City of Hope

18th Annual California Cancer Consortium Conference

PK/PD Considerations in Early Phase Clinical Trials

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August 19th, 2022

ETCTN Objectives

- Conduct high quality early clinical trials in an efficient and timely manner
- Promote collaboration and foster career development
- Integrate pharmacology, cancer biology, and imaging

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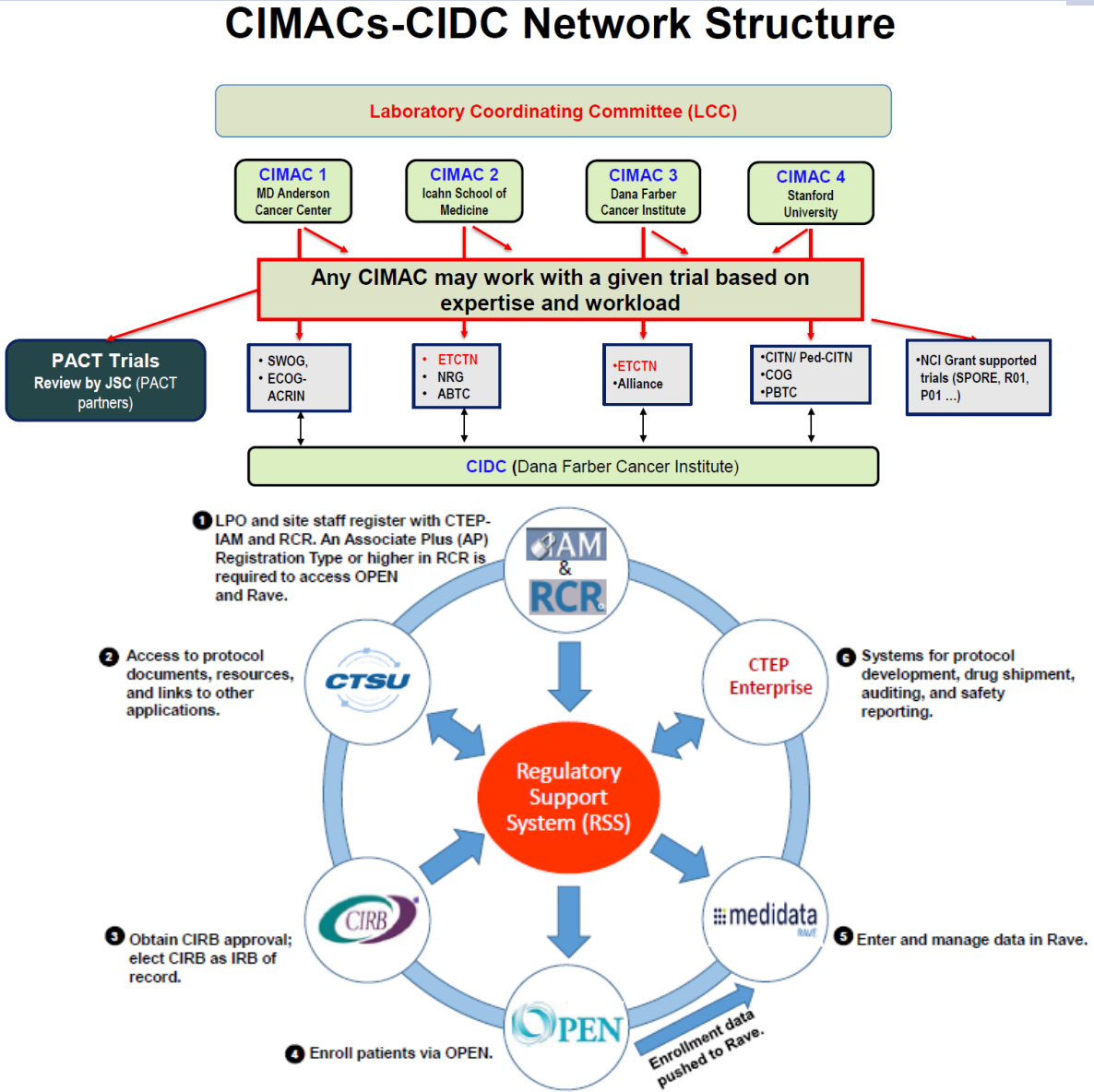
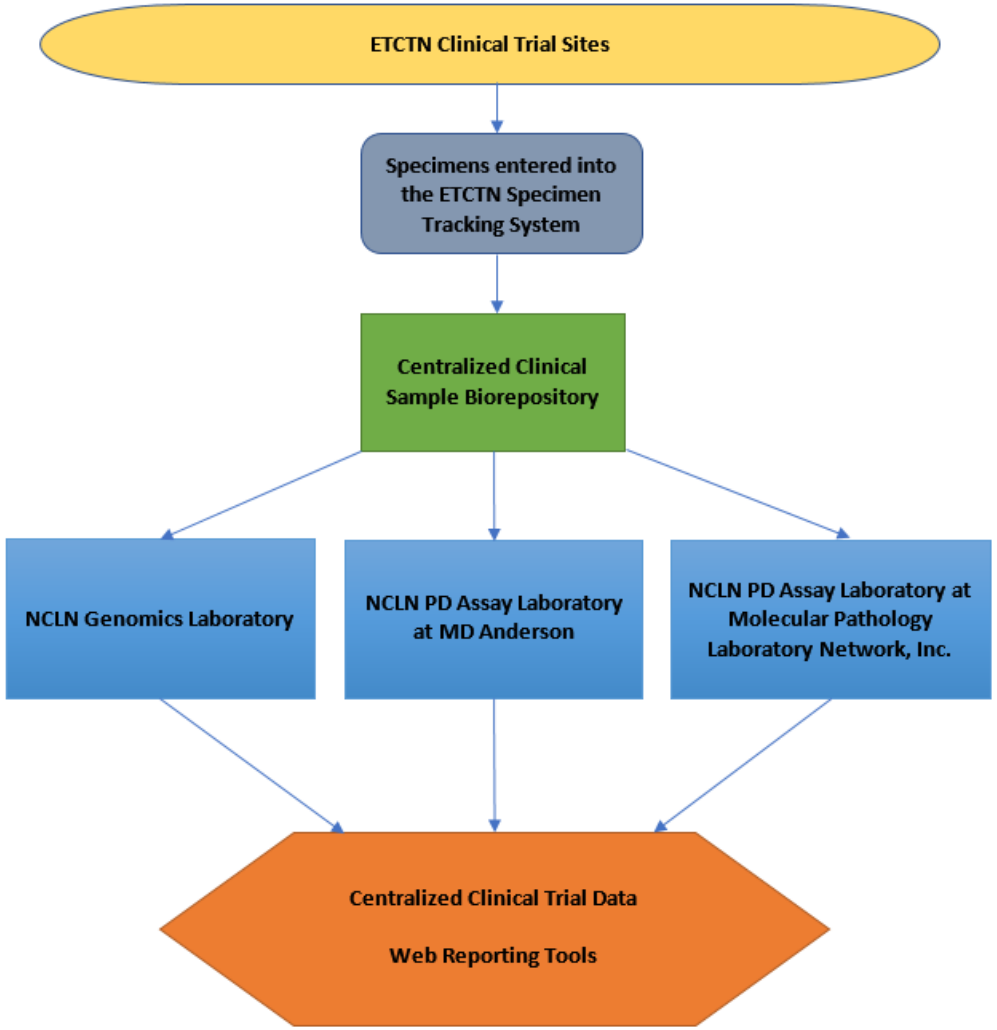
Supporting the Science





