-barrier

Potential advantages of PROTAC® protein degraders over inhibitors

Overcome Target Protein Overexpression

PROTAC® degraders can disable this common tumor resistance mechanism

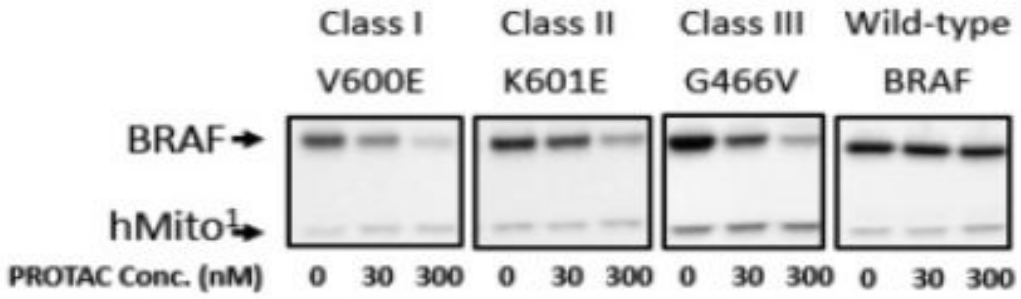
- Lapatinib alone results in HER2-overexpression, but a PROTAC created with lapatinib as the “warhead” degrades natural and overexpressed HER2
- HER2 degraded despite increased RNA levels



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)

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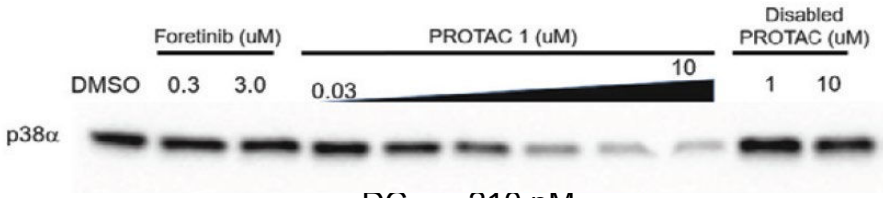
Weak or promiscuous ligands can be converted into potent and selective PROTAC® degraders

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

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

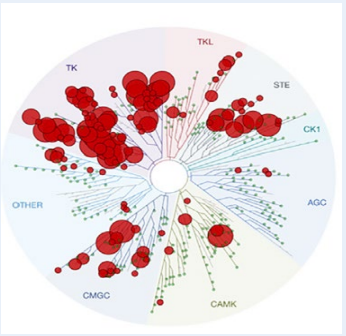


DC_{50} = 210 nM

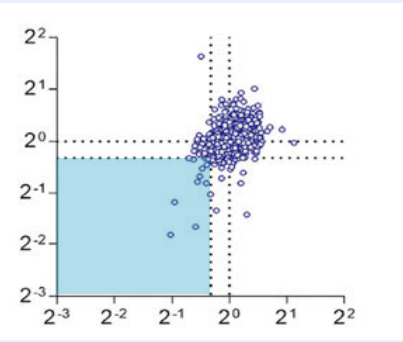
When developed into PROTAC degraders, promiscuous ligands can become selective degraders

- 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*)

