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

Gloria Huang, MD, FACOG
Associate Professor of
Obstetrics, Gynecology & Reproductive Sciences
Yale University

The Team

Gloria Huang, MD, FACOG

Associate Professor of Obstetrics, Gynecology & Reproductive Sciences
Yale School of Medicine

Gynecologic Oncology / Global Authority

Melisa Lopez-Anton, PhD

Blavatnik Fellow at Yale University
Scientist in Cancer Biology
Entrepreneur

Entrepreneur / Science

Hong Peng, PhD, MBA

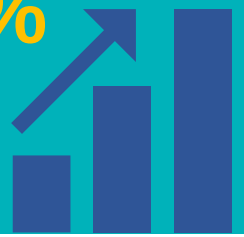
Sr. Associate Director of
Business Development
Yale Office of Cooperative Research

Business / Science

The Global Market for Ovarian Cancer Drugs

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

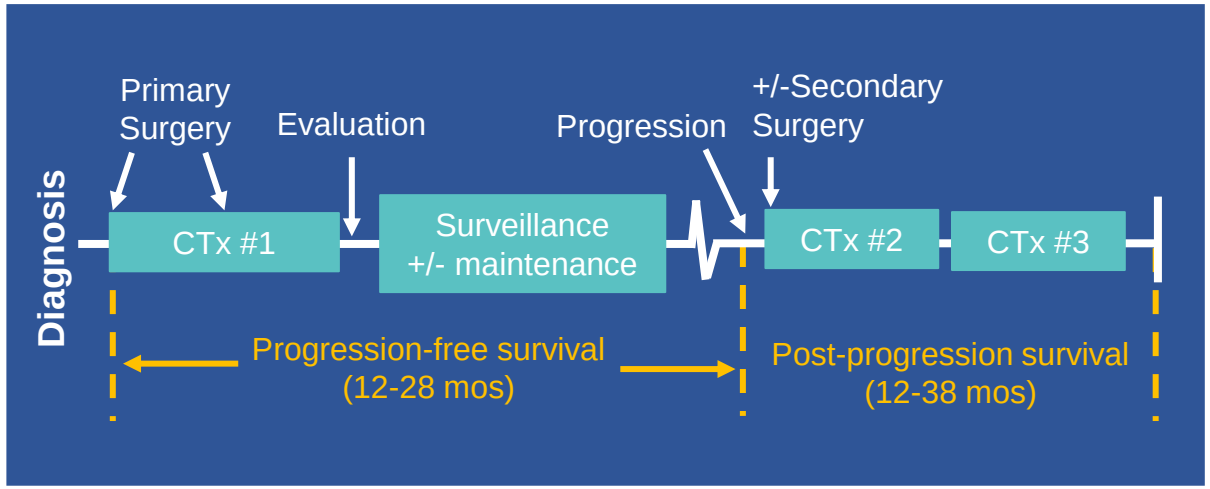
INCREASING incidence,

GENETIC understanding,

and greater use of COMBINATION THERAPIES

Ovarian cancer patients lack targeted and effective therapies

Standard Of Care: Surgery + Chemotherapy



*Ovarian clear cell carcinoma is more resistant to CTx and has worse prognosis

Approved novel therapies are limited:

MOA	Drug	Company	Indication
VEGFi	Bevacizumab	Roche	Stage III/IV and recurrent
PARPi	Olaparib	AstraZeneca	After 1st line CTx w BRCAm/+HRD After 2nd line CTx w/o BRCAm
	Rucaparib	Clovis Onc	After CTx w complete/partial response. g/sBRCAm after ≥ 2 CTx
	Niraparib	Tesaro Inc.	After 1st line for all ovarian and advanced/recurrent w complete/partial response to CTx

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

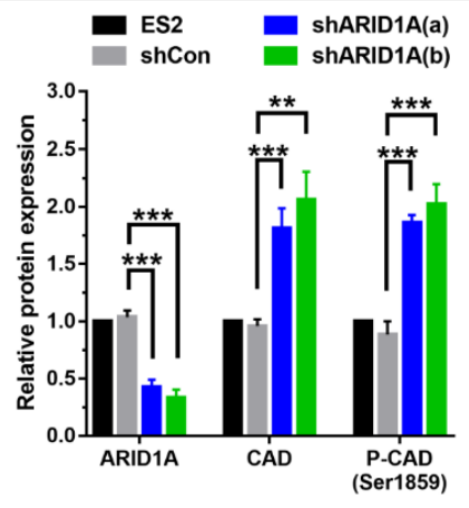
ARID1Am confers vulnerability to De Novo Pyrimidine Synthesis inhibition

