



ZENITH
EPIGENETICS

**Developing Epigenetic Combination Therapies:
Making Great Drugs Work Better & Longer
Annual General Meeting**

October 31, 2019

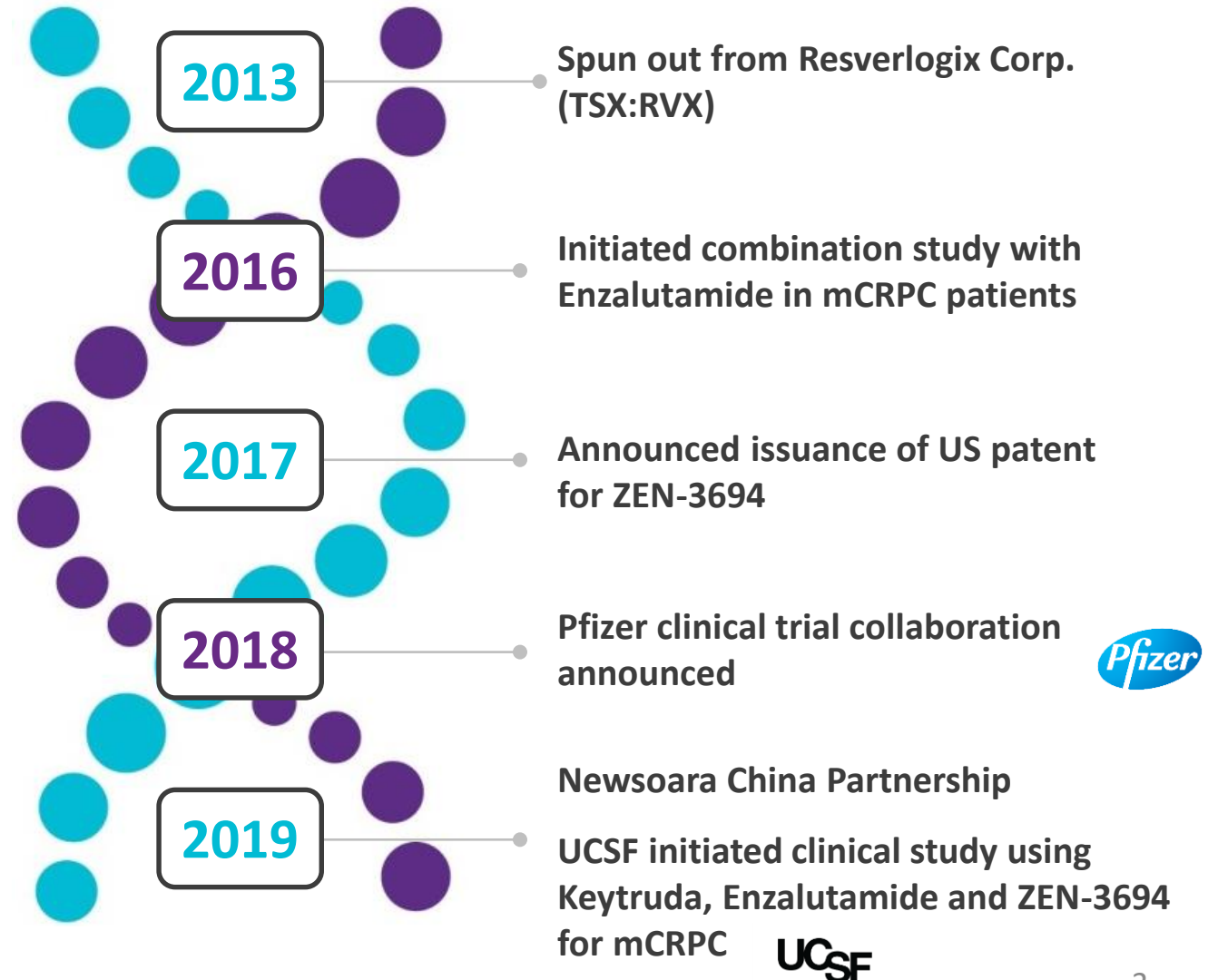
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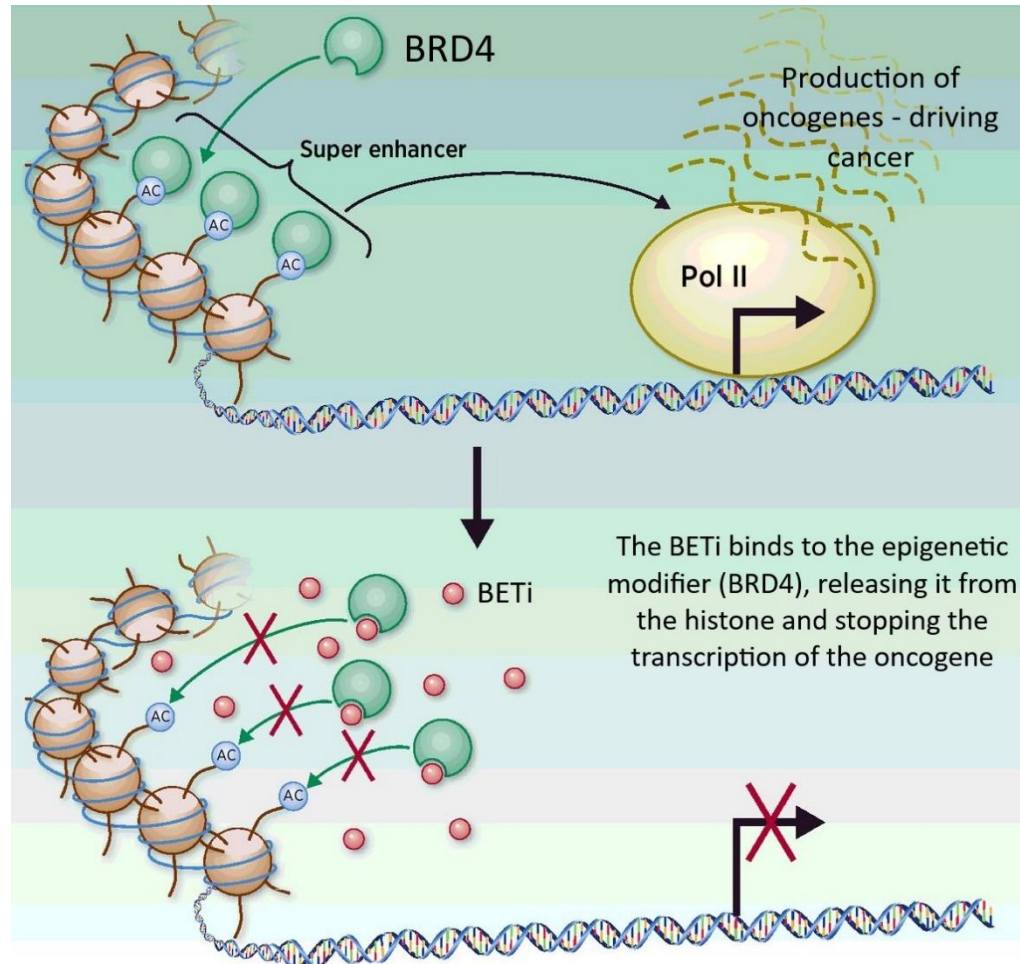
Corporate Profile and Milestones Leading to Major Collaborations