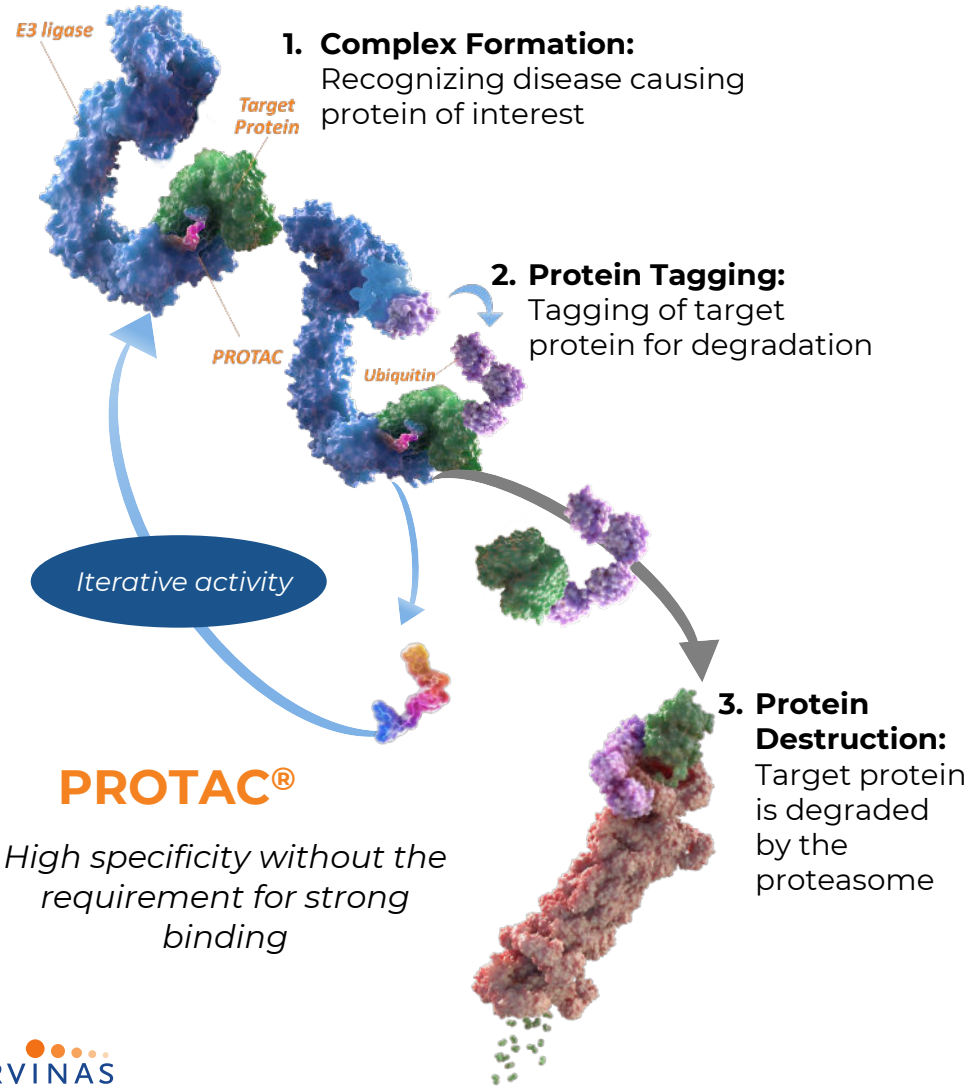
Binds 133 Kinases



Degrades <10 Proteins

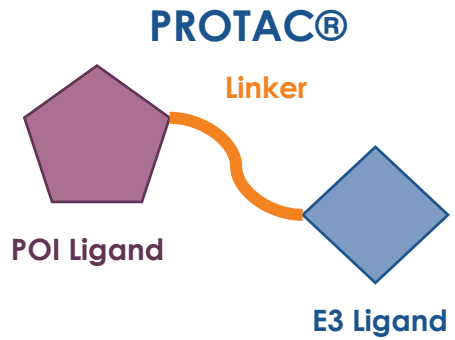


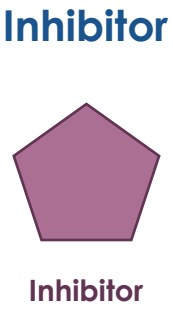
Heterobifunctional PROTAC® protein degraders pose unique challenges for drug design and development



PROTAC®

High specificity without the requirement for strong binding





Potency	
Ligand binding (x2)	Ligand binding
POI off-targets + E3 neomorphs	Off-targets
Ternary complex (linker length/exit vector)	
ADME/PK	
Oral availability: bRo5 properties	Oral availability: Usually within Ro5 space
Pharmacology of degradation	Pharmacology of inhibition

