



## **Developing Pentarin<sup>®</sup> Precision Oncology Medicines For Patients With Solid Tumor Malignancies**

March 2, 2020

Cowen 40th Annual Health Care Conference



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## Executive Summary

Clinical-stage developer of miniature drug conjugates that rapidly penetrate into solid tumors to selectively accumulate and release anti-cancer payloads

- Proprietary *Pentarin*<sup>®</sup> miniature drug conjugate platform yielding a new class of precision oncology medicines
- Two clinical stage programs advancing through key clinical milestones over next 18-24 months
- Platform momentum with preclinical pipeline of new miniature drug conjugates
- Broad IP portfolio with long duration into the 2030's
- Experienced management team with track record of advancing therapeutics through development to commercialization
- Definitive agreement to reverse merge with Organovo (ONVO) announced in December 2019, subject to stockholder approval and satisfaction of closing conditions

# Leadership

Experienced team with proven track record and vision to advance strategic objectives



**Drew Fromkin**  
President & CEO

CLINICAL DATA Merck-Medco  
*Live life well*




**Jeff Bloss, MD**  
Chief Medical Officer

Genentech gsk  
*Lee* Xencor



**Mark Bilodeau, PhD**  
Chief Scientific Officer

MERCK



**Brian Roberts, CPA**  
Chief Financial Officer

DIGITAS Insulet Corporation  
avedra



**Sudha Kadiyala, PhD**  
EVP Strategy

Johnson & Johnson

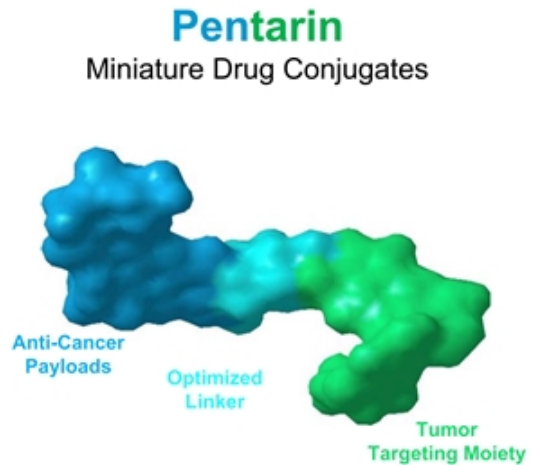
# Pentarin® Miniature Drug Conjugates

Designed to incorporate the best aspects of small molecule drugs and antibody drug conjugates to yield clinical activity while minimizing healthy tissue toxicity

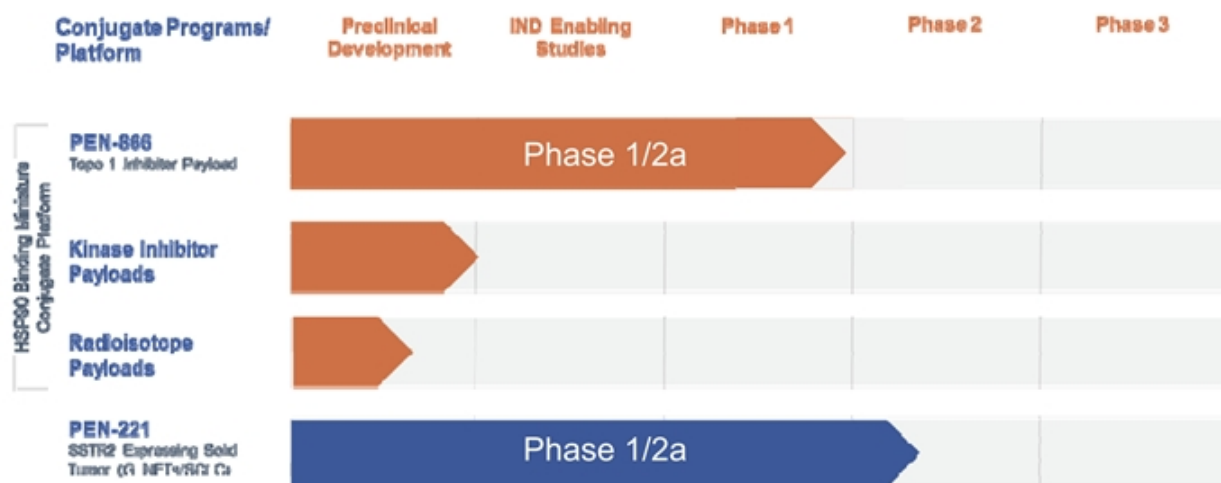
Our precision oncology medicines are designed to:

- Produce a half life of hours compared to days and weeks (antibody drug conjugates, or ADCs)
- Rapidly and deeply penetrate solid tumors while clearing normal tissues quickly
- Accumulate selectively and remain in the tumor and sustain the release their anti-cancer payloads
- Mask payloads where desired until cleaved in tumor reducing normal tissue toxicity

*Pentarins* are engineered through chemistry resulting in lower cost and complexity of manufacturing and commercialization than biologics (ADCs)



# Clinical and Discovery Pipeline

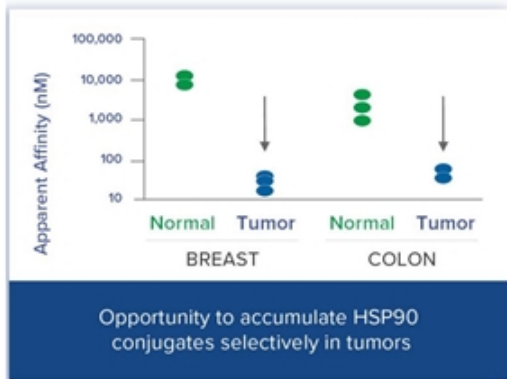


# HSP90 Binding Conjugate Platform

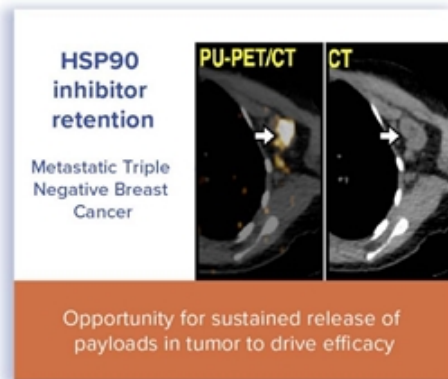
Up to 75% of solid tumors have activated HSP90, and small molecule drugs that target activated HSP90 have desirable binding properties in solid tumors vs. normal cells

Activated HSP90 is the **binding site** for our HSP90 binding miniature drug conjugates

HSP90 Small Molecule Inhibitor Has Affinity in Tumor vs Normal Tissue<sup>1</sup>



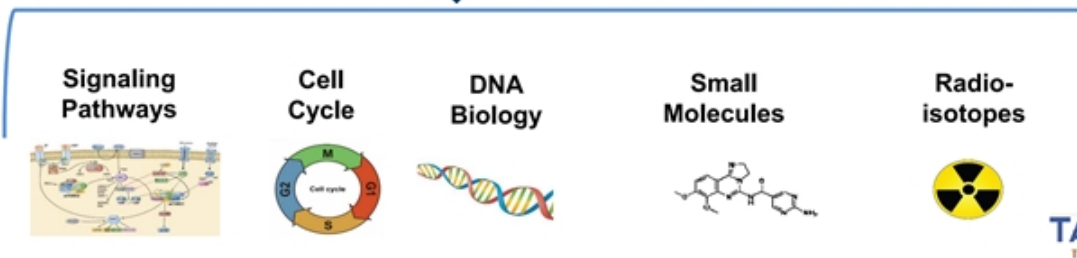
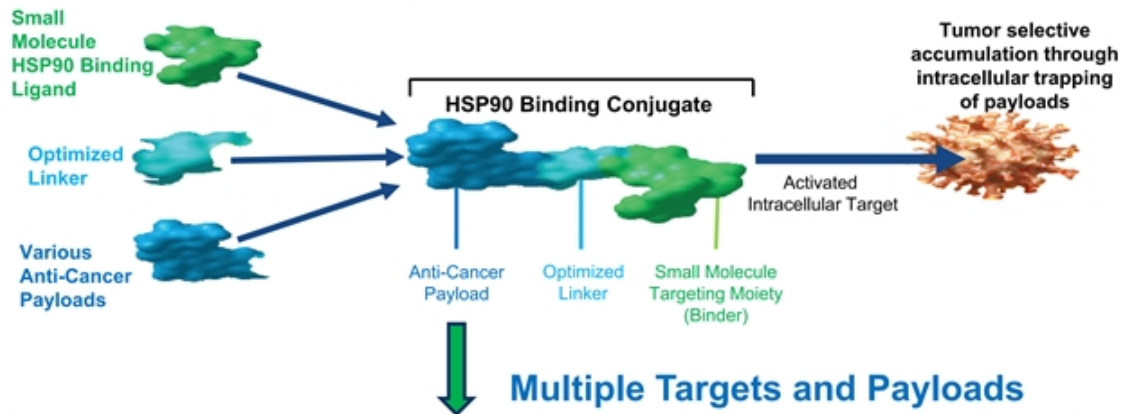
The Majority Of Patient Tumors Retain<sup>124</sup> I-labeled HSP90 Inhibitor PU-H71<sup>2</sup>