Company	Mid-clinical stage stage Epigenetics, oncology
Programs	Multiple Phase 2 POC combination clinical trials
Cash Raised	~USD\$55M
Partnerships	Newsoara 



BET Inhibitors Target Resistance Mechanisms

Re-Sensitizing Tumors to Existing Therapy



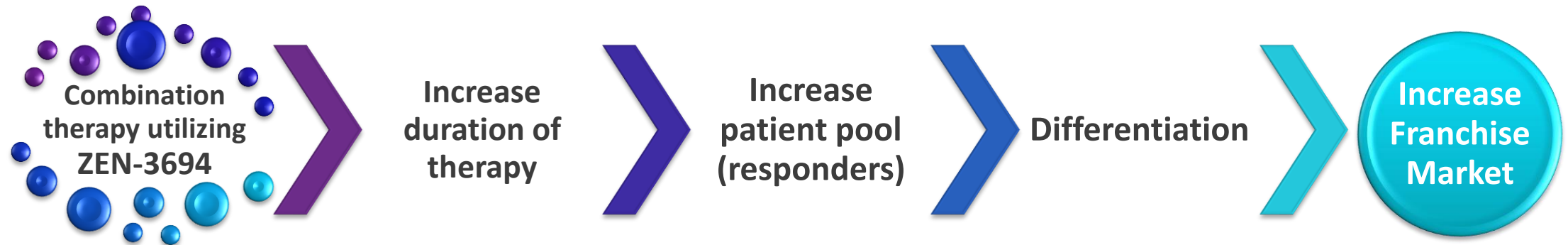
- BET (bromodomain and extra-terminal domain) proteins are key regulators of oncogenic transcription factors
- Many of the resistance mechanisms to standard of care treatments involve epigenetic modulation by BET proteins
- BET inhibitors (BETi) inhibition expression of tumor oncogenes by disruption of super-enhancers

Adopted from Clinical Cancer Research 2017, 23(7), 1647-55.

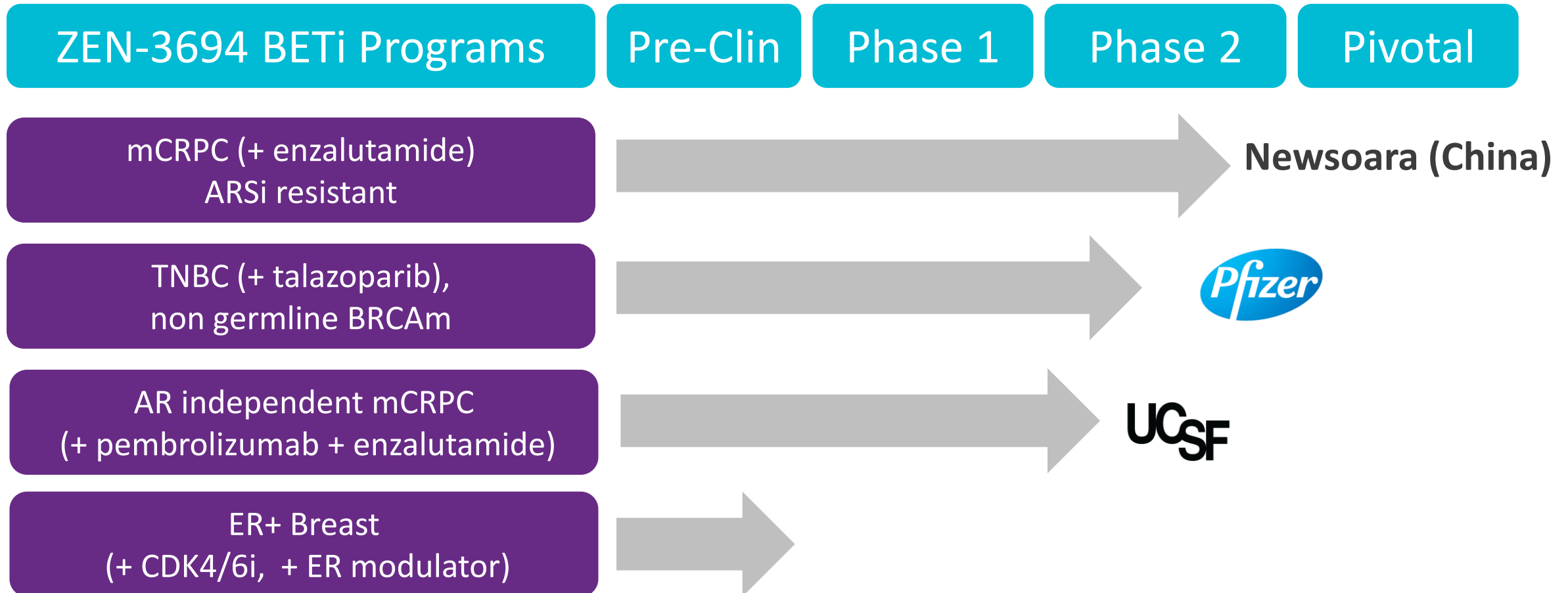
Combination therapies with ZEN-3694 represent multi-billion dollar addressable markets