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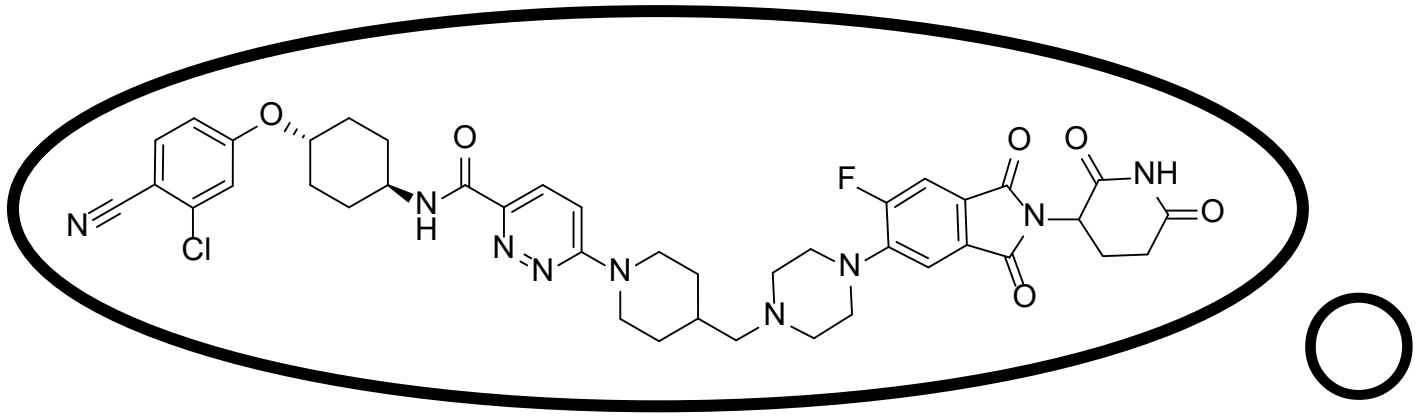
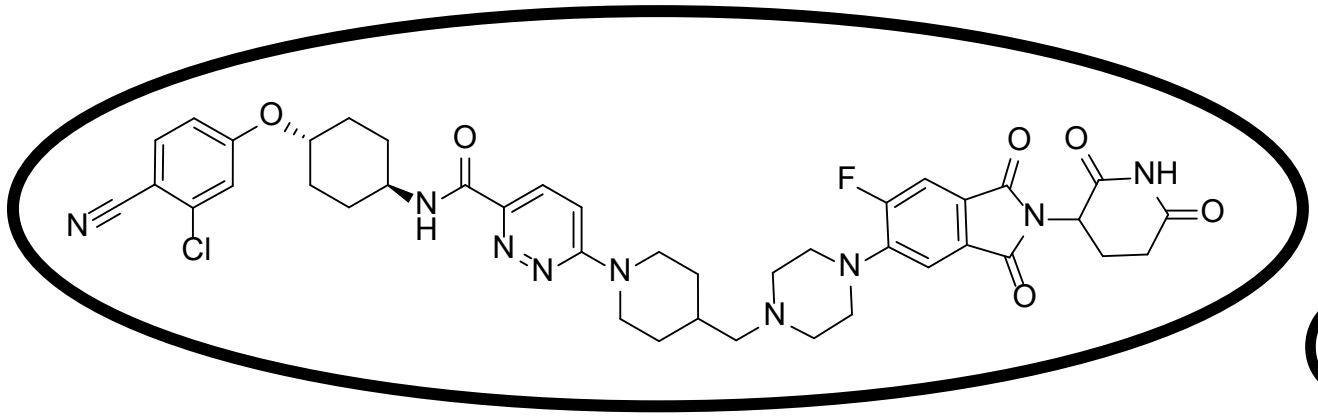
Considerations on why to Make a Molecule (or PROTAC)



- 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?

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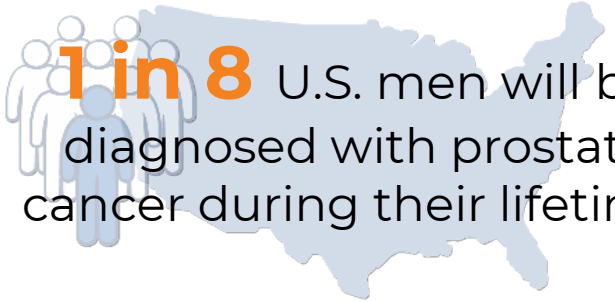
Arvinas' PROTAC® degraders eliminate the androgen receptor (AR), potentially surpassing the benefits of AR inhibitors



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

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

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

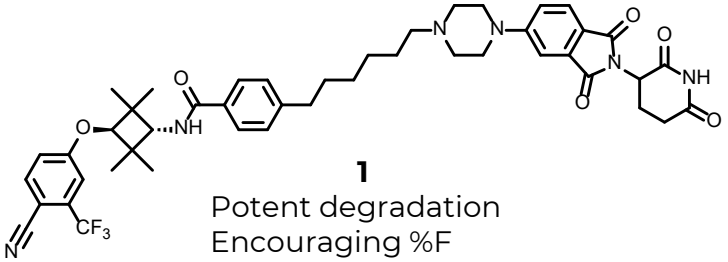
Activity in late-line settings suggests potential for even stronger benefit in earlier-line, less-pretreated patients

AR, androgen receptor

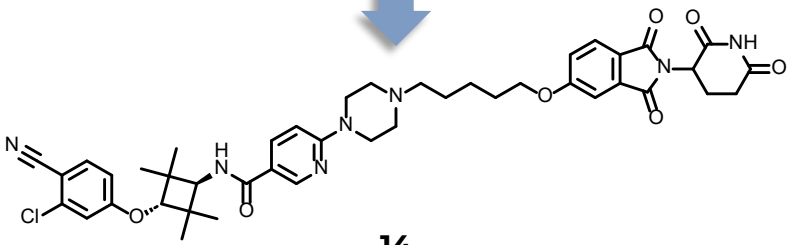
[1] ACS: https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html, accessed 2/22/22;
[2] American Cancer Society

Evolution of AR-degrading PROTACs leading to ARV-110

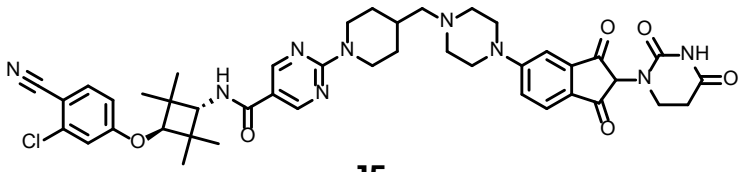
Early discovery efforts
-Multiple E3 recruiting ligands
-Multiple AR binders



