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

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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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This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data and estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.
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
Arvinas’ PROTAC® degraders eliminate the androgen receptor (AR), potentially surpassing the benefits of AR inhibitors.

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.

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

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

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AR, androgen receptor


2 American Cancer Society
Table 1. Detection rates of AR-LBD mut by Timing of Guardant360

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

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

<table>
<thead>
<tr>
<th>Gene Alteration</th>
<th>% pre-therapy</th>
<th>% gained</th>
<th>% lost</th>
<th>% post-therapy</th>
<th>aggregate change</th>
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</thead>
<tbody>
<tr>
<td>L702H</td>
<td>3.33</td>
<td>7.78</td>
<td>-0.56</td>
<td>10.56</td>
<td>+7.23</td>
</tr>
<tr>
<td>W742CL</td>
<td>3.33</td>
<td>0.56</td>
<td>-2.22</td>
<td>1.67</td>
<td>-1.66</td>
</tr>
<tr>
<td>H875Y</td>
<td>3.33</td>
<td>2.22</td>
<td>-1.11</td>
<td>4.44</td>
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<tr>
<td>F877L</td>
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<td>0.56</td>
<td>-1.11</td>
<td>0.56</td>
<td>-0.55</td>
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<td>T878A/S</td>
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<td>-1.11</td>
<td>5.56</td>
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<td>L702H</td>
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<td>0.76</td>
<td>+0.76</td>
</tr>
</tbody>
</table>

- 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.

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

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$_{50} = <1.3\text{nM}; D_{\text{max}} >91\%$
- VCaP DC$_{50} = <1\text{nM}; D_{\text{max}} >94\%$
- 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

- 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)**

- Single enantiomer
- Desired genotype coverage
- Acceptable exposure multiples over efficacious dose
- Acceptable stereochemical stability in preclinical in vivo studies

**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.

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

NHA, novel hormonal agent

Pivotal Trial
Thank You for Your Kind Attention!