De Novo Pyrimidine Synthesis Inhibition for the treatment of ARID1A mutated ovarian cancers and other solid tumors

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Entrepreneur

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**Business / Science**
The Global Market for Ovarian Cancer Drugs

Market Drivers include INCREASING incidence, GENETIC understanding, and greater use of COMBINATION THERAPIES.

Will be ACCELERATING growing at a CAGR of over 17.1% is expected to REACH $10.1 billion in 2027.

ARID1A mutated ovarian cancer is expected to REACH $1 billion in 2027.

7% of ALL cancers are ARID1A mutated an estimated market of $17.5 billion.

North America represents 42% of the global REVENUE.

Market Drivers include INCREASING incidence, GENETIC understanding, and greater use of COMBINATION THERAPIES.
Ovarian cancer patients lack targeted and effective therapies

Despite Surgery and Adjuvant Chemotherapy, ~80% of patients relapse

10% of Ovarian Cancers are ARID1A mutant clear cell and endometrioid carcinomas

We aim to develop the first targeted therapeutic option for clear cell and endometrioid carcinoma patients with ARID1A mutation

- First-in-Class
- New MOA
- Targeted therapy

Standard Of Care: Surgery + Chemotherapy

Approved novel therapies are limited:

<table>
<thead>
<tr>
<th>MOA</th>
<th>Drug</th>
<th>Company</th>
<th>Indication</th>
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<tbody>
<tr>
<td>VEGFi</td>
<td>Bevacizumab</td>
<td>Roche</td>
<td>Stage III/IV and recurrent</td>
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<tr>
<td>PARPi</td>
<td>Olaparib</td>
<td>AstraZeneca</td>
<td>After 1st line CTx w/ BRCAm/+HRD</td>
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<tr>
<td></td>
<td>Rucaparib</td>
<td>Clovis Onc</td>
<td>After 2nd line CTx w/o BRCAm</td>
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<tr>
<td></td>
<td>Niraparib</td>
<td>Tesaro Inc.</td>
<td>After CTx w complete/partial response. g/sBRCAm after ≥ 2 CTx</td>
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</tbody>
</table>

*Ovarian clear cell carcinoma is more resistant to CTx and has worse prognosis
ARID1A confers vulnerability to De Novo Pyrimididine Synthesis inhibition

1. ARID1A binds to CAD ATCase
   Identification of ARID1A interacting proteins by Mass Spectrometry

2. CAD ATCase is a key regulator of De Novo Pyrimididine Synthesis

3. ARID1A inhibits CAD ATCase and De Novo Pyrimididine Synthesis

4. ARID1A deficient tumors are sensitive to pyrimidine synthesis blockade
Combining Pyrimidine Synthesis and DNA repair inhibition is highly efficacious

Tumor Growth
(Patient-Derived Xenograft)

- Vehicle
- AZD6738 (ATRI)
- Teriflunomide
- Teri+AZD

Teriflunomide vs. Teri+AZD, $P = 0.002$
AZD6738 vs. Teri+AZD, $P = 0.001$
Competitive landscape for ARID1A ovarian cancer therapies

**Personalized Therapies** (targeting ARID1A mutation)

- **FDA-Approved**
  - SOC (SX+CTx)
  - VEGFi (Bevacizumab)
  - PARPi (Olaparib, Rucaparib, Niraparib)
  - anti PD-1 (Nivolumab)
  - ATRi (AZD6738)
  - BRD4i (PLX2853)
  - EZH2i (Tazemetostat)

- **In development**
  - DHODHi (Teriflunomide)
  - CADi

- **First-in-line potential**

**AstraZeneca** is #1 LEADING company with 13 drugs in DEVELOPMENT and 1 drug FDA-approved PARPi (Olaparib)

- AstraZeneca + Institute of Cancer Research:
  - Phase 2 interventional trial
  - ATRi (AZD6738) + PARPi (Olaparib)
  - Gynaecological Cancers with ARID1A loss/no loss

- AstraZeneca + Univ of Pennsylvania:
  - Phase 2 interventional trial
  - ATRi (AZD6738) + PARPi (Olaparib)
  - Recurrent Ovarian Cancer
## Discovery Process and Future Plans with Blavatnik Fund

### Phase 1 – Strengthen research aimed to conduct investigational trials with AstraZeneca

<table>
<thead>
<tr>
<th>In vivo</th>
<th>$80K</th>
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<tbody>
<tr>
<td>✓ IP: Method for treating ARID1A cancer with pyrimidine synthesis + DNA repair inhibitors</td>
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<tr>
<td>✓ POC in vivo: Teriflunomide + ATRi (AZD6738) is superior to ATRi alone</td>
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<tr>
<td>○ POC in vivo: Teriflunomide + ATRi (AZD6738) is superior to ATRi alone and SOC</td>
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<td>○ POC in vivo: Teriflunomide + PARPi (Olaparib)/ ATRi (AZD6738) is superior to Olaparib + AZD6738 and SOC</td>
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### Phase 2 – Discovery research aimed to increase IP and treatment-target specificity

<table>
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<tr>
<th>In Silico</th>
<th>$220K</th>
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<tbody>
<tr>
<td>○ 3D Model generation and computational chemistry</td>
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<td>○ Inhibitor design in collaboration with computational chemist</td>
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<td>○ Development of functional cell-based assay for CAD ATCase (YCMD)</td>
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<tr>
<td>○ Ready-to-go assay characterization (YCMD)</td>
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