



AGM Discussion and Q & A

NUT Carcinoma Lead Program

January 2025



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M&A Opportunity Based on NUT Carcinoma Results

Opportunity Overview

OPPORTUNITY

- To acquire the rights to a **best-in-class** bromodomain (BET) inhibitor program. The M&A process and pricing will be based on the lead program, NUT Carcinoma. Additional indications are included and confirmatory trials are in the works and fully funded by NIH, NCI & numerous pharma collaborators

NUT CARCINOMA

- A rare, under diagnosed squamous carcinoma. A new Harvard IHC test for NUTM1 antigen is rapidly expanding the market potential. Target estimates have risen annually from 200 to over 5,000 & growing
- **Proof of concept** established in several clinical trials with ZEN-3694 and other BET inhibitors, **FDA Fast Track Application** in process with expectations for Q2 2025
- Phase 2 trial ongoing in combination with chemotherapy/CDK4/6i with **impressive objective response rates (ORR)** reported to date in trials. Compassionate use application has been expanded globally

KEY ATTRIBUTES

Potential for **accelerated approval** (2025) with projected peak revenue potential of **~\$400M**

Orally bioavailable, potent, and selective with **optimal PK/PD and safety profile** for chronic dosing

IP exclusivity until October 2041

Significant opportunity for **additional indications** (mCRPC, ER+ Breast - CDK4/6i combo.) multiple trials ongoing, expenses covered

NUT Carcinoma is an underdiagnosed, rare oncology indication

Disease Overview

DISEASE CHARACTERISTICS



NUT carcinoma: A rare, highly aggressive and previously underdiagnosed squamous carcinoma characterized by a single translocation involving the **NUTM1 gene and different partner genes**

Epidemiology: underdiagnosed, estimated at ~5000 cases per year in G5



Location: occurs primary in **midline structures (thorax, head, neck)**; less frequently in other body parts

Etiology: not currently known; not affected by age/sex/ smoking

Clinical characteristics: **No symptoms** specific for NUT, some histology can be indicative



Diagnosis: **IHC test** for NUTM1 antigen – responsible for greatly increasing diagnosis

Current treatment: chemotherapy and radiation; **no targeted therapies**

Survival: Overall Survival ~ 6 months, median age at diagnosis 23.5 yrs - 50% children



Oncogenesis: **Three quarters** of NUT carcinoma cases involve **fusion of the NUTM1 oncogene** to a BET family member

- **BET inhibitors** disrupt the interaction of the **BRD4-NUT** oncoprotein and chromatin
- **Proof of concept** established in BETi clinical trials