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Objectives of Early Trials

- **What is tolerable**
- **Does the drug get to the target** } PK
- **Does the drug engage the target** } PD

- **Early response assessment**
- **Exposure-toxicity & exposure-response**

- **Identify modifying factors**
  - Intrinsic (organ function, molecular status,..)
  - Extrinsic (DDI, smoking, food,..)

U24 Consortia – ETCTN PK Resources

- **PITT-CAL**
  - U.Pittsburgh PK core - Beumer
  - City of Hope PK core - Synold

- **ChOP-KC**
  - Johns Hopkins PK core - Rudek
  - Ohio State PK core - Baker (Phelps, Sparreboom)

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PITT-CAL Specific Aims

- **AIM 1: Provide pharmacology expertise**
- **AIM 2: Analyze biological samples**
- **AIM 3: Perform PK data analyses**

U24 Consortia – Division of Labor

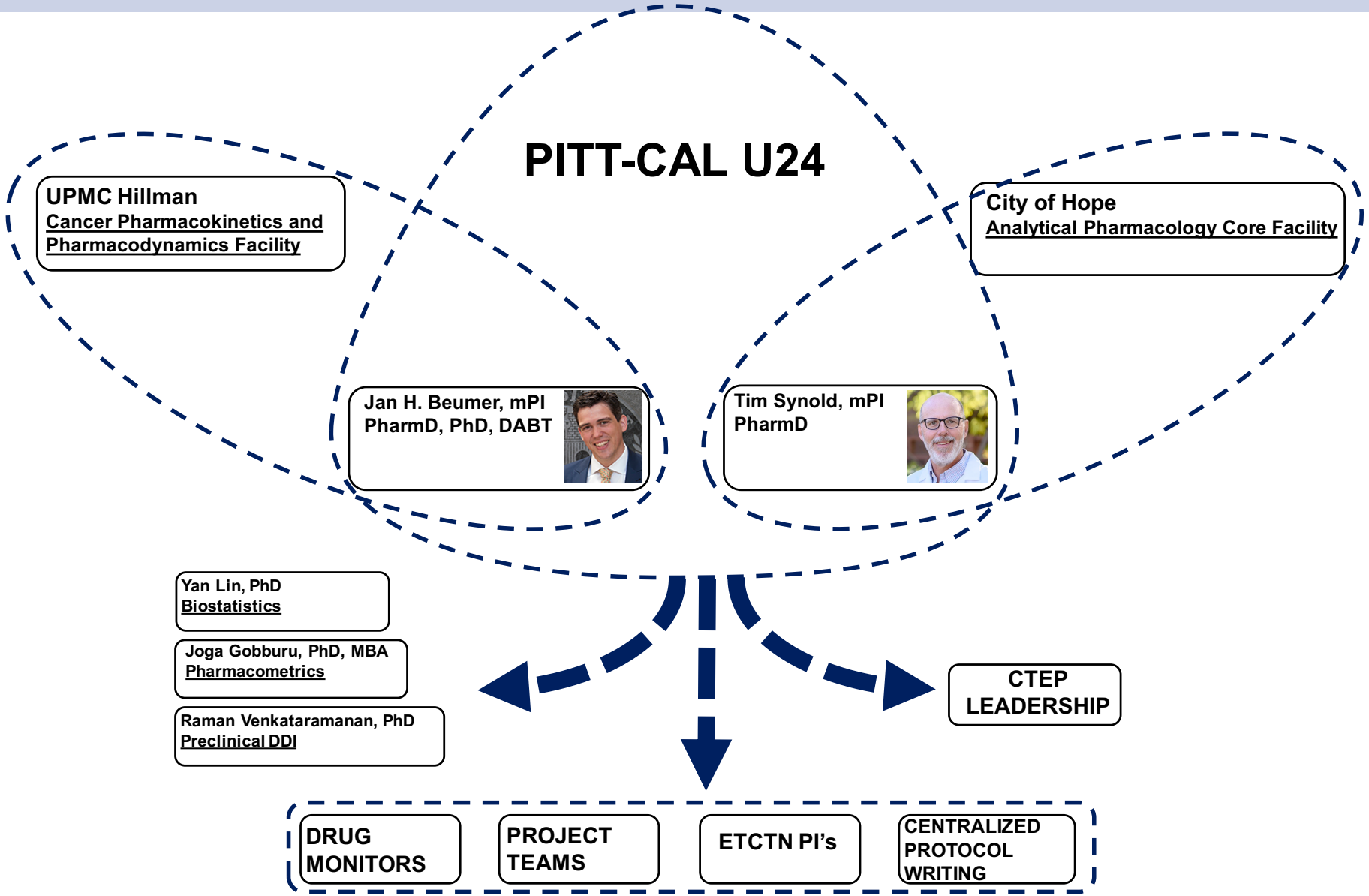
Project Team (PTMA) LOIs