Current markets include:

- AR antagonists
- PD-1/PD-L1 monoclonal antibodies
- CDK 4/6 inhibitors
- PARP inhibitors



Developing multiple epigenetic combination cancer therapies that significantly expand the value of existing standard of care therapeutics



Prostate Cancer (mCRPC) Program Review

Phase 2a completing; Phase 2b/3 Planned



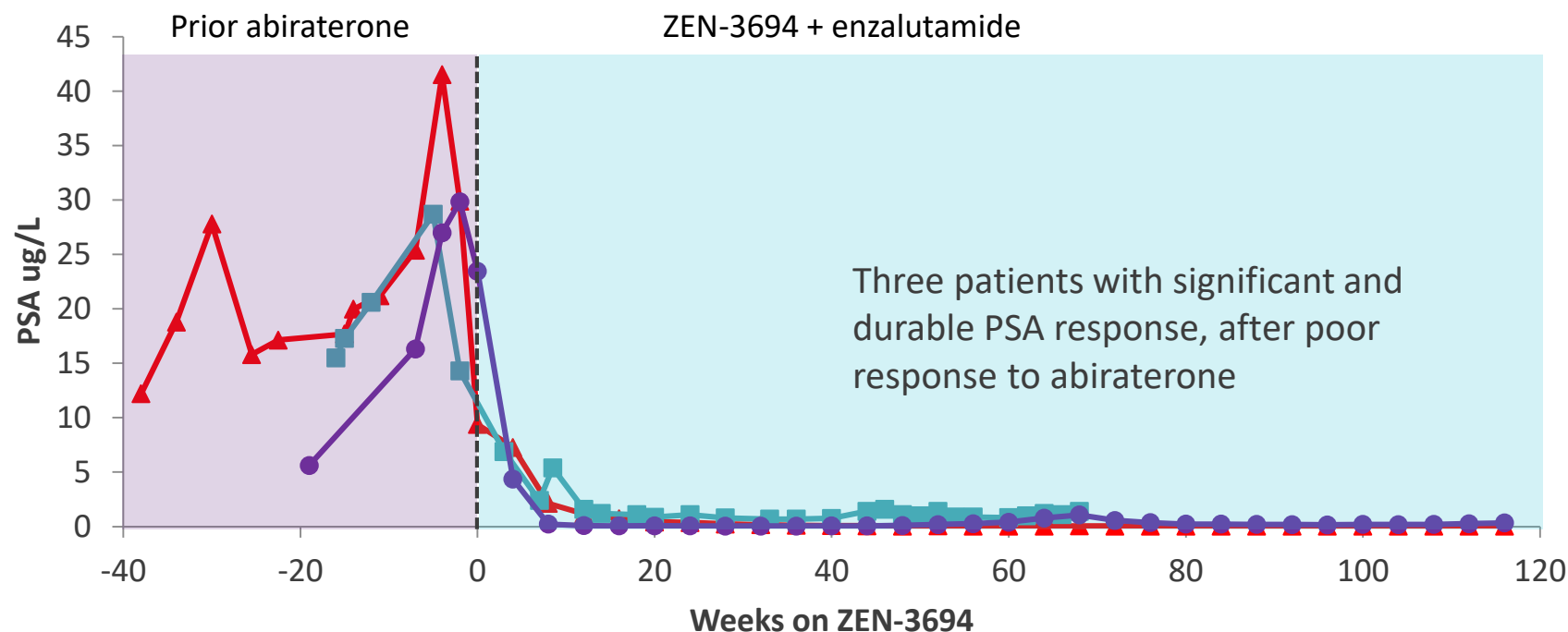
Indication	2019	2020
Metastatic Castration-Resistant Prostate Cancer (mCRPC)	Combination expansion ZEN -3694 + enzalutamide; Patients progressed on <i>abiraterone</i> or <i>enzalutamide</i>	Planned Phase 2b/3 mCRPC: Patients that progress on ARSi to ZEN-3694 + Enzalutamide vs Enzalutamide single agent