UNMET NEEDS



Fatal disease with poor prognosis

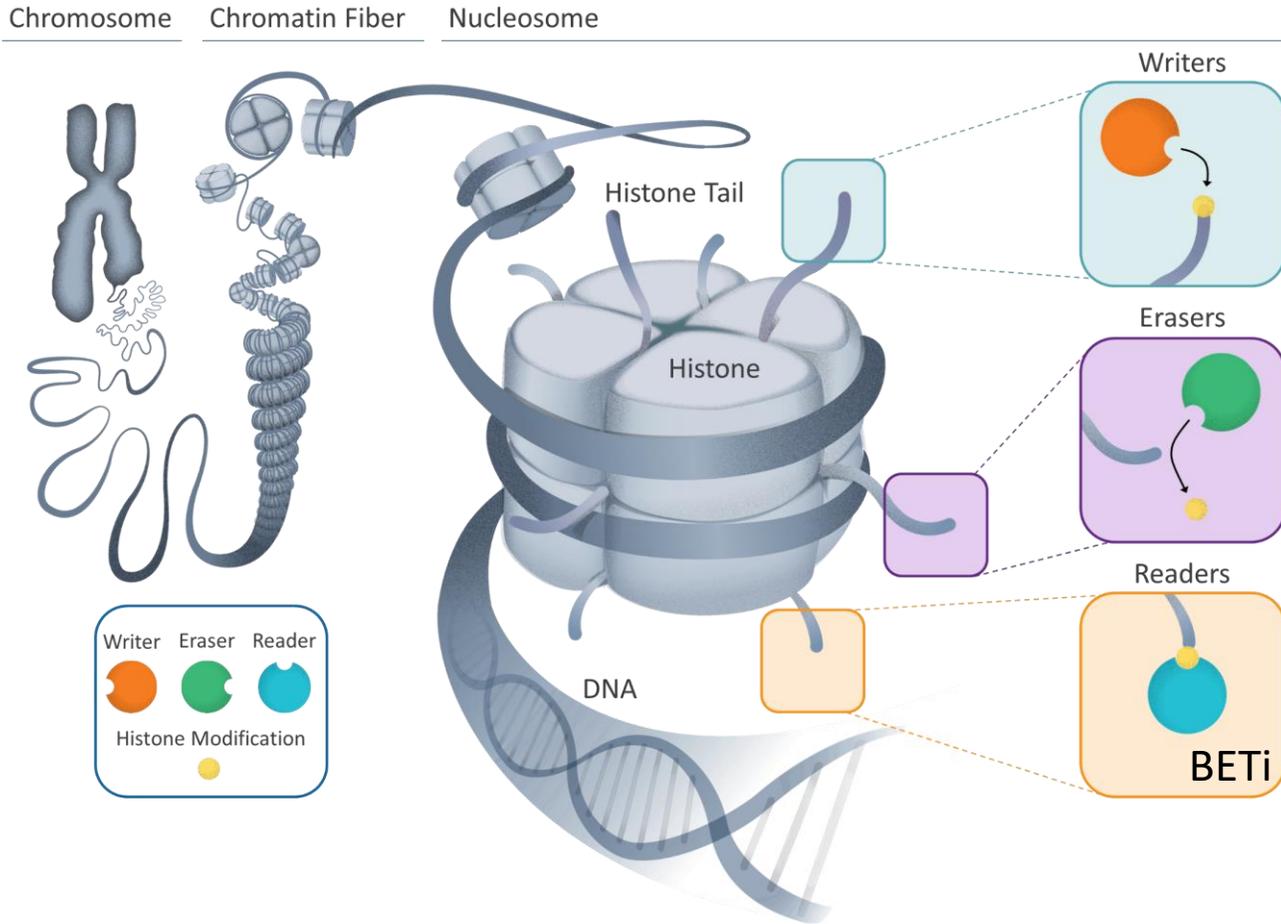
No effective therapeutic options

Largely underdiagnosed and under-reported

Lack of disease understanding

BET inhibitors work at the epigenetic level and suppress cancer growth by modulating oncogene expression

Transforming Combination Therapy in Oncology

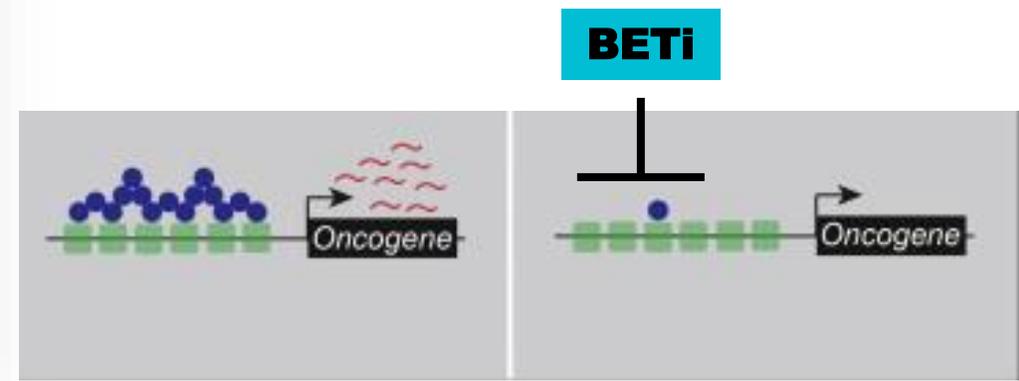


Gene expression and production of proteins regulated by epigenetics

Cancer cells hijack gene expression machinery to propagate

Cancer cells also develop resistance to therapies through epigenetic gene regulation

BET bromodomain inhibitors (BETi) have been shown to suppress cancer growth by modulating oncogene expression and restore sensitivity of cancer cells to targeted therapies



■ Super-enhancer cluster

● BRD4

A compassionate use NUT Carcinoma patient achieved near complete response with single agent ZEN-3694

Compassionate Use Case



- Progressing on bone and lung lesions prior to treatment
- 12/18/22 : Single agent ZEN-3694 treatment started at 48mg/qd
- ~3/7/23: Scans show a near complete response in thoracic lesion, hip and abdomen lesions were irradiated
- 6/15/23 Patient progressed but continued on ZEN-3694 as deriving clinical benefit, lesion near heart still under control
- 8/23 Patient off treatment