- Distributed based on bandwidth, interest, and equity

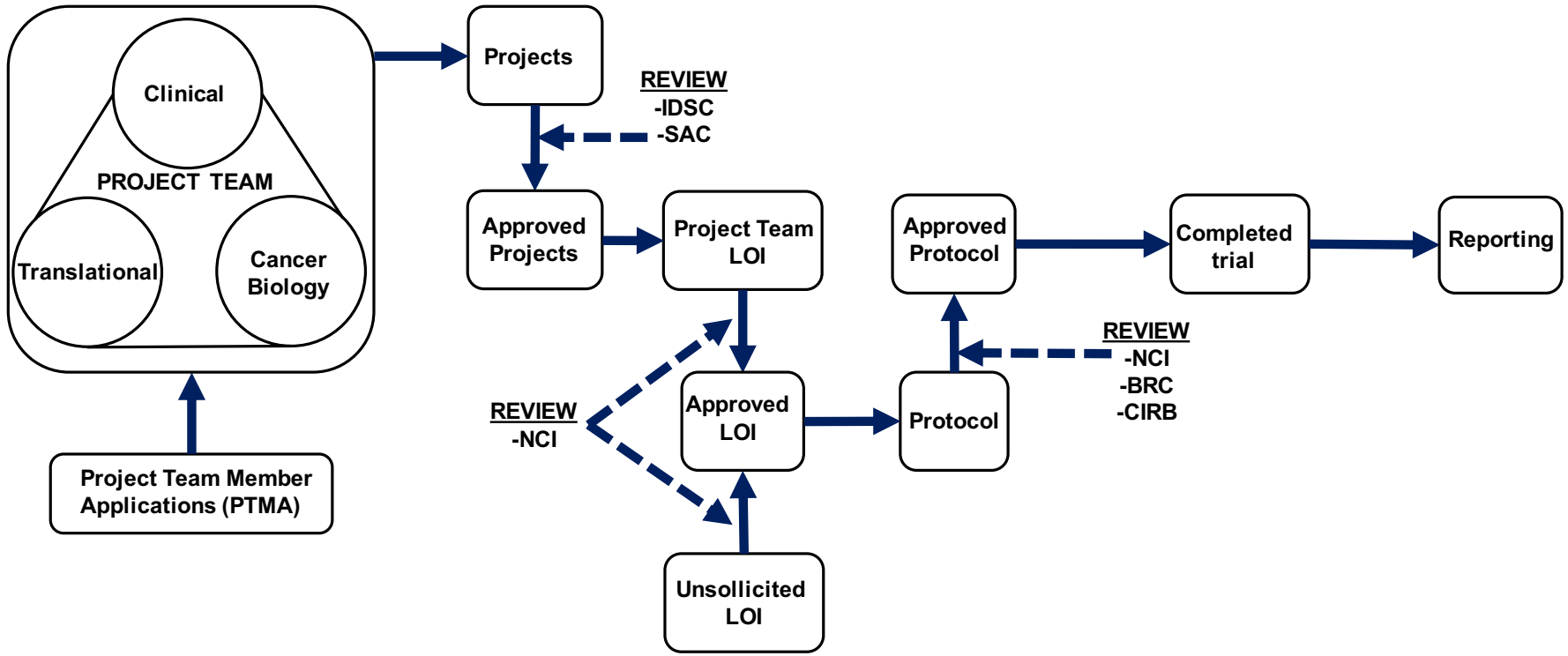
Unsolicited LOIs (i.e. non-Project Teams)

- Each U24 responsible for their UM1 LAOs
  - PITT-CAL = CCC (LAO) and PITT (LAO)
  - ChOP-KC = JHU (LAO) and OSU (LAO)
- Other UM1 LAOs (Princess Margaret, Dana Farber, Yale, and MD Anderson) to contact U24 PI's for assignment

PITT-CAL Interactions



PITT-CAL Activities



PITT-CAL ACTIVITIES

-Evaluate existing PK data -Identify PK needs and opportunities -PK integration into trial design	-Inform and educate clinical team -Negotiate and design PK sampling -Develop PK statistic design	-Draft PK sections -Operationalize sample collection, storage, shipment -Finalize statistic design	-Sample receipt -Sample analysis -PK analysis -Interim PK reports	-Draft PK reporting -Statistical analyses -Explore PK-PD relationships -Draft manuscript sections -Explore POP-PK analyses