- Prolonged rPFS of 44.6 wks with ZEN-3694 + enzalutamide compared to expected rPFS of 20-24 wks with single agent enzalutamide
- 75/75 patients dosed to date, LPLV 11/19
- Well tolerated, chronic daily dosing
- Very positive FDA feedback for design of registration enabling study

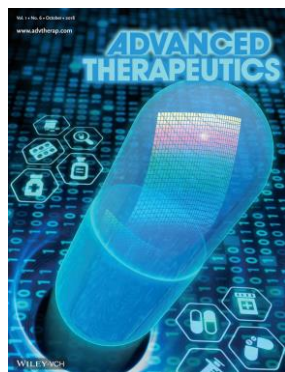
- >\$3B* opportunity for ZEN-3694 in mCRPC
 - Will also increase overall market of ARSi to \$5B* in mCRPC

Durable PSA90 responses

In patients with primary resistance to abiraterone



Clinical data and AI platform show that both ZEN-3694 and enzalutamide required for durable PSA response



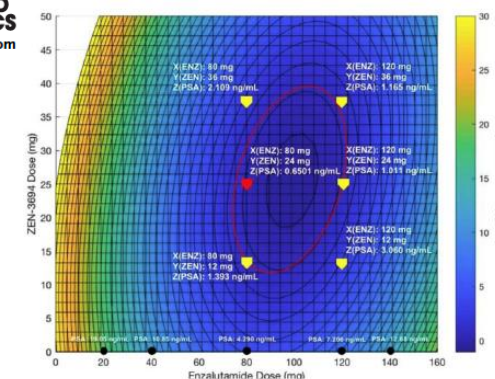
FULL PAPER

Artificial Intelligence

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Modulating BET Bromodomain Inhibitor ZEN-3694 and Enzalutamide Combination Dosing in a Metastatic Prostate Cancer Patient Using CURATE.AI, an Artificial Intelligence Platform

Allan J. Pantuck,* Dong-Keun Lee, Theodore Kee, Peter Wang, Sanjay Lakhotia, Michael H. Silverman, Colleen Mathis, Alexandra Drakaki, Arie S. Beldegrun, Chih-Ming Ho,* and Dean Ho*



Leading principal investigators and institutions for CRPC trial



Name	Institution	Comments
Rahul Aggarwal, MD Developmental Therapeutics Specialist, Genitourinary Oncologist	University of California, San Francisco (UCSF)	National PI for Zenith's Phase 1b/2a study
Eric Small, MD Chief, Dept. of Medicine		Lead PI of Apalutamide registration study (JNJ), Apalutamide , multiple \$B forecast
Wassim Abida, MD, PhD Medical Oncologist	Memorial Sloan Kettering Cancer Center (MSKCC)	Experience with BETi and PARPi Experience with ARSi trials
Joshi Alumkal, MD Leader of the Prostate/Genitourinary Medical Oncology Section and Associate Division Chief for Basic Research in the Hematology-Oncology Division	University of Michigan	Expert in epigenetics and prostate cancer research
Tom Beer, MD	Oregon Health Sciences University	Developed enzalutamide - #1 CRPC drug, now owned by Pfizer
Michael Schweizer, MD Oncologist	University of Washington Fred Hutchinson Cancer Center	Experience with ARSi
David M. Nanus, MD Chief, Division of Hematology and Medical Oncology	Weill Cornell Medicine	Genitourinary oncology specialist



Zenith Epigenetics Announces Clinical Trial Collaboration with Pfizer

November 20, 2018

Collaboration to evaluate ZEN-3694 in combination with Talazoparib in TNBC patients; Phase 1b/2 trial expected to initiate 1Q 2019

CALGARY, Alberta, Nov. 20, 2018 (GLOBE NEWSWIRE) -- Zenith Epigenetics Ltd. ("Zenith" or the "Company"), a wholly-owned subsidiary of Zenith Capital Corp., announced today that it has entered into a clinical trial collaboration with Pfizer Inc. ("Pfizer"; NYSE: PFE) to evaluate the safety and efficacy of a novel anti-cancer combination of Zenith's investigational bromodomain and extra-terminal domain inhibitor ("BETi"), ZEN-3694, and Pfizer's poly ADP ribose polymerase inhibitor ("PARPi"), talazoparib, in patients with locally advanced or metastatic triple negative breast cancer ("TNBC").

"Zenith is excited to announce this partnership with Pfizer, a leader in oncology," said Don McCaffrey, Chief Executive Officer of

Zenith Epigenetics Announces U.S. FDA Clearance of Investigational New Drug Application for ZEN-3694 in TNBC Program

March 18, 2019

Pfizer / Zenith TNBC program collaboration on target to dose first patient in April 2019

Under the terms of the agreement, Zenith Epigenetics and Pfizer will collaborate on a Phase 1b/2 TNBC clinical study. Pfizer will provide talazoparib, Zenith will provide ZEN-3694, and both parties will fund the study. Zenith Epigenetics retains all rights to ZEN-3694.

herited BRCA gene mutations may
initial focus on triple negative breast

test in patients that are proficient in
pair genes and can thus potentially

Supportive Scientific Literature

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Repression of BET activity sensitizes homologous recombination-proficient cancers to PARP inhibition

Article

Cancer Cell

BRD4 Inhibition Is Synthetic Lethal with PARP Inhibitors through the Induction of Homologous Recombination Deficiency