FDA Expedited Pathway Planning Progress

Key findings – 50% Objective Response Rate (ORR) Achievable in NUT Carcinoma



Single Agent and Combination therapy development: efficacy and duration of response

- Both mono and combo approaches have established 48 mg, by utilizing a standard 3 plus 3 dosing approach, as the safe and efficacious dose level for ZEN-3694
- Combination with CDK4/6i results in improved duration of patient response and efficacy
- 48 mg of ZEN-3694 + 100 mg of CDK4/6i (abemaciclib), in NUT carcinoma and solid tumors, have already shown safety
- The next step is to increase abemaciclib to its highest level of 150 mg which is expected to be the final dose combination level with 48mg of ZEN-3694
- Two ongoing combination trials are showing significant activity of ZEN-3694 in NUT carcinoma (Dana Farber Cancer Institute)
 - i. ZEN-3694 + Etoposide/Cisplatin in NUT carcinoma:
 - ii. ZEN-3694 + CDK4/6i (abemaciclib) in NUT carcinoma and solid tumors

FDA Fast Track and Commercial Development: ORR greater than 50% has been achieved

- In Q1 2025, The National Institute of Health (NIH) is planning to submit a final application to the FDA for expedited approval of ZEN-3694 and abemaciclib. The FDA has a 90-day response window.
- A dozen additional sites have been coordinated to identify the final 30 patients estimated to provide expedited approval status
- All clinical trial costs have been covered by the NIH and the drug development partners.



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Cencora Commercialization Support Study - formal KOL and payer group pricing interviews

Methodology

Interviews & Discussions with Clinical KOLs

Limited KOLs available globally for NUT due to rarity of cancer; interviewed >90% top KOLs in the field

| KOL | Payer |
|---|---|
|  <i>Medical Oncologist Dana Farber</i> |  <i>Pharmacy Director Kaiser Permanente</i> |
|  <i>Pathologist Dana Farber</i> |  <i>Medical Director Blue Shield of California</i> |
|  <i>Medical Oncologist Yale Medicine</i> |  <i>Senior Commissioning Phase NHS, Integrated Care Board</i> |
|  <i>Medical Oncologist NUT Carcinoma leading institution</i> |  <i>Expert on Reimbursement Independent, self-employed</i> |
| Key Affiliations | |
|  |  <i>Head HE & Policy, SHI G-BA advisor AOK Rheinland/Hamburg SHI</i> |
|  |  <i>Oncology Product Consultant Augmentium Pharma Consulting Inc</i> |
|  | |

Interviews with Payers

6 payer calls were conducted (2 for US, and 1 each for UK, FR, DE, CA)