PITT-CAL Portfolio – Study Design

LOI/PT	Type	Lead Agent	Other Drugs	LAO	PI	Role/Activity
#	U, S, or PT					
ACTIVATED						
10324	S	M3814 (PEPOSERTIB)	Doxil	LAO-MD017	Grisham	Support trial and PK design
10313	U	M6620	GEM-CARBO Avelumab	LAO-PA015	Villaruz	Support trial and PK design
10366	S	M3814 (PEPOSERTIB)	IR	LAO-MD017	Davis	Design PK protocol
10402	S	BAY1895344	IRINO/TOPO	LAO-CT018	Das	Design PK protocol
10403	S	BAY1895344	GEM	LAO-MA036	Cleary	Design PK protocol
10433	U	ZEN-3698	NIVO+/-IPI	LAO-PA015	Mahdi	Support trial and PK design
10483	U	ERDAFITINIB	enfortumab-vedotin	LAO-11030	Jain	Support trial and PK design
10406	S	BAY1895344	FOLFIRI	LAO-PA015	Krishnamurthy	Support trial and PK design
10492	PT	IPATASERTIB + CHEMO RT	CISPLATIN	LAO-11030	Mattes	Support trial and PK design
PENDING						
10404	S	BAY1895344	GEM-CIS	LAO-CA043	Parikh	Design PK protocol
10500	U	TAZEMETOSTAT BELINOSTAT		LAO-CT018	Amengua	Consulted during LOI development
10522	U	CA-494	paclitaxel	LAO-CT018	Park	Design PK protocol
10525	U	ZEN-3694	paclitaxel	LAO-MA036	Garrido-Castro	Consulted during LOI development
10527	U	M3814 (PEPOSERTIB)	M1774	LAO-MA036	Cote	Design PK protocol
10563	U	M3814 (PEPOSERTIB)	Doxil	LAO-MA036	Haddox	Design PK protocol
NRG-UC2055	PT	IPATASERTIB	MPA	NRG	Grinsfelder	Design PK protocol
IN DEVELOPMENT						
10579	U	ZEN-3694	capecitabine	LAO-PA015	Hsu	Consulted during LOI development
DTS-2106	U	ZEN-3694, M1774		NRG	Simpkins	Consulted during LOI development
TBD	U	TALAZOPARIB	NIVOLUMAB	LAO-CA043	Hanna	Consulted during LOI development

