Discovery of ARV-766, an androgen receptor degrading PROTAC® for the treatment of men with metastatic castration resistant prostate cancer

Lawrence B Snyder, Arvinas Inc, New Haven, CT

ARVINAS

Disclosure Information

Lawrence Snyder

I have the following relevant financial relationships to disclose:

Employee of: Arvinas

Stockholder in: Arvinas

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 arrangements with Yale University, 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.

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

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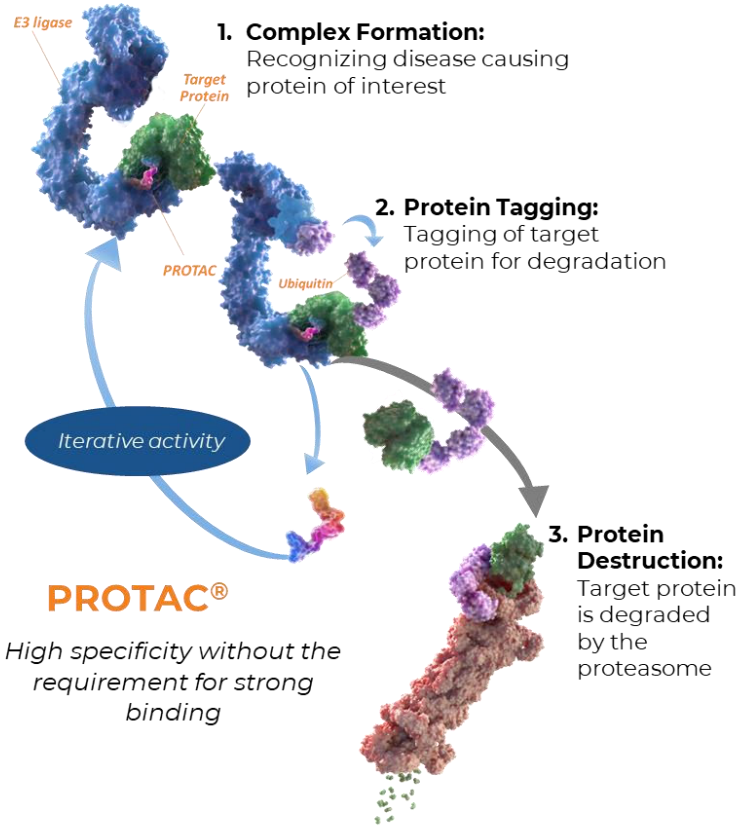

Arvinas' proteolysis-targeting chimera (PROTAC®) degraders can:

- 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

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

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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

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L702H is highly represented AR mutation in men with advanced PCa

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Table 1. Detection rates of *AR*-LBD mut by Timing of Guardant360

Patient Population	Detection Rate	Prevalence
AR-LBD muts pre-any 2nd-gen ARPi	59 / 387	15%
Emergence of *AR*-LBD muts as acquired resistance mechanisms to 1st-gen ARPi *	115 / 747	15%
AR-LBD muts post only one 2nd-gen ARPi any line	353 / 1628	22%
AR-LBD muts post 2nd Gen ARPi in two lines	509 / 2118	24%

Increasing mutation rate with AR Pathway Inhibition (ARPi) treatment

Table 2. Gains and losses of *AR*-LBD muts post Abi or Enza initiation among those with Guardant360 both before and after treatment

	Gene Alteration	% pre-therapy	% gained	% lost	% post-therapy	aggregate change
Abiraterone (N=180)	**L702H**	**3.33**	**7.78**	**-0.56**	**10.56**	**+7.23**
	W742C/L	3.33	0.56	-2.22	1.67	-1.66
	H875Y	3.33	2.22	-1.11	4.44	+1.11
	F877L	1.11	0.56	-1.11	0.56	-0.55
	T878A/S	**1.67**	**5.00**	**-1.11**	**5.56**	**+3.89**
	M896T/V	0.00	0.00	0.00	0.00	0.00
Enzalutamide (N=131)	**L702H**	**5.34**	**6.87**	**-0.76**	**11.45**	**+6.11**
	W742C/L	2.29	1.52	-1.52	2.29	0.00
	H875Y	4.58	1.53	-1.53	4.58	0.00
	F877L	**0.00**	**3.82**	**0.00**	**3.82**	**+3.82**
	T878A/S	**7.63**	**5.34**	**-3.05**	**9.92**	**+2.29**
	M896T/V	0.00	0.76	0.00	0.76	+0.76