(1) Kamal, A et al (2003) Nature 425, 407-410  
(2) Rodina et al (2016) Nature 538, 397-401

# HSP90 Binding Miniature Drug Conjugate Design

- Binding ligand has high affinity for the activated form of HSP90 found in solid tumors
- Tuned linkers for desired cleavage kinetics
- Anti-cancer payloads selectively accumulate and release in tumors





# PEN-866 - First Clinical Stage Program From Our Pentarin® HSP90 Binding Miniature Drug Conjugate Platform

- Comprised of an HSP90 binding ligand linked to a topoisomerase-1 (SN-38) payload
- **Accumulation and elongated duration retention** of HSP90 conjugate PEN-866 in xenograft and PDX models, now demonstrated in Phase 1 patient biopsies
- **Completing Phase 1**, all comers trial in advanced patients
- **Early clinical activity observed and well tolerated**
- **Large market opportunity** across solid tumors with major treatment gaps as single or combo agent
- **Composition of matter patent issued** with long duration protections



Broad Opportunity in Topo-1 Sensitive Solid Tumors



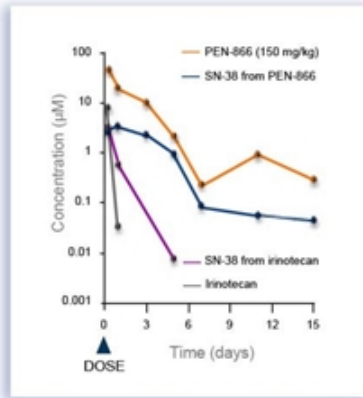
## PEN-866 Potential Indications

Squamous Cell
SCLC
Endometrial
Sarcoma
Pancreatic
Gastric

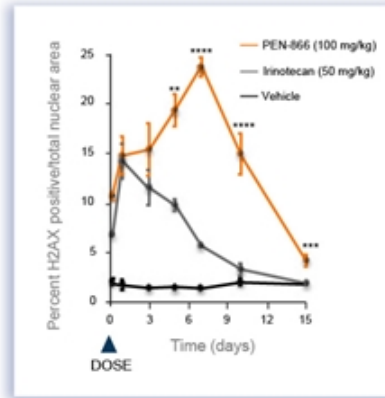
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THERAPEUTICS

# PEN-866 Preclinical Data Demonstrates Elongated Binding And Payload Activity in Solid Tumors

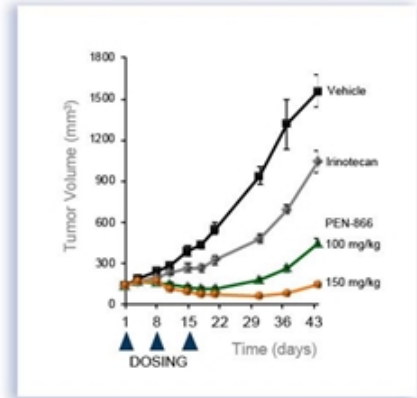
Sustained Tumor Tissue Retention



Enhanced And Prolonged Tumor DNA Damage



Significantly Improved Efficacy



MDA-MB-231 breast xenograft model  
 \*\* p=0.0013; \*\*\* p=0.0002; \*\*\*\* p>0.0001

## PEN-866 Demonstrates Higher Concentrations Of Conjugate And Payload In Tumor vs Plasma In Phase 1 Patient Biopsies

- PEN-866 Pentarin design is now supported by patient biopsies at 1 and 7 days
- Biopsies demonstrate higher levels of PEN-866 and SN-38 in tumor versus plasma
- Tumor uptake and retention of conjugate and intra-tumoral release of SN-38 shown for both timepoints