1. ARID1A binds to CAD ATCase

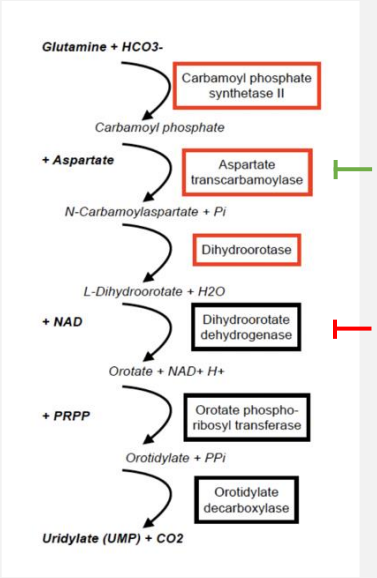
Identification of ARID1A interacting proteins by Mass Spectrometry

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

3. ARID1A inhibits CAD ATCase and De Novo Pyrimidine Synthesis

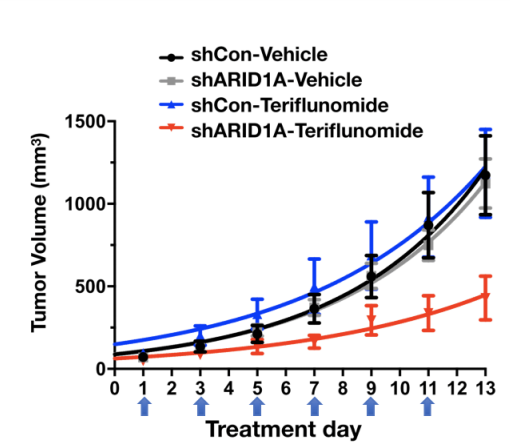


4. ARID1A deficient tumors are sensitive to pyrimidine synthesis blockade



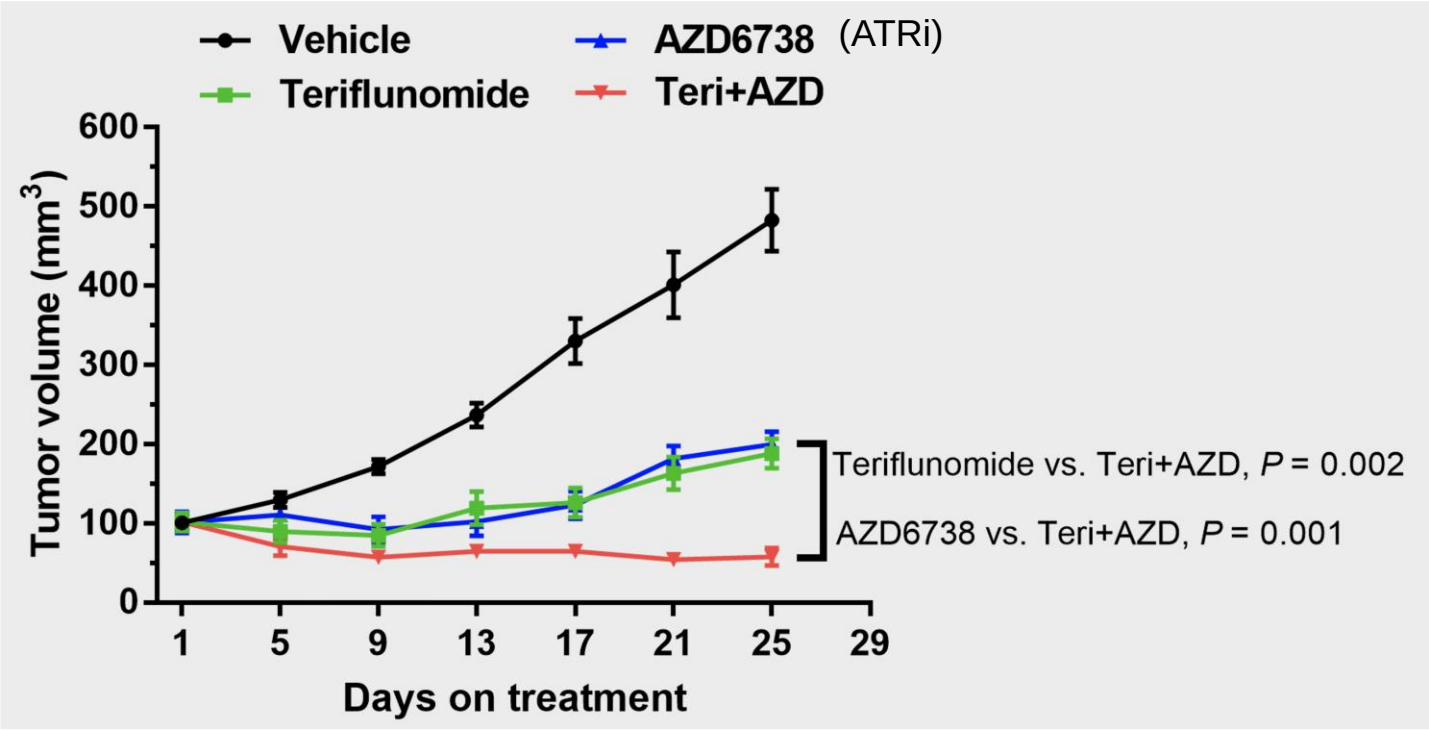
CAD ATCase

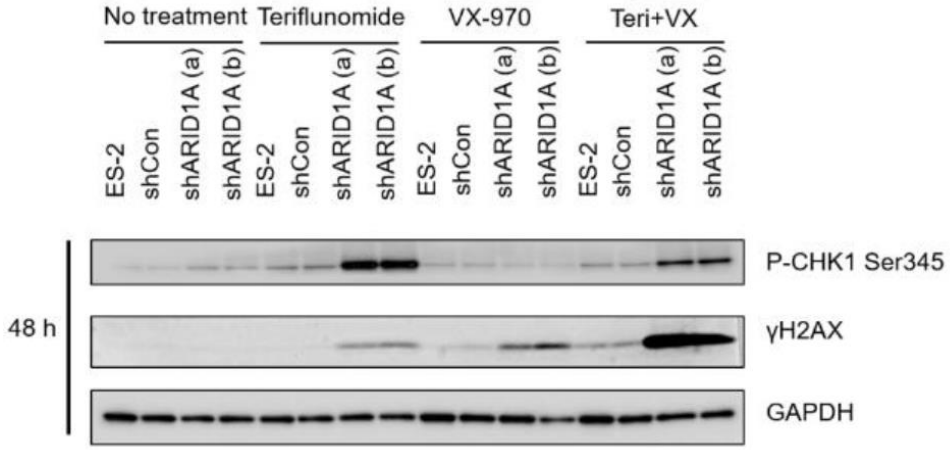
Teriflunomide

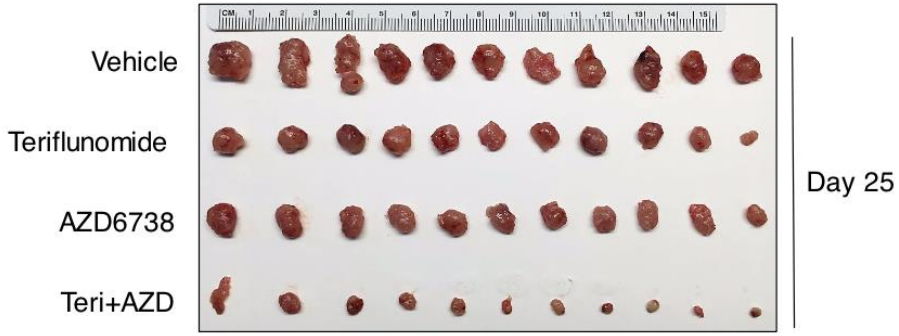