Selected institutions



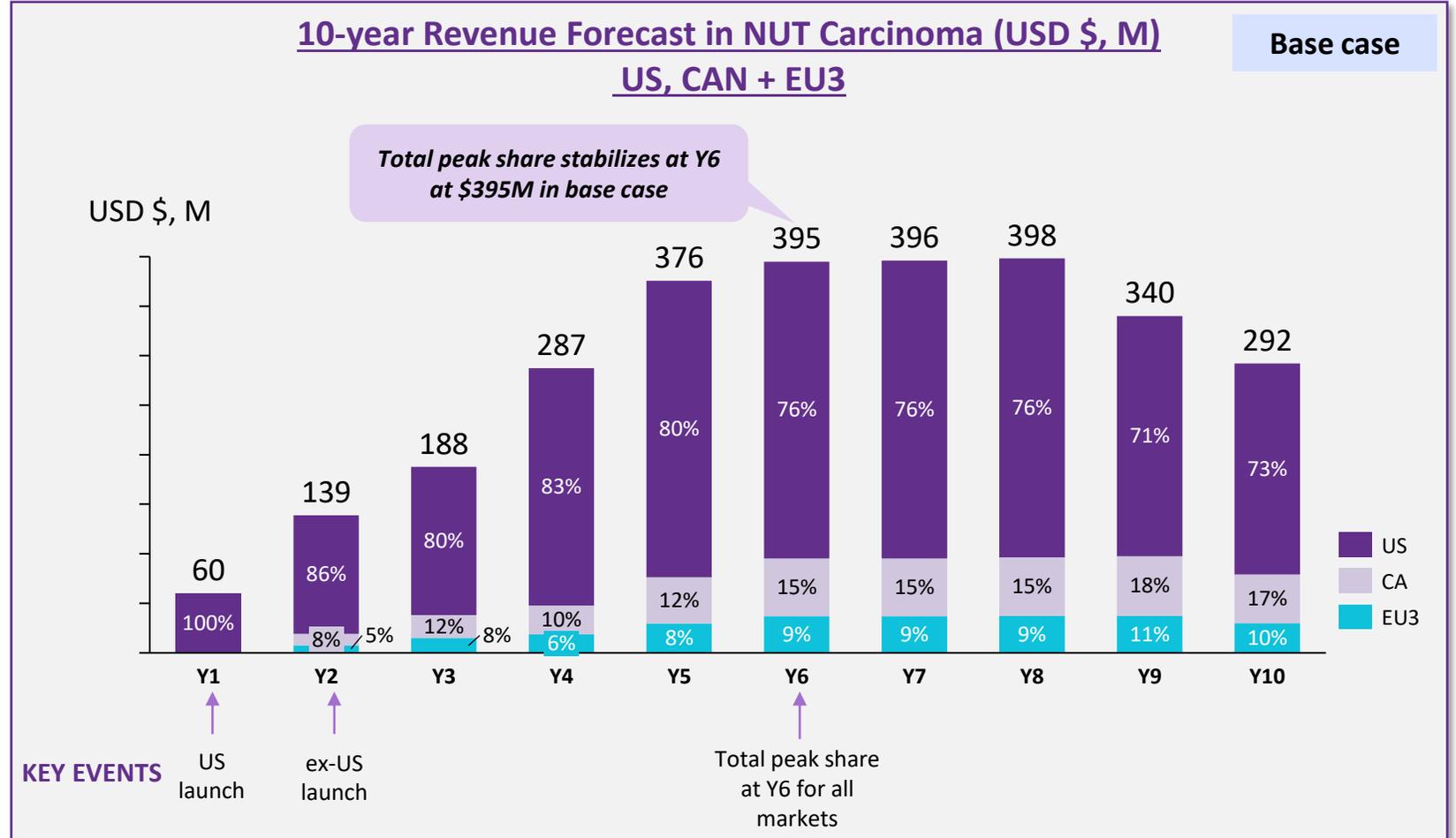
Selected titles

- Pharmacy Director
- Medical Director
- Head HE & Policy, SHI G-BA advisor
- Ex- transparency commission of HAS

Executive Market Size Summary

ZEN-3694 Revenue in NUT Carcinoma (US, CA, EU3) – Post this analysis, Australian and other high IHC usage markets will also be targeted

| Base Case Inputs | Assumptions |
|---------------------------|--|
| Total Incidence (2024) | 5000 |
| Eligibility | 85% <i>BRD1-4, NSD3 thoracic</i> |
| Diagnosis | 10% ->60% <i>5x increase at Y3 and 60% at Y8</i> |
| Market access | 100% <i>Full coverage if reimbursed</i> |
| Launch year | 2026 (US) 2027 (Ex-US) <i>Aggressive development plan</i> |
| Time to peak | 5 years |
| Market share | 100% -> 70% <i>No new product could launch before 2034</i> |
| Duration of therapy | 6 months <i>Median OS</i> |
| Monthly price (\$ USD, K) | 50 (US), 22 (CA), 8 (EU) |