### Tumor and Plasma Levels for 24 hour Biopsy

	Amount in Tumor (nM)	Amount in Plasma (nM)
PEN-866	318	94.7
SN-38	86.6	2.43

### Tumor Biopsy (day 7) and Plasma Levels (day 8)

	Amount in Tumor (nM)	Amount in Plasma (nM)
PEN-866	31	0.27
SN-38	2	BLQ*

\*Below limit of quantitation of 0.25 nM

Preliminary data from PEN-866 Phase 1, Formal Cleaning To Be Completed

# PEN-866 In Phase 1 Summary

- Designed to achieve rapid escalation to MTD
  - "All comers" advanced cancer population facilitates enrollment
  - Objectives; Identify a safe and optimal dose for Phase 2a, demonstrate sustained tumor DNA damage, preliminary efficacy observations in advanced solid tumor patients
- Heavily Pre-Treated Population
  - 63% had progressed on Irinotecan
  - End stage patients: Over 50% died from Progressive Disease within 6 Months from Enrollment
- Phase I Profile
  - Achieved MTD and determined Ph2a Dose
  - Demonstrated single agent activity in a range of tumor types
  - Exhibited a wide therapeutic window (clinical activity over a wide range of doses) in a range of solid tumor types
  - Demonstrated a high therapeutic index (activity at doses with minimal toxicity)
  - With its therapeutic index and tolerability, PEN-866 may be suitable for combination with DDR, IO and other cancer regimens

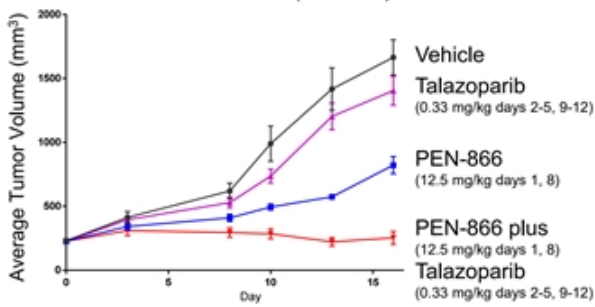
Patient Characteristics (n=30)	Data
Sex	17M, 13F
Age, median (range)	61, (29 – 77)
Tumor Type	
Sarcoma	3
Pancreatic Ca	7
Cholangiocarcinoma	2
Ovarian Ca	1
SCLC	2
Colon	9
Anal	1
Acinar Cell	1
NET (unknown)	1
Small Bowel	1
Esophagus	1
Prostate	1
Prior Therapies, median (range)	4, (1 – 10)

Preliminary data from PEN-866 Phase 1, Formal Cleaning To Be Completed

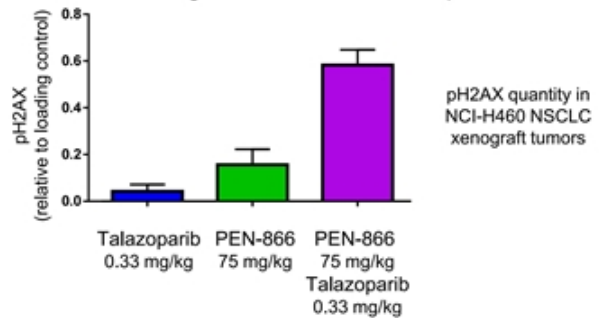


# PEN-866 Demonstrates Compelling Synergy With A PARP Inhibitor In Multiple BRCA Wild Type Models

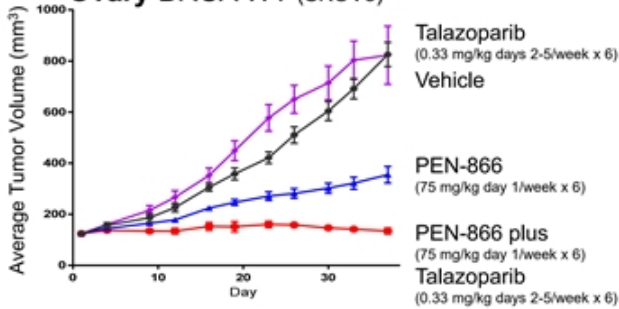
## SCLC BRCA WT (NCI-H69)