Combining Pyrimidine Synthesis and DNA repair inhibition is highly efficacious

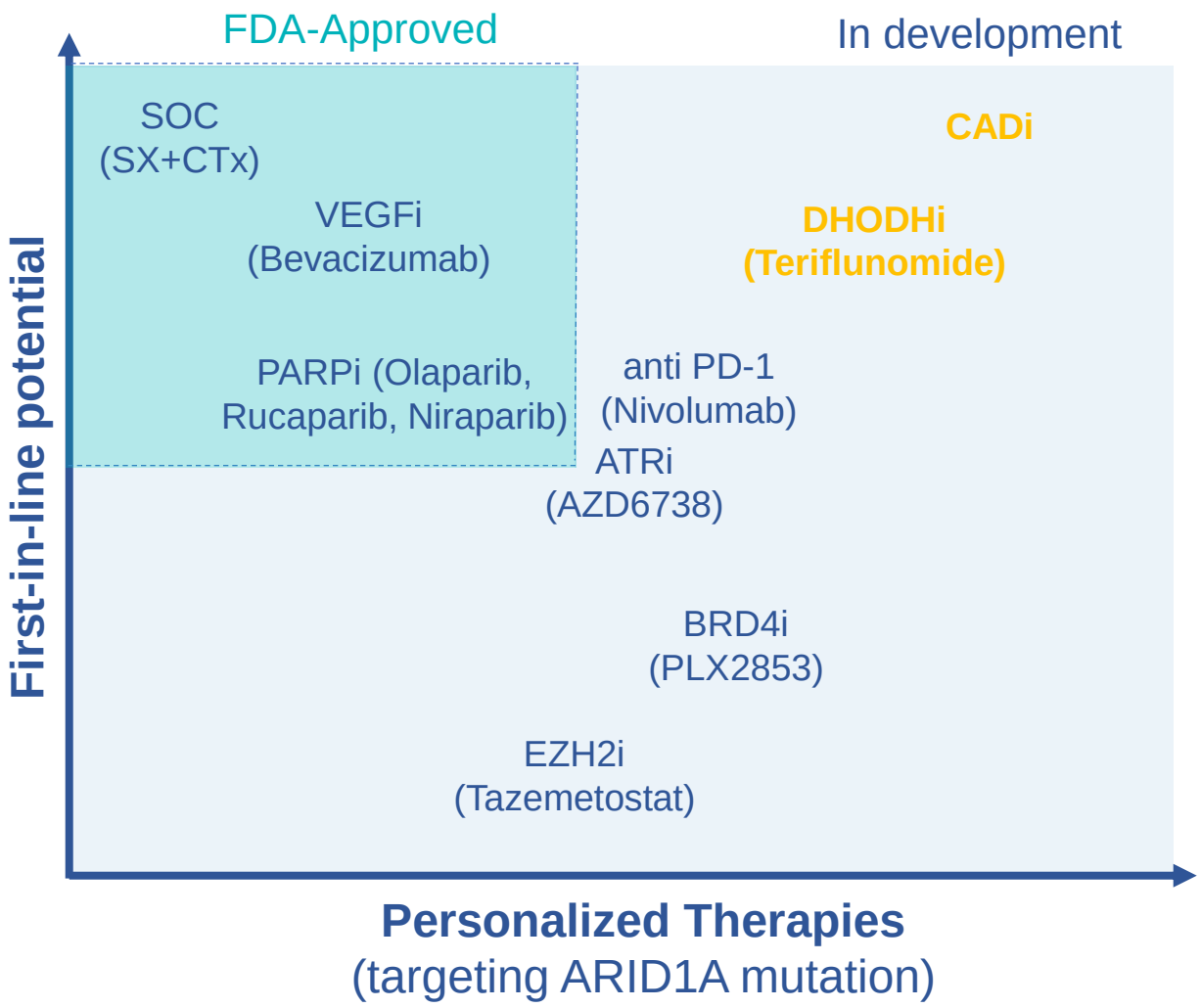
Tumor Growth
(Patient-Derived Xenograft)







Competitive landscape for ARID1A ovarian cancer therapies



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 **w 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

In vivo

- ✓ IP: Method for treating ARID1A cancer with pyrimidine synthesis + DNA repair inhibitors
- ✓ POC in vivo: Teriflunomide + ATRi (AZD6738) is superior to ATRi alone
- ○ POC in vivo: Teriflunomide + ATRi (AZD6738) is superior to ATRi alone and SOC
- ○ POC in vivo: Teriflunomide + PARPi (Olaparib) is superior to Olaparib alone and SOC
- ○ POC in vivo: Teriflunomide + PARPi (Olaparib)/ ATRi (AZD6738) is superior to Olaparib + AZD6738 and SOC

$80K

Phase 2 – Discovery research aimed to increase IP and treatment-target specificity

In Silico

- ○ 3D Model generation and computational chemistry
- ○ Inhibitor design in collaboration with computational chemist

Cell Biology (In house YCMD)

- ○ Development of functional cell-based assay for CAD ATCase (YCMD)
- ○ Ready-to-go assay characterization (YCMD)

$220K