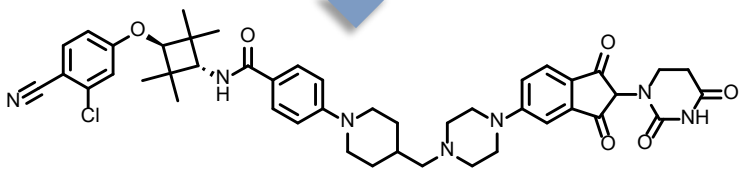
1
Potent degradation
Encouraging %F
High Cl



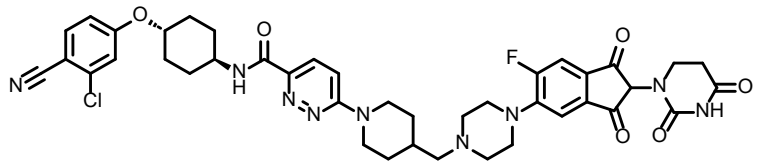
14
Possible candidate
In vivo potency suboptimal
Crystallized to high melting solid



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

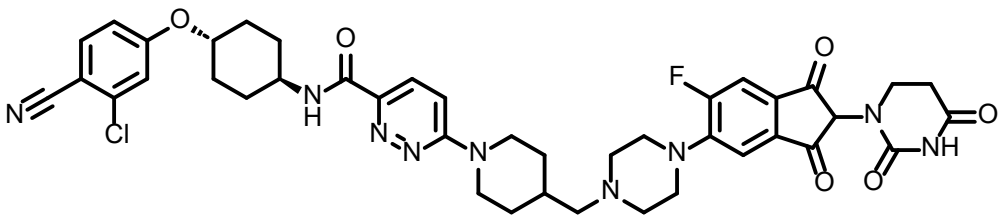


16
Possible candidate
Dose escalation exposure suboptimal

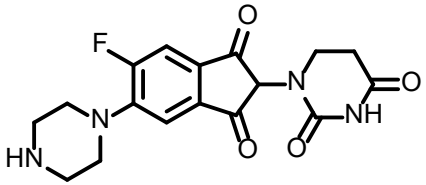


Bavdegalutamide
(ARV-110)

Bavdegalutamide (ARV-110) retrosynthesis

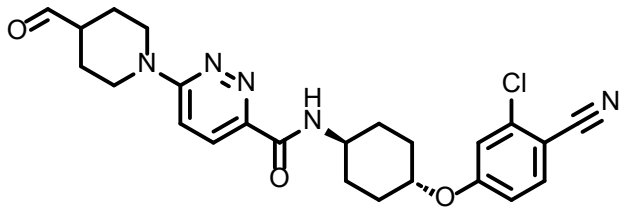


Bavdegalutamide
(ARV-110)