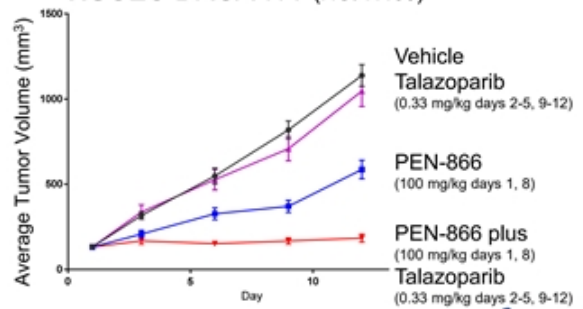
## Sustained And Synergistic DNA Damage 7 Days After Dosing PEN-866 Plus Talazoparib



## Ovary BRCA WT (SKOV3)



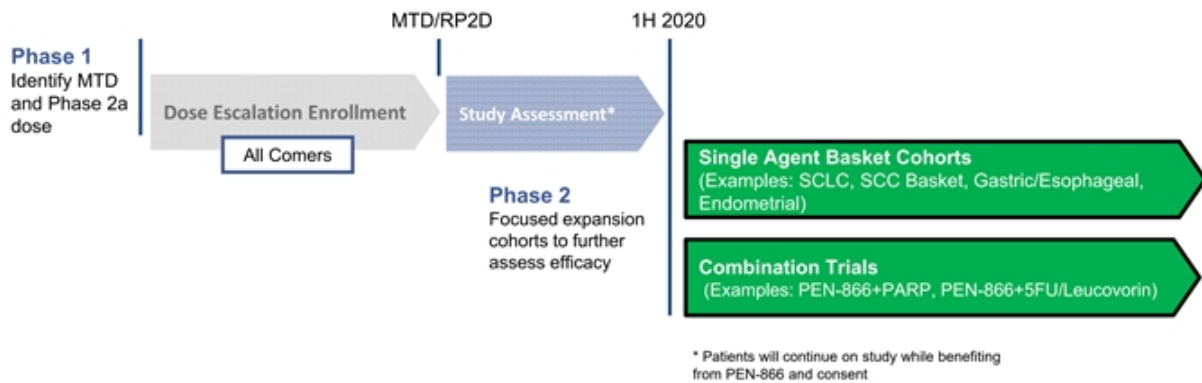
## NSCLC BRCA WT (NCI-H460)



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# PEN-866 Clinical Development In Tumor Types Sensitive To Topoisomerase Inhibition

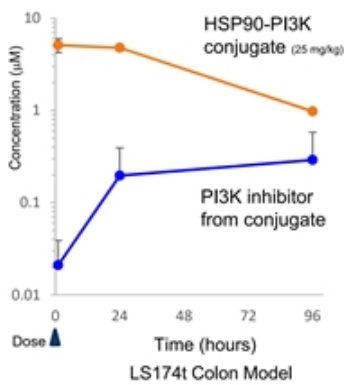
- Phase 1 data to be presented at medical conference(s)
- Phase 2a expansion cohorts in tumor types with high unmet need where topoisomerase I inhibitors are effective; single agent and combination studies



# Nonclinical Proof Of Concept With New HSP90-PI3K Binding Conjugate Showing Superiority To A PI3K Inhibitor Alone

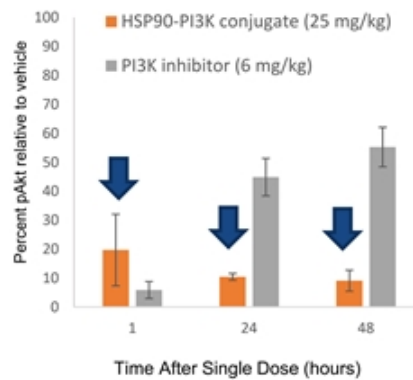
- Accumulation and retention of HSP90-PI3K conjugate in tumor xenograft with a strong and sustained pharmacodynamic response
- Significant tumor growth inhibition is observed with HSP90-PI3K conjugate by comparison to the PI3K payload alone