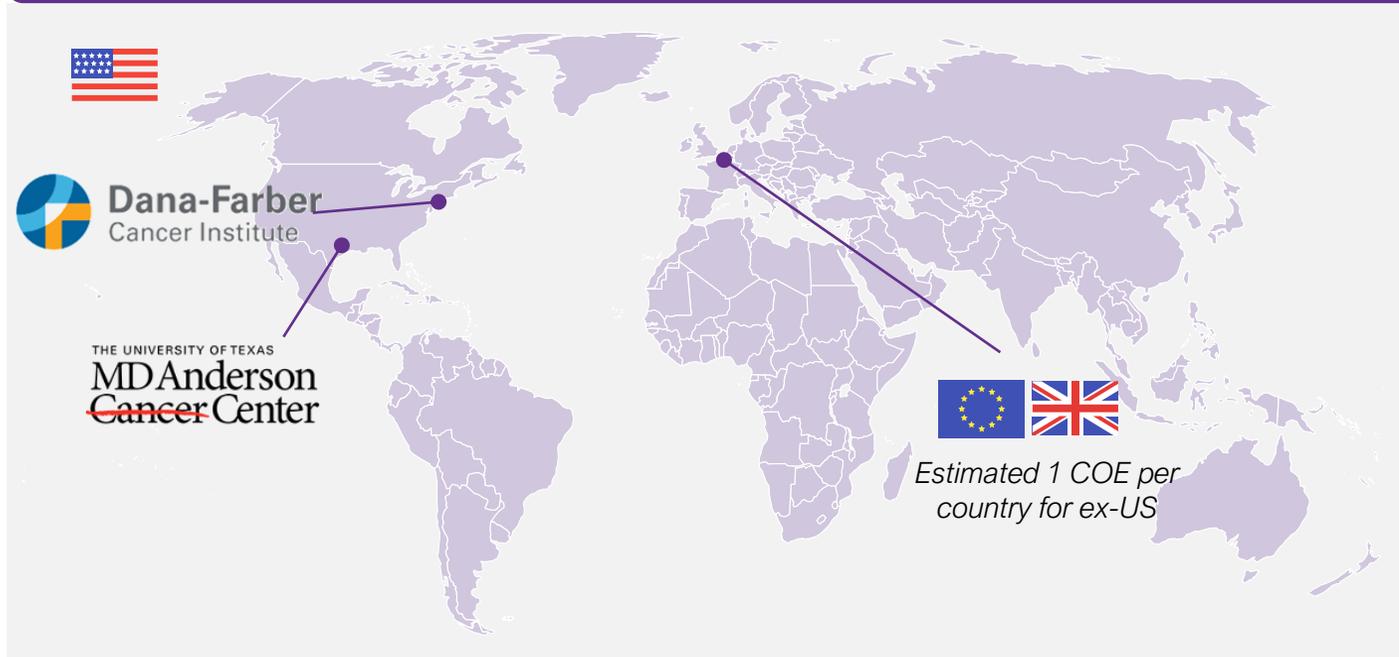


NB: EU3 (UK, DE, FR), * Ramp up curves for diagnosis rate and market share is detailed in market sizing section
 Australian compassionate use patient levels have been significantly higher due to their use of IHC screening.

Targeted Sales Force Strategy - based around concentrated COEs can be used in NUT Carcinoma

Commercial Upside: Targeted Sales Force

CENTRES OF EXCELLENCE (COE) FOR NUT CARCINOMA



As of today, COEs are international reference for NUT carcinoma treatment

COMMERCIAL IMPLICATION



Targeted sales force due to concentrated COEs

Strong existing relations with Key Opinion Leaders in the field

Summary - The NUT Carcinoma program has two ongoing trials, presenting a \$400M USD peak revenue opportunity in the US, CA & EU3

Program Overview

CURRENT PROGRAM

Stage:
Phase
1b/2

Combinations:
Multiple



NATIONAL
CANCER
INSTITUTE



Dana-Farber
Cancer Institute

Lilly

Partners:



Product Profile: ZEN-3694 + CDK4/6i, or etoposide and cisplatin, is positioned for 1st line treatment of NUT carcinoma patients



Target Population: Patients with metastatic or unresectable NUT carcinoma (BRD/NUT fusion). Underdiagnosed disease.



Standard of Care: No approved therapies ; patients are treated with chemotherapy (etoposide and cisplatin) and radiation, with a median survival of only six months.

COMMERCIAL IMPLICATIONS



Peak Market Size: 5,000 *(2023 estimate)*

>2500 (diagnosed cases per year; estimates for US+CAN+EU3)



Peak Revenue: ~\$400M *(for US+CAN+EU3)*



Est. Market Entry: 2027 *(accelerated approval potential with orphan designation)*



Upcoming Milestones: FDA Fast Track Submission Early 2025



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PI Initiated/ Compassionate Use Update

- 10 NCI and 2 other PI initiated trials are ongoing,
- Most trials in late stage dose escalation with progression to dose expansion in 1H 2025
 - Addressing AEs with protocol modifications etc. and optimizing dosing regimen
- PRs noted in 5 combination trials with ZEN-3694
 - NUT carcinoma (+CDK4/6i)
 - NUT carcinoma (+ chemotherapy)
 - NUT carcinoma (+ HDACi)
 - Endocervical (+ MEKi)
 - Ovarian and CRC (+ PD-1 inh.)
- Compassionate Use
 - Single agent PRs in NUT carcinoma
 - Metabolic CR (maintenance) in MPNST (+ MEKi)
- MPNST trial and bipolar androgen therapy (BAT) in planning stages