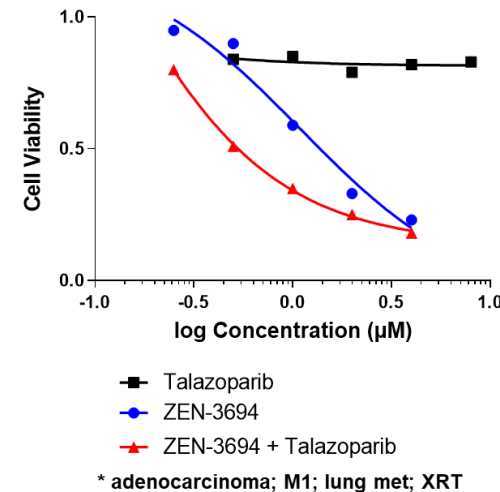
Report

Cell Reports

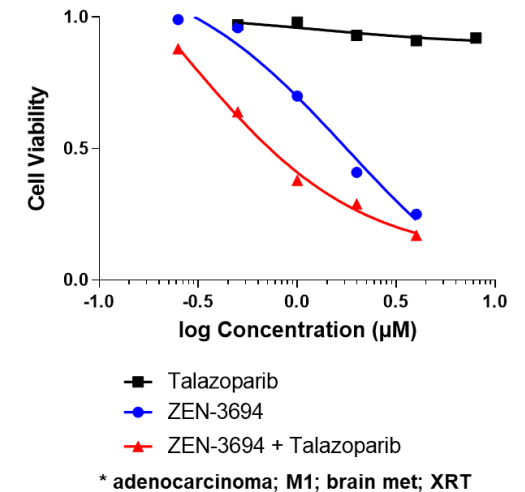
BET Bromodomain Inhibition Synergizes with PARP Inhibitor in Epithelial Ovarian Cancer

ZEN-3694 and talazoparib synergy in PDX spheres

Anti-tumor efficacy of ZEN-3694 in combination with talazoparib in MAXFTN '401 PDX (mBRCA)



Anti-tumor efficacy of ZEN-3694 in combination with talazoparib in MAXFTN '1384 PDX



Indication	2019	2020
Pfizer Collaboration: Triple Negative Breast Cancer (TNBC, non- BRCA 1/2m)	Phase 1b/2: Combination with PARPi (N~50)	

- **Objective:** Show safety and activity of ZEN-3694 + talazoparib in TNBC patients, non germline BRCA1/2m
- **Design:** Part 1: Dose escalation, Part 2: Simon 2-stage
- **Patient population:** TNBC: non-germline BRCA1/2 mutations, locally advanced or metastatic
- **Endpoints:** Part 1: Safety, PK/PD, MTD, RP2D; Part 2: Objective response rate (ORR), Duration of response (DOR), rPFS

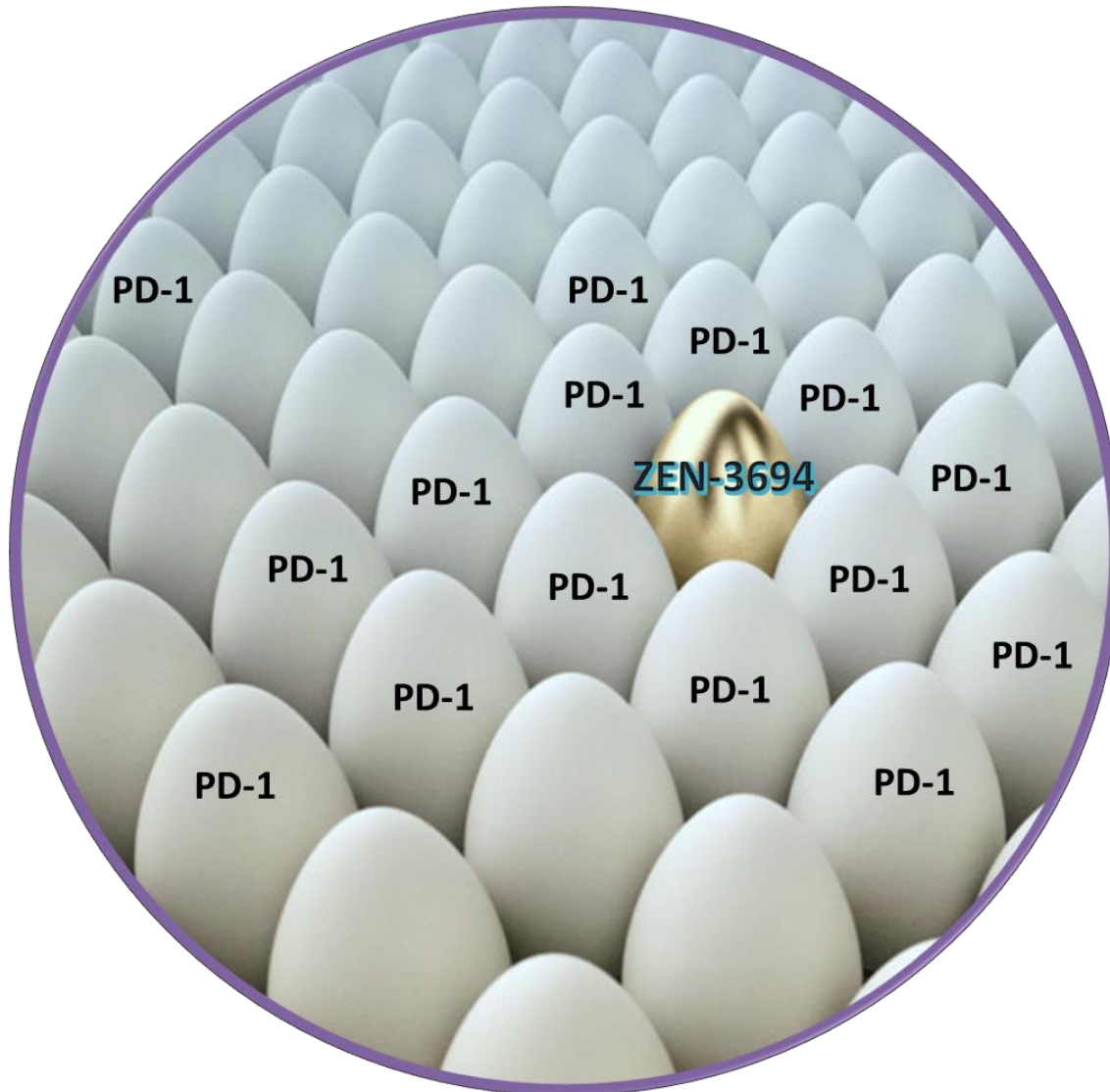
- ~\$400M* peak revenue for ZEN-3694 with significant upside
 - Movement to neo-adjuvant and 1st line TNBC
 - Expansion to other indications combining ZEN-3694 + PARPi in homologous proficient tumors (Ovarian, CRPC, ER+ breast)