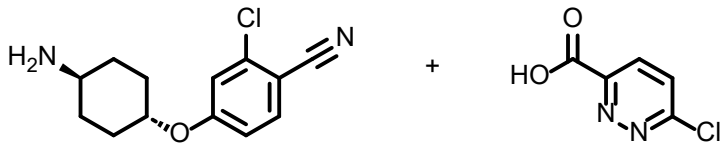
Intermediate-1

+



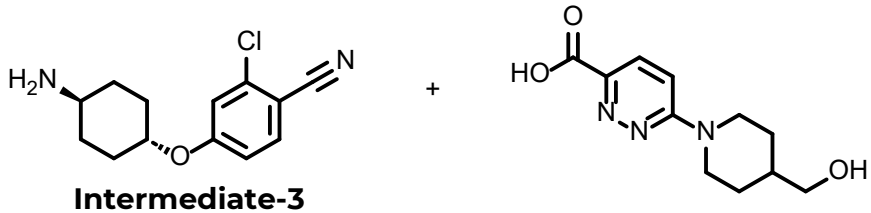
Intermediate-2

Second generation



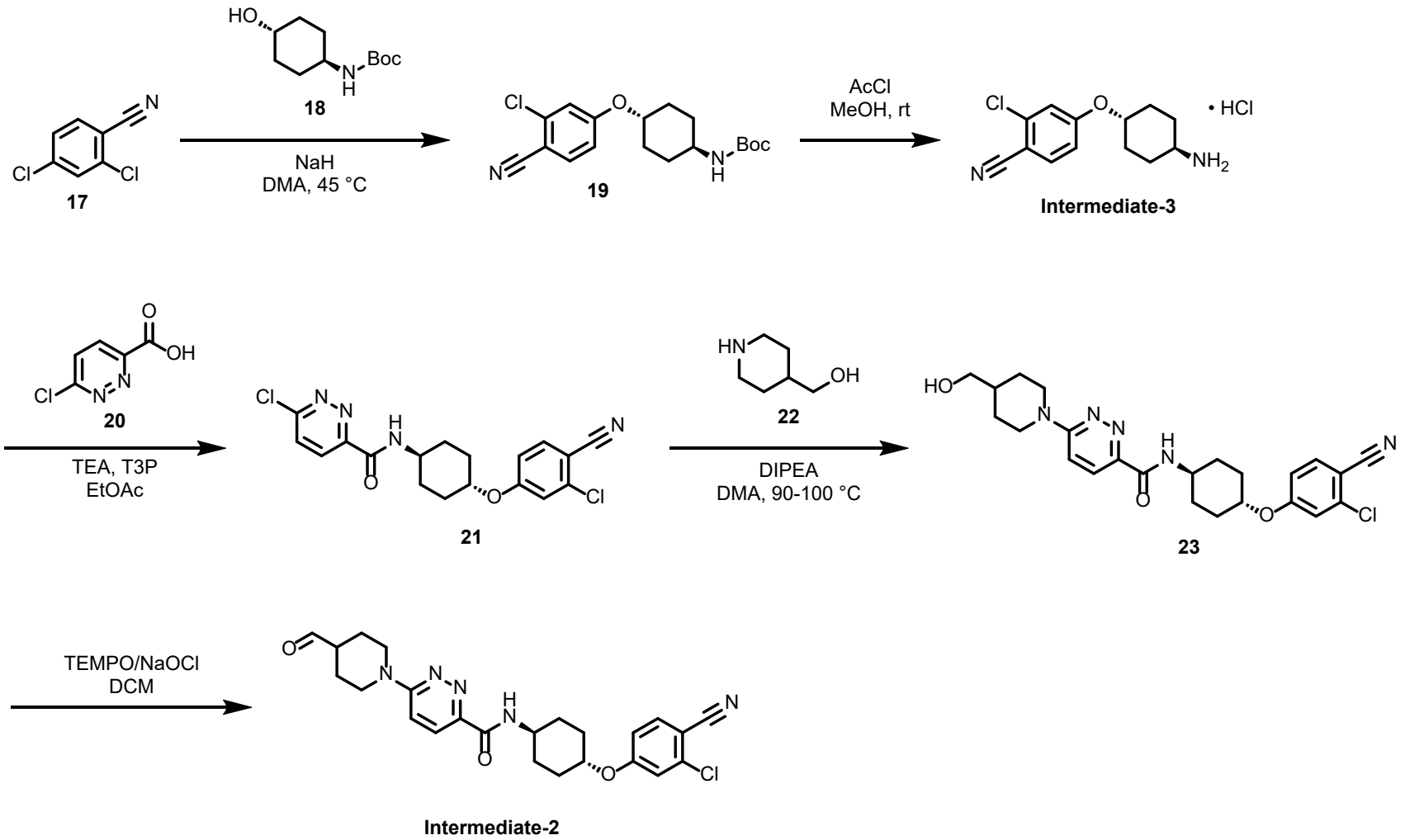
Intermediate-3

Fifth generation

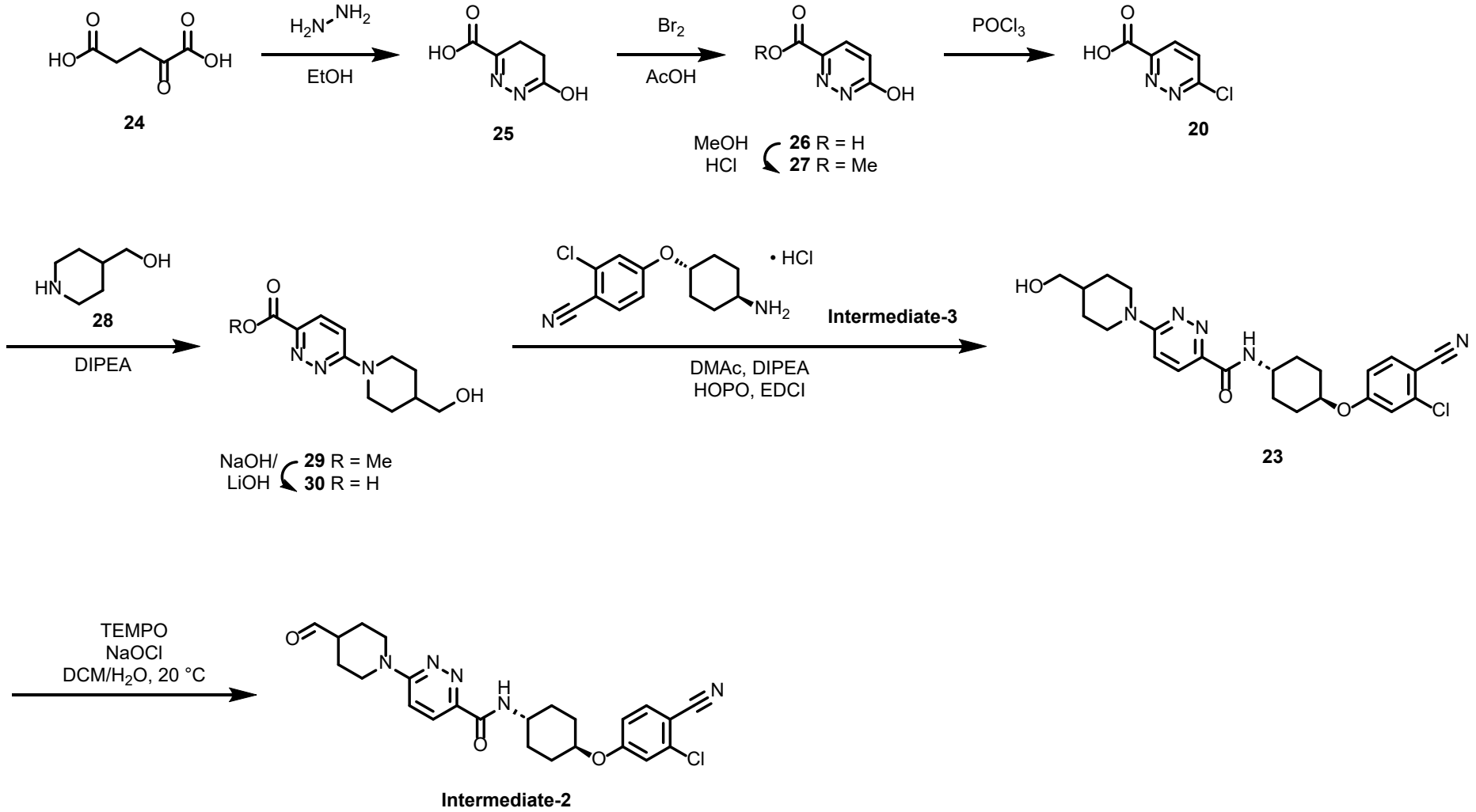


Intermediate-3

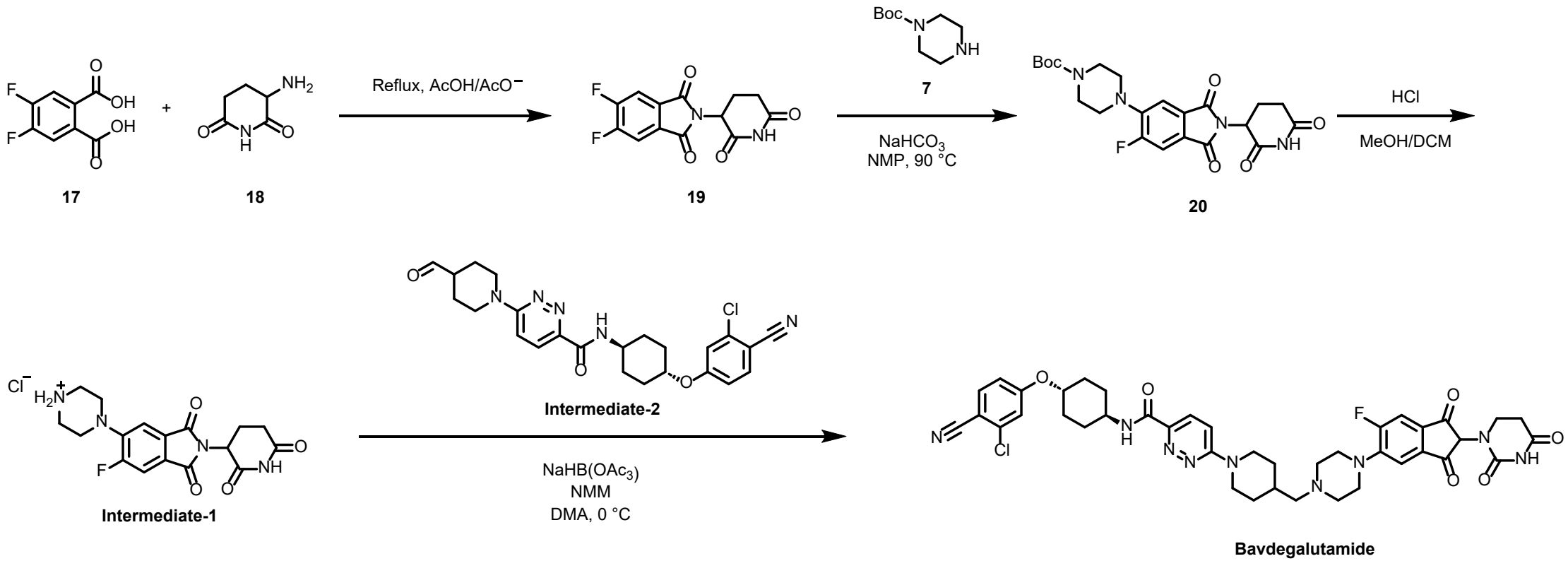
Intermediate 2: Second generation