A Phase 1 Study of ZEN003694 (ZEN-3694) in
Combination with Cetuximab and Encorafenib in
Patients with Refractory BRAF V600E Metastatic
Colorectal Cancer
Protocol 10605

Scott Kopetz, M.D.(PI), Salvador Alonso, M.D. (co-P.I.)
skopetz@mdanderson.org salonso1@mdanderson.org

Phase 1/1b ZEN003694 + Nivolumab +/- Ipilimumab in solid tumors and ovarian cancer

Mahdi, UPitt NCT04840589



6 evaluable at DL1
3 evaluable at DL2
3 evaluable with triple combo

ZEN-3694 + Nivolumab +/- Ipilimumab

Metastatic or recurrent solid tumors
(no BRCA selection)
Cycles 1-4 ZEN-3694 (-2 dblt RP2D to dblt RP2D PO QD) + Nivo (240 mg IV D1 Q21) + Ipi (1 mg/kg IV D1 Q21)
Cycles 5+ ZEN-3694 + Nivo 480mg IV D1 Q28
3+3 design, n=9-18

Metastatic or recurrent solid tumors
(no BRCA selection)
ZEN-3694 (36-72 mg PO QD) + Nivo (480mg IV D1 Q28)
3+3 design, n=12-18

Dose escalation

Recurrent ovarian carcinoma
BRCAwt
Platinum resistant
ZEN3694 (48mg PO QD) + Nivo (240mg IV) + Ipi (1m/kg IV D1)
n=15

Recurrent ovarian carcinoma
BRCAwt
platinum resistant
ZEN3694 (trplrt RP2D PO QD) + Nivo (240mg IV) + Ipi (1m/kg IV D1)
n=15

Dose expansion

Primary: Safety and tolerability, RP2D

Secondary: ORR, PFS, OS, AEs, CBR

Inclusion: ≤5 lines of prior therapy in escalation or expansion
≤ 2 prior lines in platinum resistant setting in expansion

Exclusion: Primary refractory ovarian cancer (progressed while on primary 1L platinum therapy) in expansion
Prior therapy with PD-1, PD-L1, or CTLA-4 inhibitors

ETCTN Trial 10579: Phase I Trial of ZEN003694 (ZEN-3694) in Combination with Capecitabine in Patients with Solid Tumors