PITT-CAL Portfolio – Assay Development and Analysis

Trial #	Clinical Trial Name	LAO	PI	Pharmacology endpoints relevant to the U24 (i.e. PK endpoints)	Analytes	# New Methods Developed and Validated (or Cross-validated) for Trial (RP)	# New Methods Developed and Validated (or Cross-validated) for Trial (Cumulative)
8282	A Phase 1 Study of Chronica	LAO-PA015	Puhalla	DLin, E-R	VELIPARIB+		
8620	A Phase 1 Study of ABT-888	LAO-PA015	Puhalla	IND	VELIPARIB		
9892	Phase I Dose-Escalation Bio	LAO-PA015	Taylor	DLin, E-R	TRIAPINE		
9938	Phase I Clinical Trial of VX-9	LAO-PA015	Villaruz	DDI, E-R	M6620, IRINO+		
9938	Phase I Clinical Trial of VX-9	LAO-PA015	Villaruz	DDI, E-R	M6620, IRINO+		
9947	A Randomized Phase 2 Trial	LAO-CA043	Pal	E-R	M6620, GEM		
9947	A Randomized Phase 2 Trial	LAO-CA043	Pal	E-R	M6620, GEM		
9950	A Phase I Study of M6620 (V	LAO-MD017	Owonikoko	E-R	M6620		
10217	A Phase 1b Biomarker-Drive	LAO-TX035	Yap	DDI, E-R	COPAN, OLA, DURVA		OLA
10273	A Phase 1 Study of M3814 ir	LAO-CA043	Jonas	DDI, E-R	M3814, MITOX, ETOP+, araC		M3814+
10273	A Phase 1 Study of M3814 ir	LAO-CA043	Jonas	DDI, E-R	M3814, MITOX, ETOP+, araC		ETOP+
10273	A Phase 1 Study of M3814 ir	LAO-CA043	Jonas	DDI, E-R	M3814, MITOX, ETOP+, araC	araC+	M3814+, ETOP+, araC+
10324	A Phase I/Ib Dose Escalation	LAO-MD017	Grisham	DDI, E-R	M3814+, DOXIL+		M3814+
10324	A Phase I/Ib Dose Escalation	LAO-MD017	Grisham	DDI, E-R	M3814+, DOXIL+	DOXIL+	DOXIL+
10313	A phase IB and randomized (	LAO-PA015	Villaruz	E-R	M6620, GEM		
10366	A Phase 1/2 Study of M3814	LAO-MD017	Davis	IND	M3814+		M3814+
10388	A Phase I Trial of Triapine ar	LAO-OH007	Chauhan	E-R	TRIAPINE		
10402	BAY 1895344 Plus Topoisor	LAO-CT018	Das	IND, E-R	BAY1895344, TOPO+, IRINO+	TOPO+	BAY1895344, TOPO+
10404	A Phase 1 Trial of the ATR I	LAO-CA043	Parikh	IND, E-R	BAY1895344, GEM+		BAY1895344
10406	Phase I/Ib Trial of ATR Inhibi	LAO-PA015	Krishnamurthy	IND, E-R	BAY1895344, FU, IRINO+		BAY1895344
10406	Phase I/Ib Trial of ATR Inhibi	LAO-PA015	Krishnamurthy	IND, E-R	BAY1895344, FU, IRINO+	FU	BAY1895344
10433	Phase I/Ib trial evaluating the	LAO-PA015	Mahdi	DLin, E-R	ZEN-3698	ZEN-3694+	ZEN-3694+
10449	A Phase I Study to Investigat	LAO-TX035	Piha-Paul	D-Lin, DDI, E-R	ZEN-3694+, Binimetinib	ZEN-3694+	ZEN-3694+
10450	A Phase 1b Study of M3814	LAO-OH007	Chauhan	IND	M3814		M3814+
10483	Phase Ib trial of Erdafitinib c	LAO-11030	Jain	DDI, E-R	ERDAFITINIB, MMAE	ERDAFITINIB, MMAE	ERDAFITINIB, MMAE
10492	Phase 1/1b Study of AKT Inh	LAO-11030	Mattes	E-R	IPATASERTIB, M1	IPATASERTIB+	IPATASERTIB+

Goals of PK

- **Phase I**
  - Disposition (Cmax, Tmax, AUC, CL, Vd, T1/2)
  - Dose dependence
  - Drug-drug interactions
  - Drug-disease interactions (co-morbidities, organ function, age, genotype, etc)
- **Phase II**
  - Relationship between exposure and outcome
  - Sources of PK variability

Goals of PD

- Provides proof-of-mechanism
- Allows rationale go/no-go decisions
- Can add to or replace PK information
- Guide dose and schedule decisions
- Used to select patients most likely to respond/fail
- Gain understanding of resistance mechanisms
- Inform rational combination therapies