- *Increasing L702H prevalence with ARPi treatment*
- *Most prevalent LBD mutation*

Antonarakis et al, Abstract 395182, ASCO/GU 2023

AR L702H mutation emerges post Novel Hormonal Agent (NHA) treatment and is associated with progression

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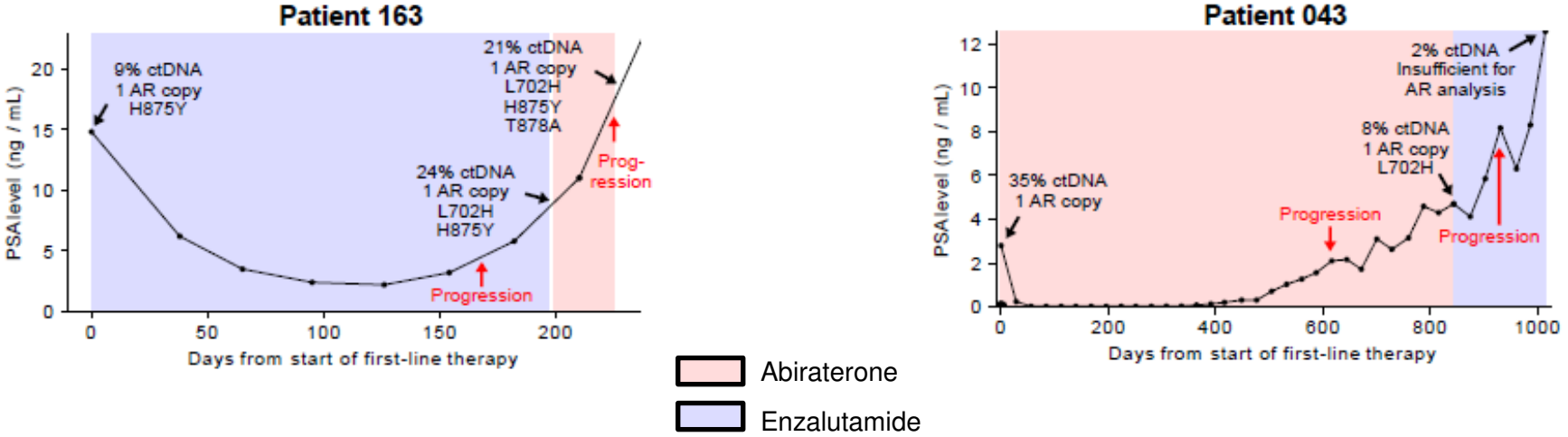


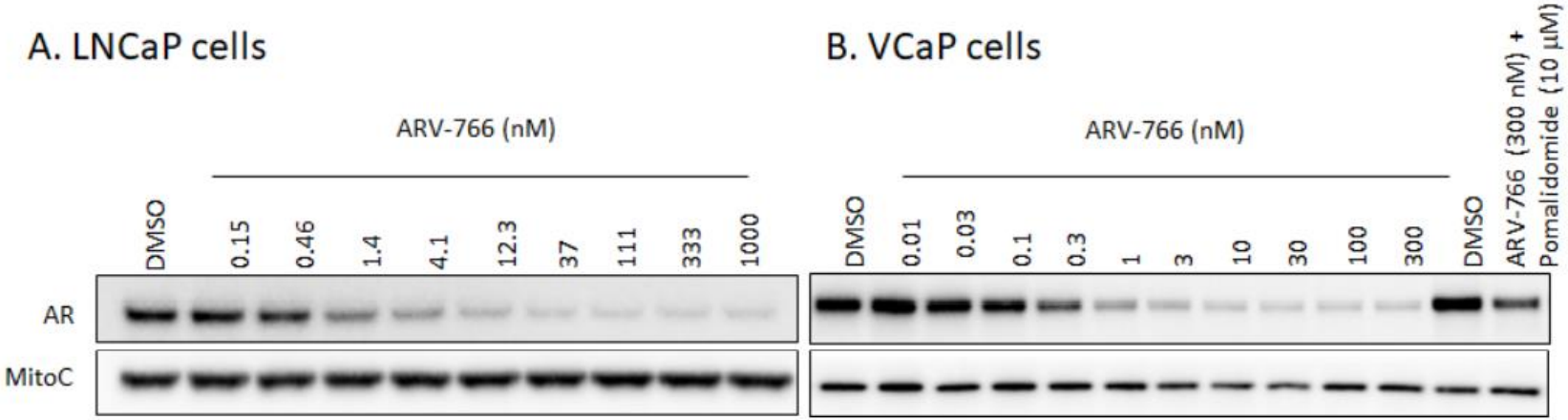
Appearance of AR L702H post NHA at progression supports hypothesis that it drives resistance