Dennis Hsu, MD

Hillman Cancer Center

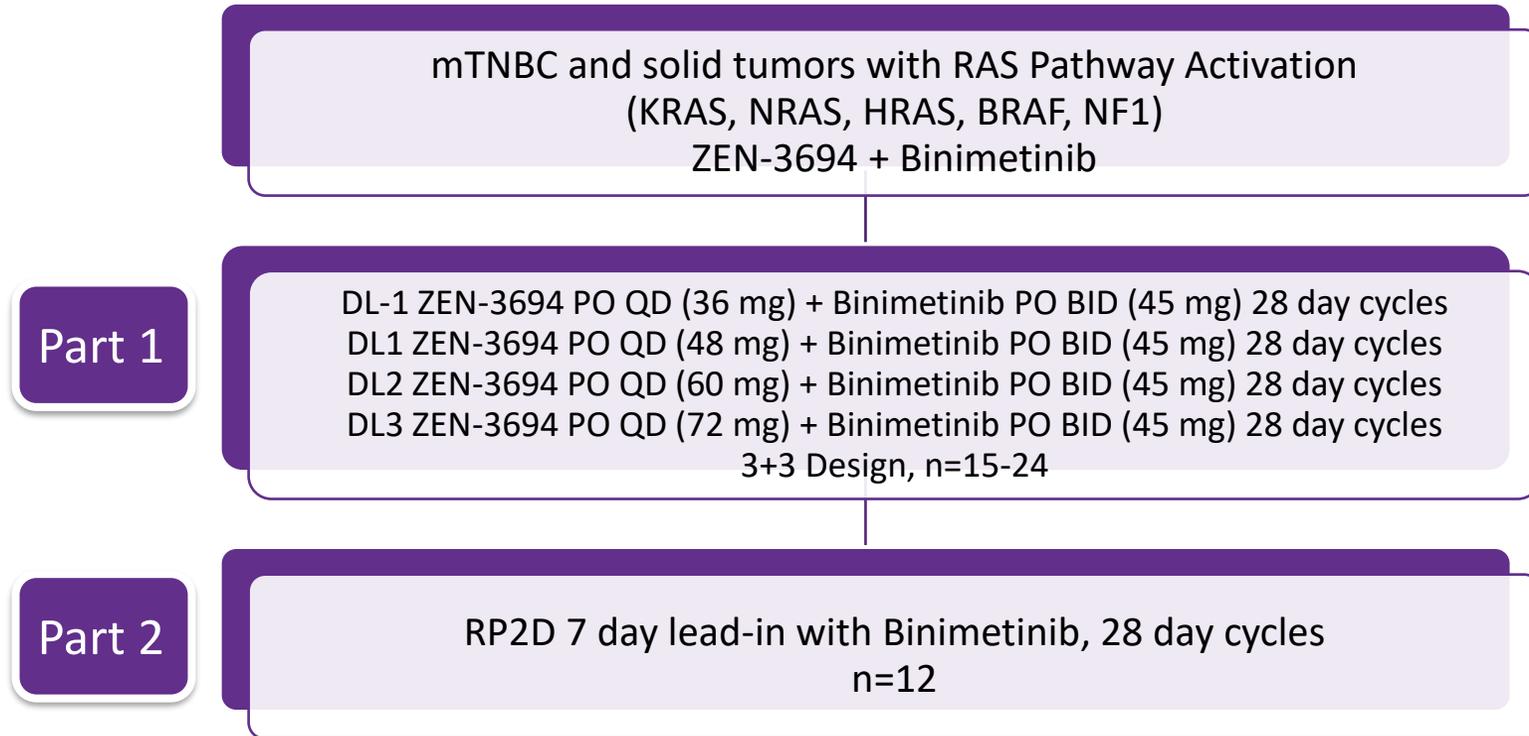
University of Pittsburgh

November 8th, 2024

djh138@pitt.edu / ETCTN10579@upmc.edu

Phase 1 ZEN-3694 + binimetinib in patients with RAS pathway alterations and TNBC

Piha-Paul Meric-Bernstam, MDACC NCT05111561



PBMC/cfDNA taken at screening, C1D1, C1D8, C1D15, C1D22, C2D1
Biopsies taken at screening, D6/7, D15

- Primary: Part 1 - MTD and RPD , Part 2 - ORR
- Secondary: Part 1 - Safety and tolerability, PK, clinical activity, Part 2 – PFS, DOR, DCR, PD
- Exploratory: PK, biomarkers of response and resistance
- Inclusion/Exclusion: Part 1 - TNBC, Solid tumor with genomic alteration(s) activating RAS signaling including activating KRAS, NRAS, HRAS, or BRAF mutations, inactivating NF1 mutations, or BRAF fusions. Part 2 – TNBC only

**NCI 10449: A PHASE 1 STUDY OF ZEN003694 IN
COMBINATION WITH BINIMETINIB
IN SOLID TUMORS WITH RAS PATHWAY ALTERATIONS AND
TRIPLE NEGATIVE BREAST CANCER**

MDACC Local Protocol 2022-0244

Principal Investigator: Sarina Piha-Paul, MD
University of Texas, MD Anderson Cancer Center



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NRG - GY031

**A PHASE IB STUDY OF COMBINATION ATR (M1774)
AND BET INHIBITION (ZEN003694) TO EXPLOIT
ARID1A LOSS IN RECURRENT OVARIAN AND
ENDOMETRIAL CANCER**