Methodologic Considerations

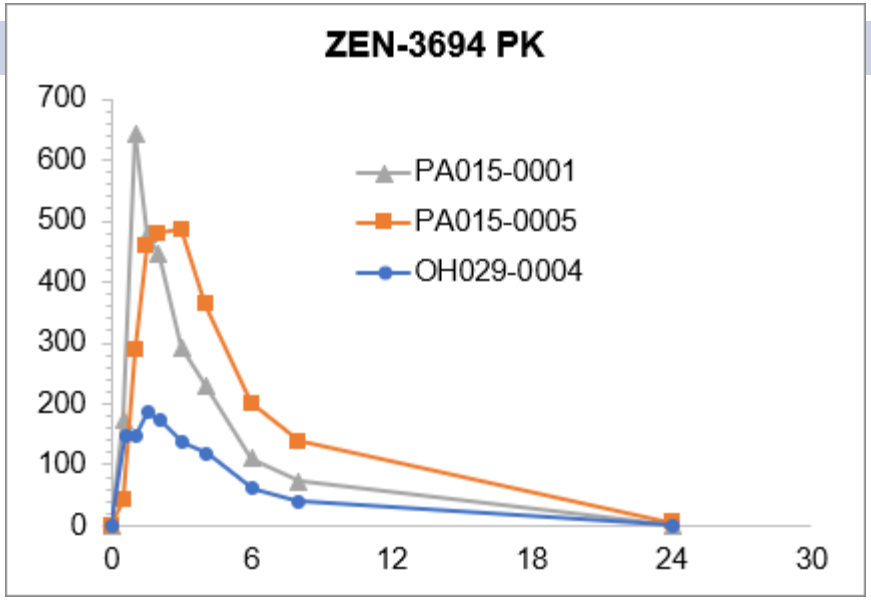
- **Assay related factors**
  - Assay should be appropriately validated
- **Biomarker and sample related factors**
  - Intrinsic variability of the parameter to be measured
  - Minimal intra- and inter-observer variability
  - Baseline sampling is critical
  - Surrogate tissues can be used
  - Other key issues include quantity of sample, and collection, processing, and preservation of samples
  - Important to establish stability of the marker in the sample

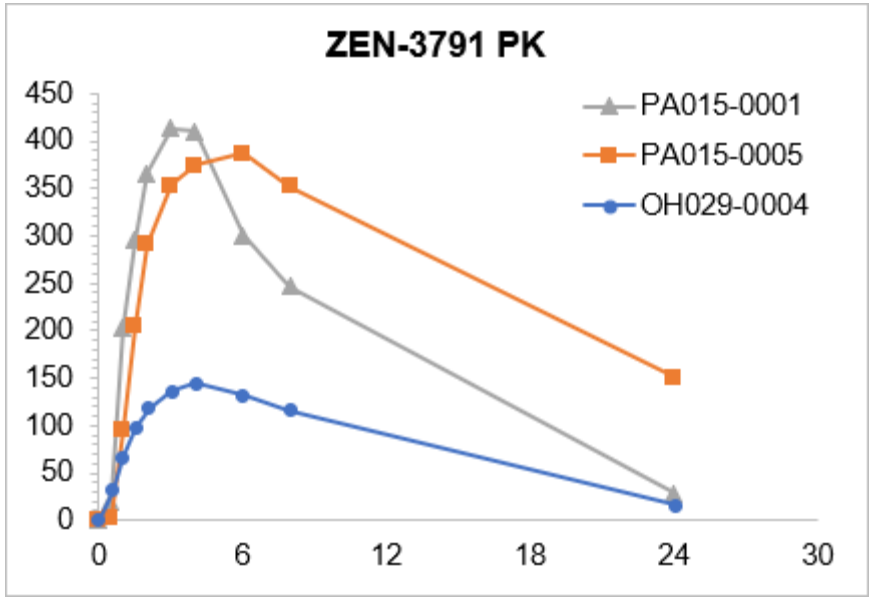
Recent Example of an U24-Supported PK Application

- NCI #10433 - Phase I/Ib trial evaluating the safety and efficacy of ZEN-3694 plus nivolumab with or without ipilimumab.
- ZEN-3694 and metabolite, ZEN-3791, are pan-BET bromodomain inhibitors, leading to epigenetic regulation of gene expression.
- Given daily po on a 28-day cycle.
- Dose escalation started well below the RP2D for single agent.
- One patient in first cohort had a DLT (prolonged grade 3 ↓plt).
- **PI suspected a possible DDI.**

Recent Example of an U24-Supported PK Application

- Combined AUC for 0005 was 39% higher than 0004 and 216% higher than 0001.
- Impact was greatest on elimination of ZEN-3791.
- ↓platelets = 0005>>0001>>>0004.
- Protocol amended to exclude fluoxetine coadministration and 0005 was been replaced.





Summary

- PK and PD are essential parts of successful drug development (preclinical → post-marketing).
- PK/PD can help guide dosing decisions, explain variability in response and toxicity, provide a rationale for novel combinations, and inform new precision medicine approaches.
- PK and PD resources are available within the CCC and ETCTN.

Questions?

- Thanks for staying awake