Annala et al, Clin Can Res (2021)

ARV-766: An oral AR degrader that targets all major AR Ligand Binding Domain (LBD) mutations

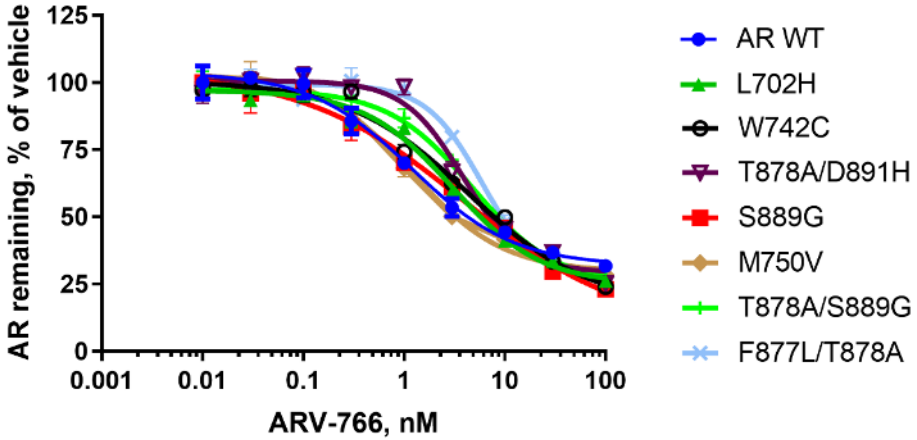
- Potently degrades wildtype Androgen Receptor (AR)
- Potently degrades multiple clinically relevant AR mutants, including L702H
- Provides robust degradation and anti-proliferative activity in murine models
- Is currently in clinical trials and Phase 1 data will be reported on in 2Q 2023

Degradation of AR in WT LNCaP and VCaP cells by ARV-766



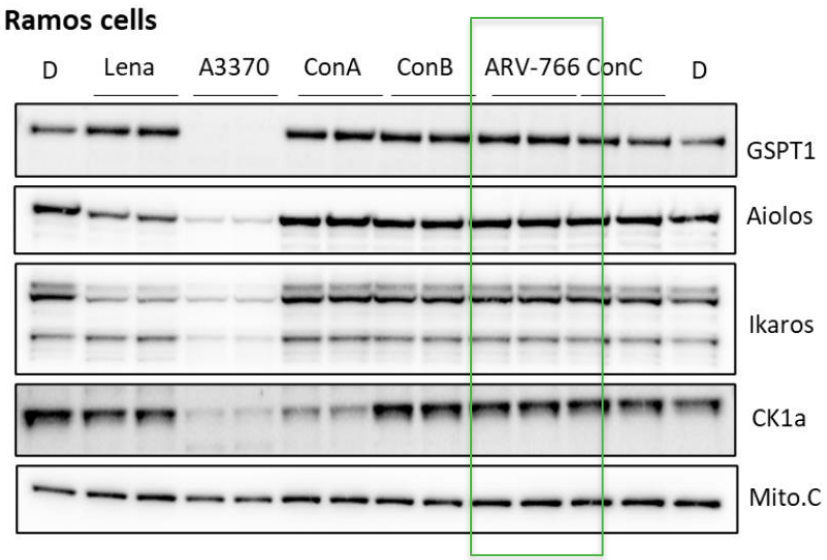
- LNCap DC_{50} = <1.3nM; D_{max} >91%
- VCaP DC_{50} = <1nM; D_{max} >94%
- Competition with pomalidomide rescues degradation
  - Degradation mediated by CBN

ARV-766 degrades L702H and additional ligand binding domain mutants



Similar degradation efficiency for other clinically relevant mutants

ARV-766 does not degrade key cereblon neomorphic substrates



- 1μM of ARV-766, other PROTAC controls (Con A-C), A3370 (known neomorphic substrate degrader) and 10μM lenalidomide
- ARV-766 engages the cereblon protein at same site as IMiDs
- Lenalidomide and A3370 induced CBN neosubstrate degradation as expected
- *ARV-766 does not lead to degradation of key cereblon neomorphic substrates, and any potential liabilities ascribed to the IMiD class (thalidomide, pomalidomide, lenalidomide) should not apply to ARV-766*