Pfizer / Zenith Clinical Trial Collaboration

Prominent Clinical Sites and Investigators; PARPi and breast cancer experts

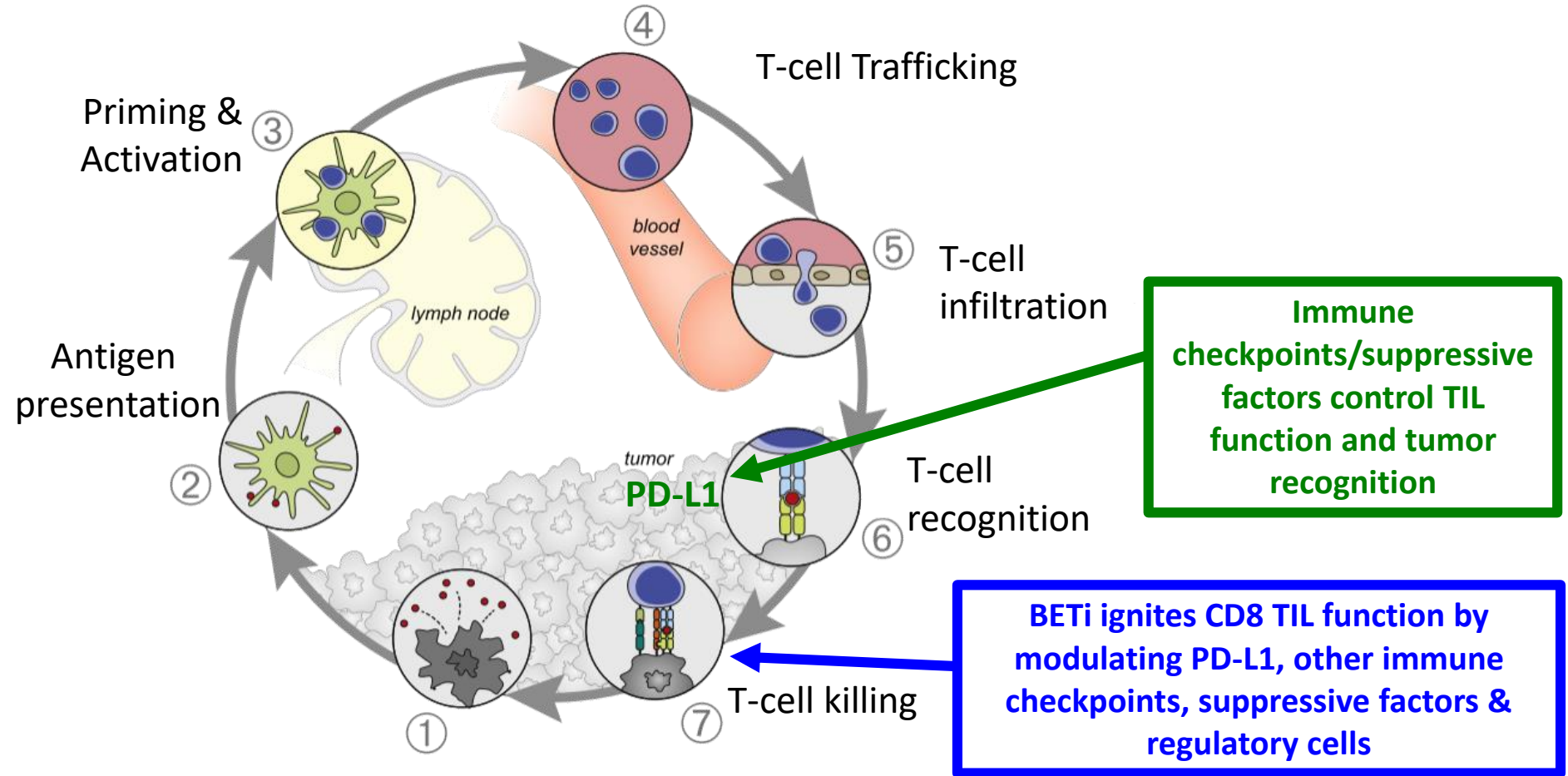


Institution	Investigator	Background
MSKCC	Mark Robson – Study Lead PI Ayca Gucalp - PI	Led OlympiAD breast cancer registration trial
MD Anderson	Jennifer Litton	Led EMBRACA breast cancer registration trial
Jules Bordet, Belgium	Philippe Aftimos	Led Merck and BI BETi trials
Banner Health	Lida Mina	Investigator on Phase 1, 2 and 3 Talazoparib trials
University of Kansas	Priyanka Sharma	TNBC specialist
University of Penn	Payal Shah - PI (Susan Domchek)	Talazoparib investigator, breast cancer specialist
Sarah Cannon	Erika Hamilton	Breast cancer specialist
UZ Leuven, Belgium	Kevin Punie	Breast cancer specialist
VHIO, Spain	Mafalda Oliveira	Investigator on Gilead and GSK ER+ BETi trials
StartMadrid, Spain	Valentina Boni	Breast cancer specialist