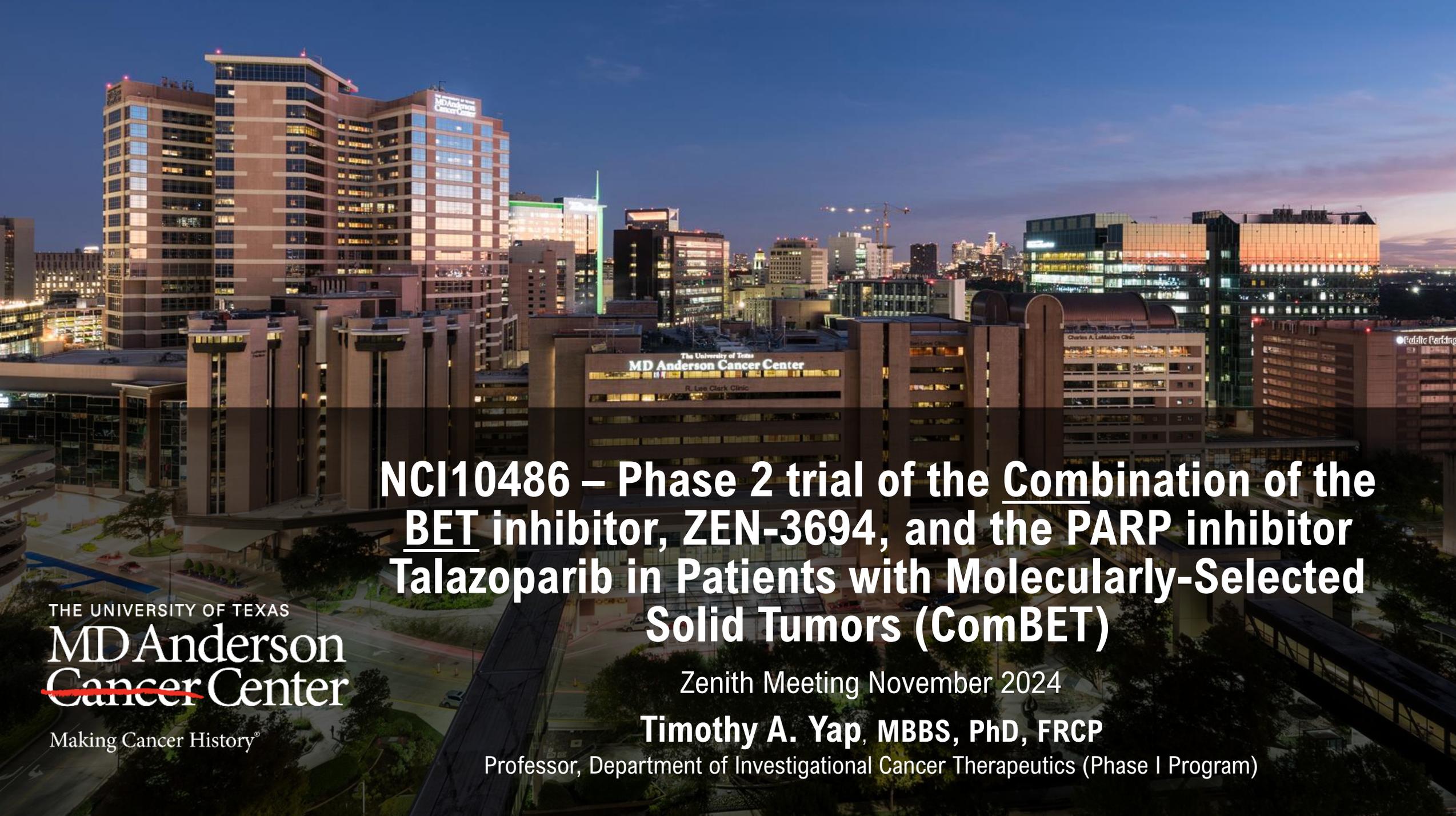
A phase 1b trial of ZEN-3694 with pembrolizumab and nab-paclitaxel in patients with metastatic triple-negative breast cancer

Overall PI: Ana C. Garrido-Castro, MD

Translational PI: Geoffrey Shapiro, MD, PhD

Statistician: Nabihah Tayob, PhD

NCI CTEP Meeting – Nov 8, 2024



NCI10486 – Phase 2 trial of the Combination of the BET inhibitor, ZEN-3694, and the PARP inhibitor Talazoparib in Patients with Molecularly-Selected Solid Tumors (ComBET)

Zenith Meeting November 2024

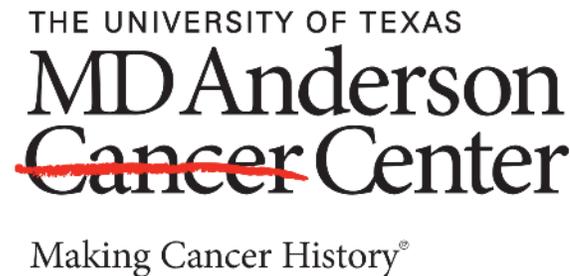
Timothy A. Yap, MBBS, PhD, FRCP

Professor, Department of Investigational Cancer Therapeutics (Phase I Program)

THE UNIVERSITY OF TEXAS
**MD Anderson
Cancer Center**

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Our Partners and Collaborators



NUT Carcinoma “First To Market Focused” Program Collaborators:



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