ARV-766 displays robust tumor growth inhibition in the presence of high androgen concentrations

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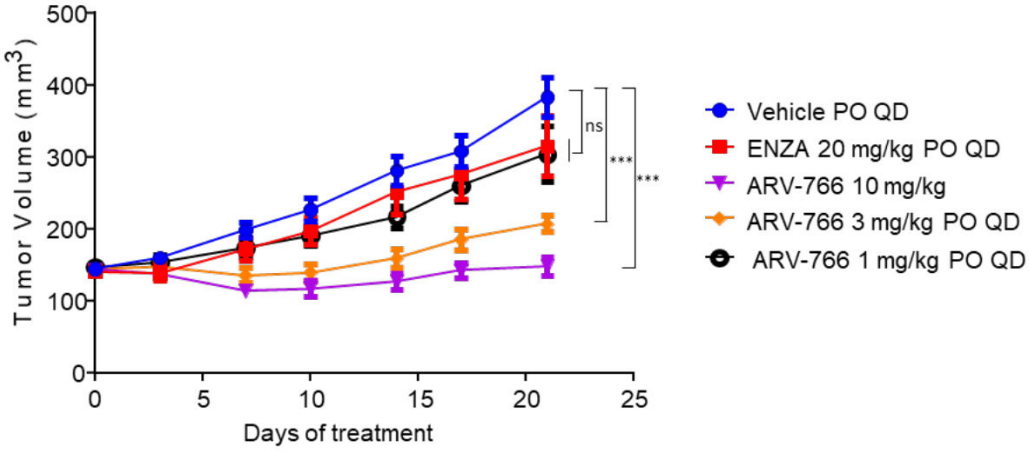
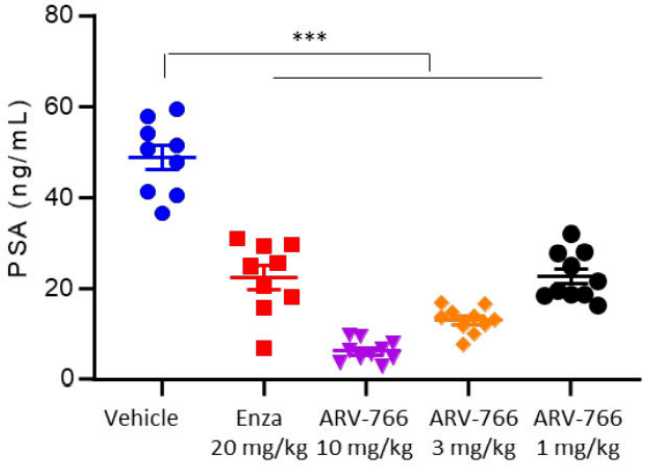
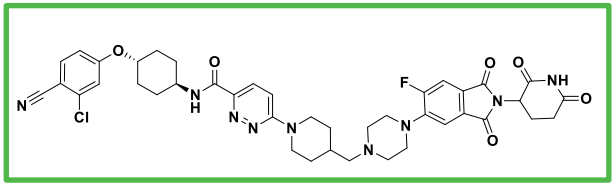




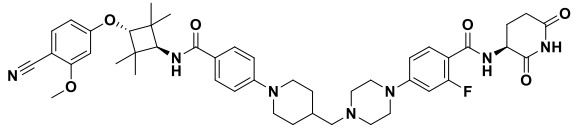
- Intact (non-castrated) CB17/scid mouse model to mimic incomplete testosterone suppression
- ARV-766 treatment of 10, 3, and 1mg/kg/day resulted in 98%, 74%, and 34% TGI
- Limited efficacy observed for mice treated with enzalutamide

- 10mg/kg and 3mg/kg ARV-766 reduced PSA levels more robustly than 20mg/kg enzalutamide
- PSA reduction correlates with TGI

ARV-766 structure and selected SAR



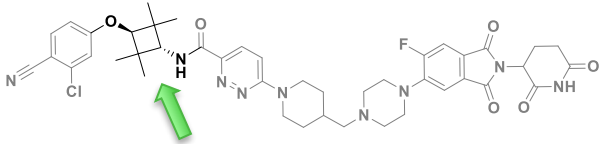
ARV-110 (Bavdegalutamide)