- ZEN-3694 works by blocking tumor immune evasion
- Combination potential with checkpoint mAbs
- Triple combination (ZEN-3694 + Keytruda + Enzalutamide) mCRPC

ZEN-3694 BET inhibition Disrupts Tumor Immune Evasion



Trigger full potential of native CD8 TIL cascade & tumor killing
by combining BETi + immune checkpoint drug therapy

Immuno-Oncology Opportunity: Strong Rationale for Checkpoint Combinations

Supportive Scientific Literature

Cell Reports

BET-Bromodomain Inhibitors Engage the Host Immune System and Regulate Expression of the Immune Checkpoint Ligand PD-L1

BET bromodomain inhibition enhances T cell persistence and function in adoptive immunotherapy models

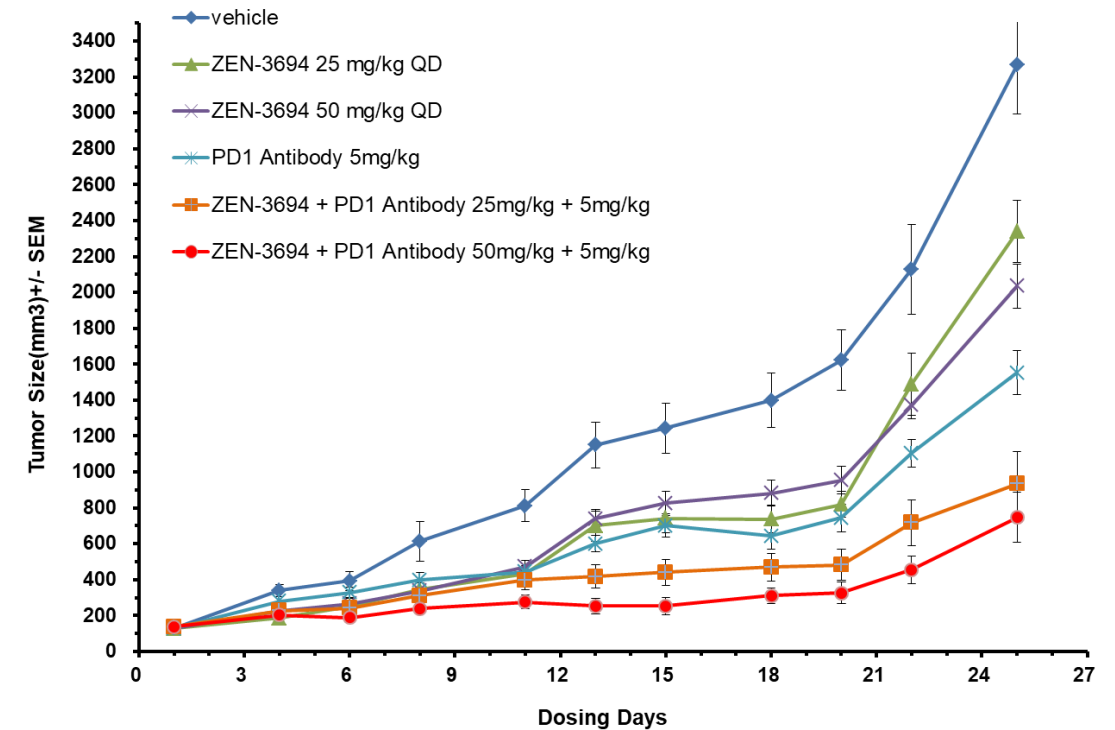
Yuki Kagoya,¹ Munehide Nakatsugawa,¹ Yuki Yamashita,¹ Toshiki Ochi,¹ Tingxi Guo,^{1,2} Mark Anczurowski,^{1,2} Kayoko Saso,¹ Marcus O. Butler,^{1,2,3} Cheryl H. Arrowsmith,^{4,5} and Naoto Hirano^{1,2}

¹Tumor Immunotherapy Program, Campbell Family Institute for Breast Cancer Research, Campbell Family Cancer Research Institute, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada. ²Department of Immunology, University of Toronto, Toronto, Ontario, Canada. ³Department of Medicine and ⁴Structural Genomics Consortium and ⁵Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada. ⁶Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada.