Intermediate 2: Fifth generation

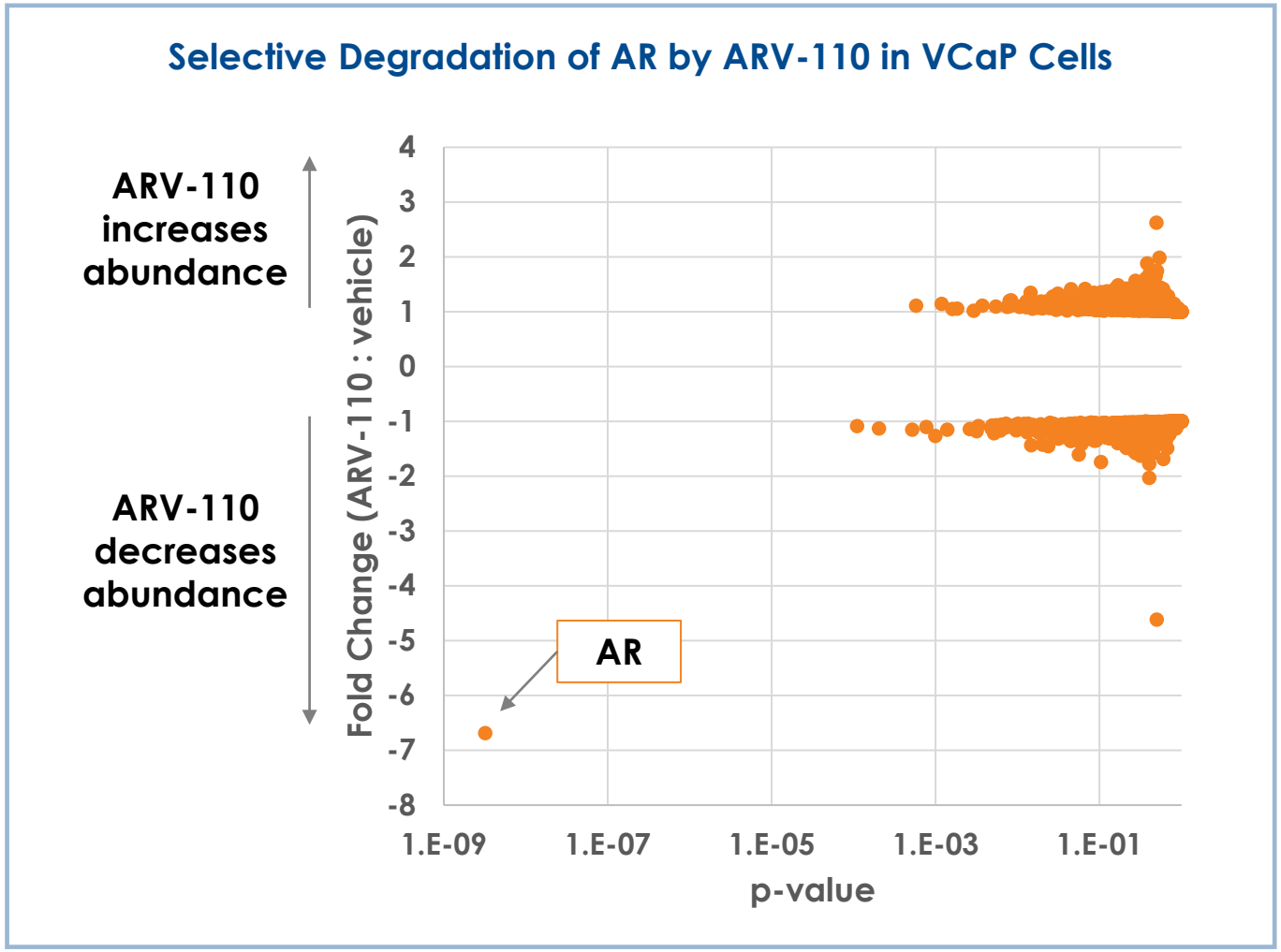


Intermediate 1 and final steps



Bavdegalutamide (ARV-110) is shown to robustly and selectively degrade AR

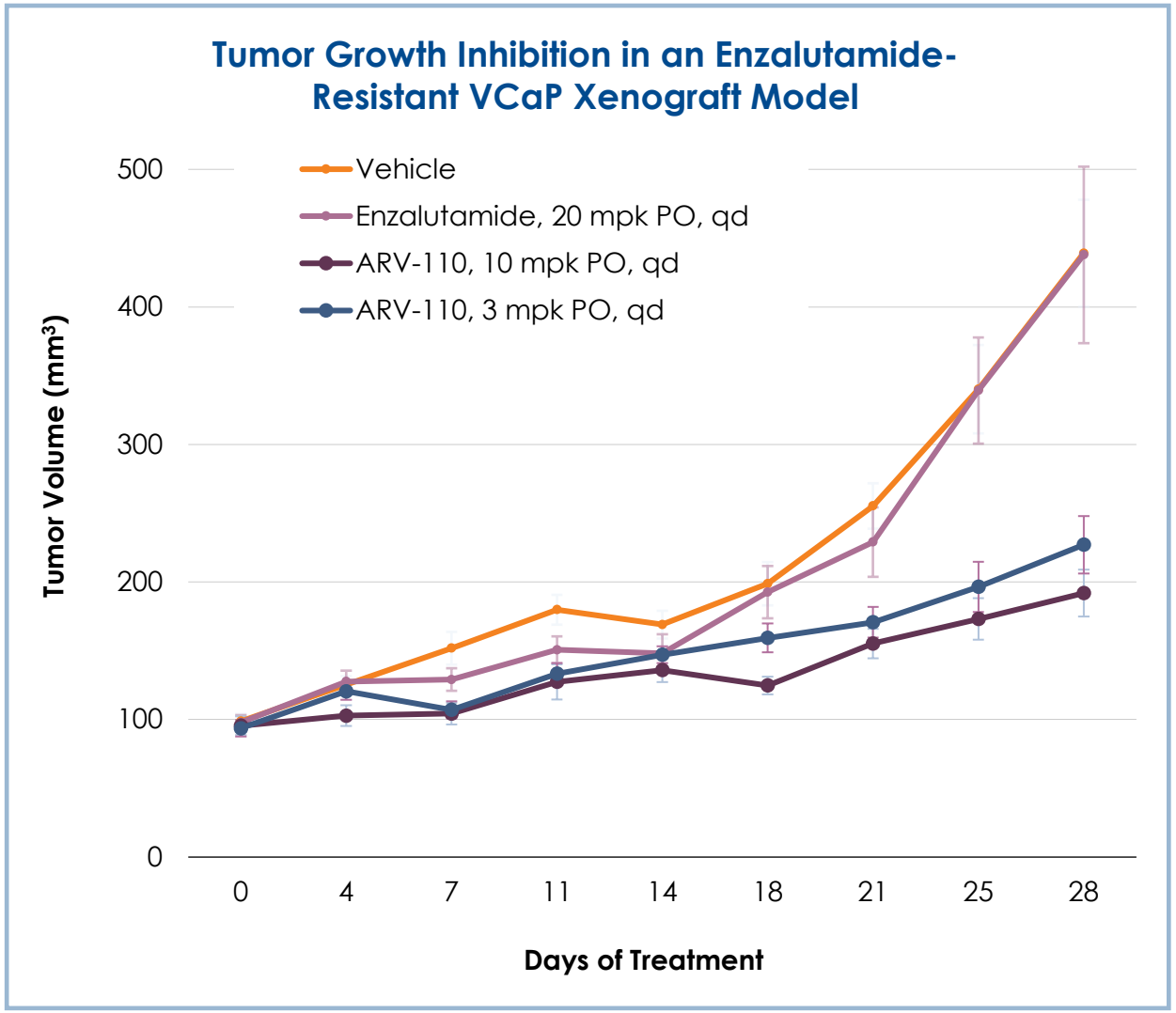
- Assessed **ARV-110** selectivity by proteomics
- After 8 hours of treatment of VCaP cells[1] with 10 nM **ARV-110** *in vitro*, AR was the only degraded protein among the nearly 4,000 proteins measured
  - 85% D_{max}[2] (DC50 = 1 nM in VCaP cells)
  - p-value: $3x10^{-9}$



1 VCaP, Vertebral Cancer of the Prostate
2 D_{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



Bavdegalutamide (ARV-110) in the Clinic

Androgen Receptor (AR) Franchise Clinical Trials	Phase 1	Phase 2	Phase 3	Status
Post-NHA	★ Bavdegalutamide pivotal Phase 3 trial			Anticipated 2H23
	Bavdegalutamide/ abiraterone combo Phase 1B			Ongoing
	ARV-766 Phase 2 dose expansion			Ongoing
	ARV-766 Phase 1 dose escalation			Data expected 2Q23
Pre-NHA	Phase 1B/2			Expect to begin in 2023

★ *Pivotal Trial*

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

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