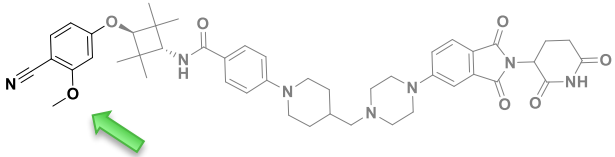
ARV-766

- Single enantiomer
- Desired genotype coverage

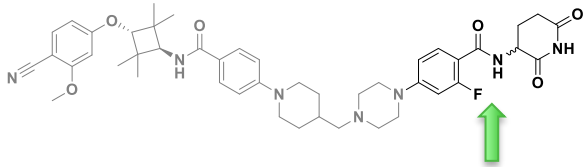
Internal discoveries along the way to ARV-766:



Desired genotype coverage



Improved in vivo exposure in some cases



- Acceptable exposure multiples over efficacious dose
- Acceptable stereochemical stability in preclinical in vivo studies

In 2023, we expect to begin a pivotal trial for bavdegalutamide and to begin AR PROTAC® investigations in pre-NHA settings

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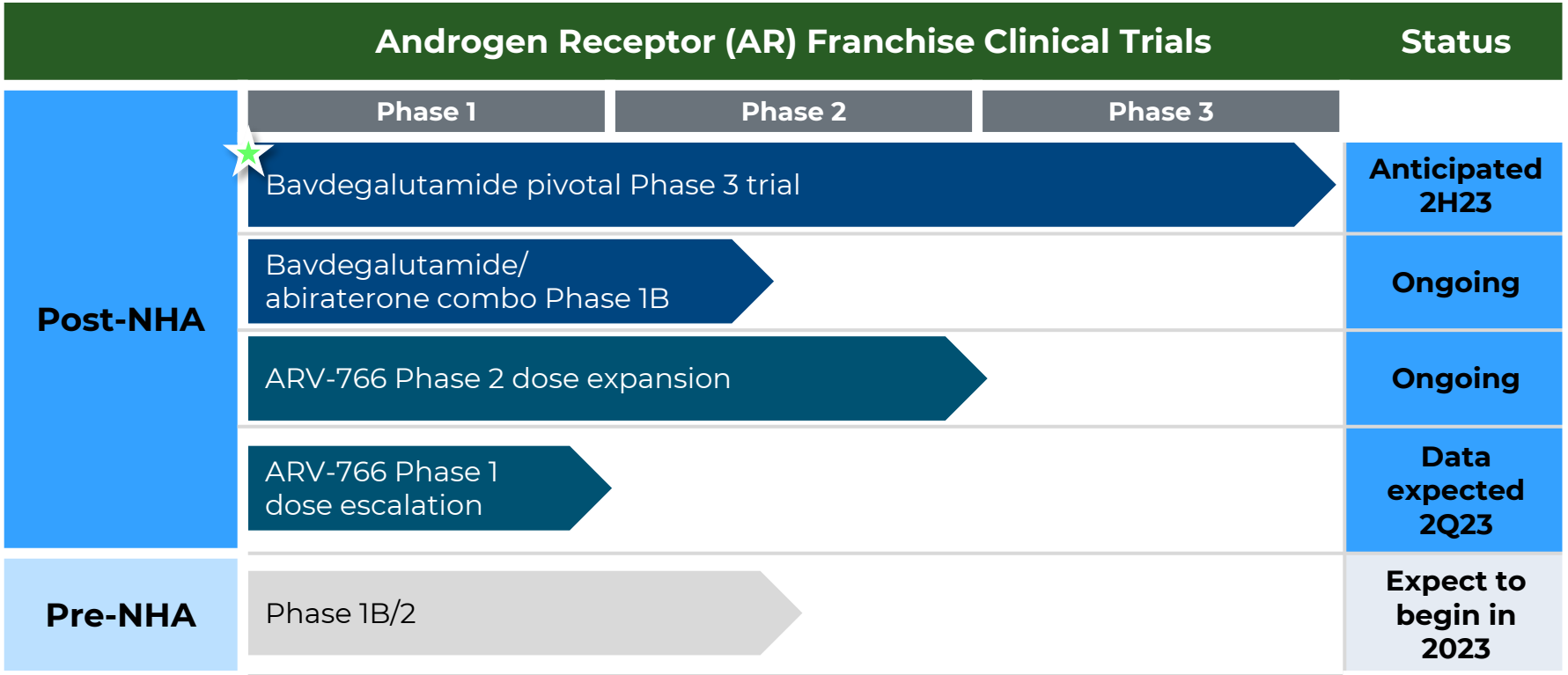

NHA, novel hormonal agent

Pivotal Trial

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Thank You for Your Kind Attention!

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