BET bromodomain inhibition cooperates with PD-1 blockade to facilitate antitumor response in Kras-mutant non-small cell lung cancer. Adeegbe DO, et al.
Cancer Immunol Res. 2018

Article

ZEN-3694 enhances anti-PD1 activity in the syngeneic CRC model MC-38



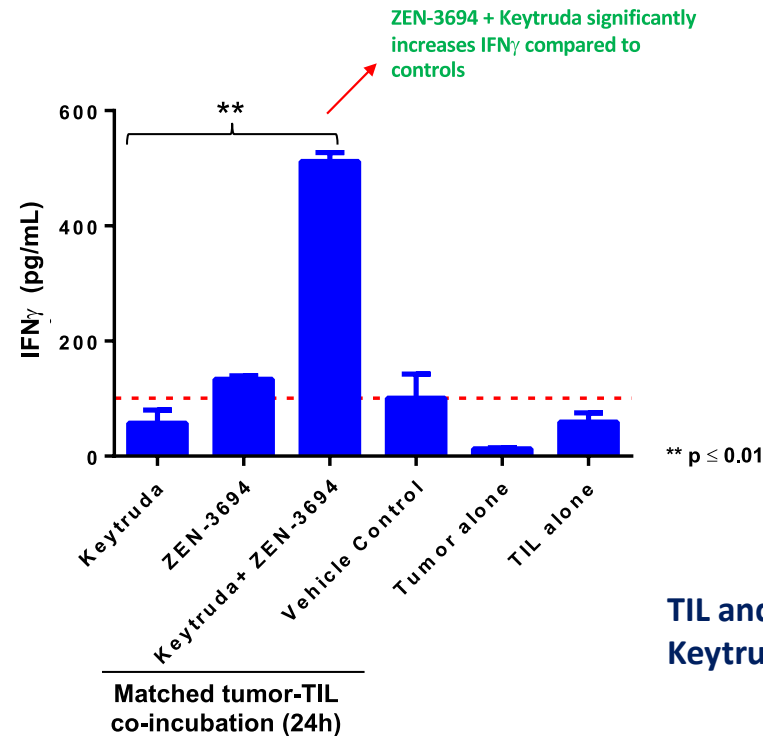
Immuno-Oncology Combination Therapy with a BETi

Prostate Cancer – a cancer where immuno-oncology therapies have been unsuccessful

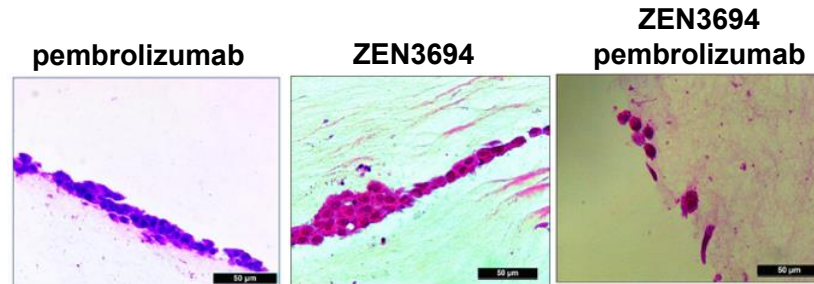
Functional effects of ZEN-3694 + Keytruda in Keytruda resistant model

Clinical Blood Data

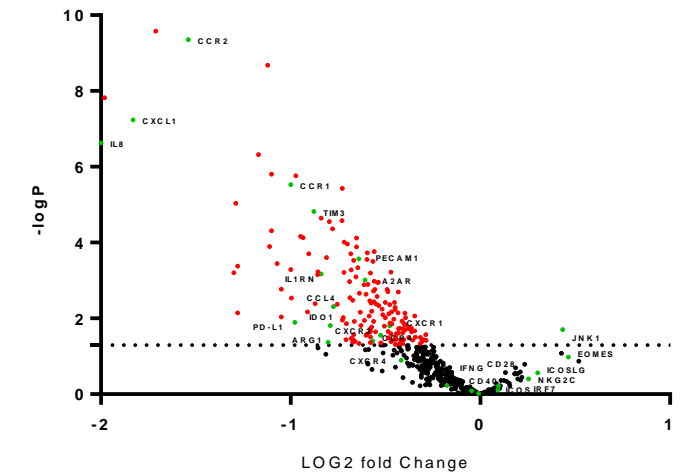
#1. ZEN-3694 increases anti-PD1-induced IFN-g expression



#2. ZEN-3694 + Keytruda demonstrates lysis of tumor cells



#3. Blood gene expression changes at 4h, mCRPC clinical trial



TIL and Melanoma Tumor 004
Keytruda-resistant (ImmunAccel)

Objective:

Revert primary/secondary resistance to anti PD-1 or PD-L1 inhibitors

Phase 1B/2: Renal/Melanoma/HNSCC/NSCLC/Bladder
ZEN-3694 + Checkpoint mAb combination

Rationale:

- BETi modulate PD-L1, suppressive and regulatory cells, other checkpoints

Study design:

- Dose escalation: ZEN-3694 + checkpoint mAb
- Dose Expansion : ZEN-3694 + checkpoint mAb, n~9 per tumor type (expand to additional 14 patients for tumor type with 1 or more responders)

Patient Population:

- Patients who become resistant to checkpoint inh. therapy (primary or secondary) - potentially select short duration responders

Endpoints:

- ORR, Safety

Zenith is focused on ZEN-3694 combinations with SOC extending and expanding the value of existing therapeutics

Multiple Phase 2 POC clinical trials

- **Prostate Cancer Program:** Promising clinical activity of ZEN-3694 + Enzalutamide in ARi resistant mCRPC patients, Very favorable FDA feedback for registration enabling study
- **Pfizer and Zenith collaboration (TNBC/PARPi):** Ph. 1b/2 of ZEN-3694 + PARPi in TNBC (non germline-BRCA1/2m) initiated
- **Immuno-oncology Program: ZEN-3694 + Pembrolizumab + Enzalutamide** in AR independent CRPC, Significant potential in other resistant tumors