## Significant Xenograft Tumor Accumulation And Retention

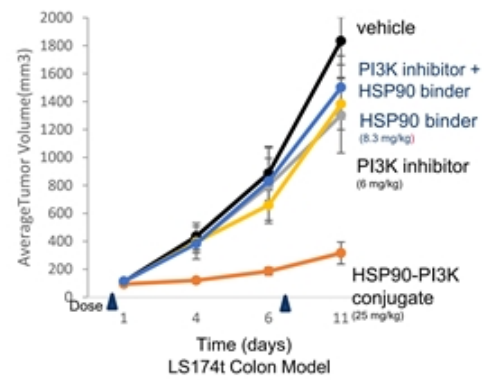


## Sustained Target Engagement In Xenograft Tumor

Decrease In pAkt



## Superior Efficacy With HSP90-PI3K Conjugate Compared To PI3K Inhibitor Alone

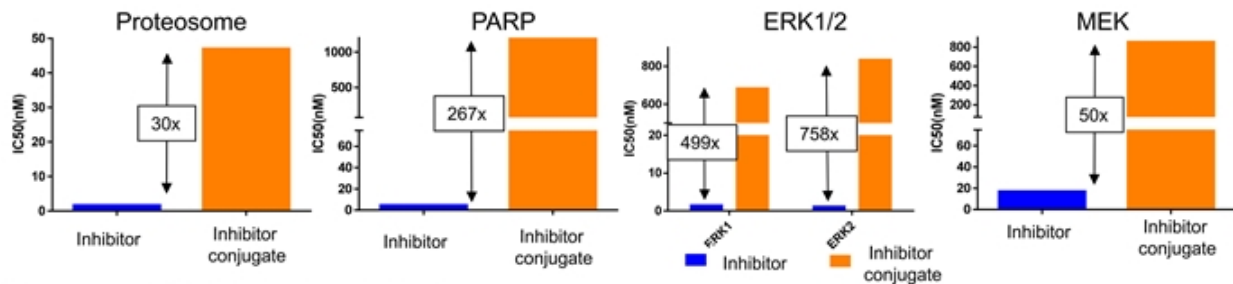


PI3K inhibitor = copanlisib

# Masking A Wide Range Of Payloads To Reduce Normal Tissue Toxicity While Releasing The Potent Payload On Linker Cleavage

- Conjugates derived from multiple payloads are significantly less active in their respective in vitro functional assays while still retaining HSP90 binding
- Through the HSP90 platform, toxicity is mitigated by masking the payload's active site until it can be delivered to the tumor.

Conjugates block the target activity of their respective payloads



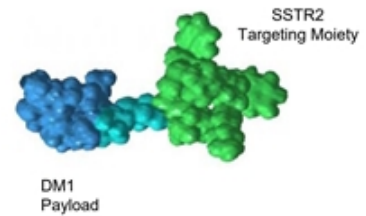
Conjugates retain high affinity for HSP90

Conjugate	Proteasome inhibitor conjugate	PARP inhibitor conjugate	ERK1/2 inhibitor conjugate	MEK inhibitor conjugate
HSP90 K <sub>D</sub>	5.8 nM	0.33 nM	1.0 nM	1.2 nM



# PEN-221 Offers Potential Clinical and Commercial Advantages

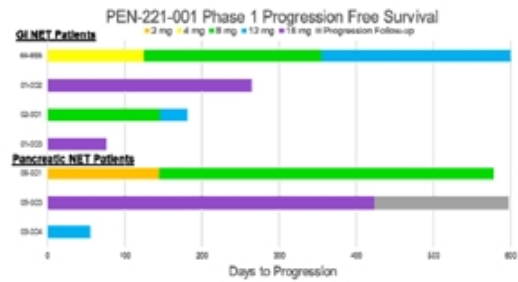
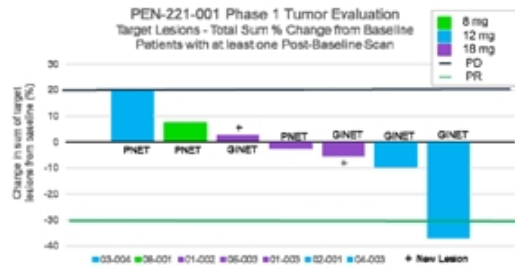
- PEN-221 is a Somatostatin Receptor 2 (SSTR2) targeting peptide linked to the potent DM1 payload
- **Enrolling Phase 2a** in patients with neuroendocrine tumors (NETs) and SCLC
- **Targeted drug with patient selection strategy**
  - Validated receptor biology
  - 80% - 90% of gastrointestinal (GI) and other neuroendocrine tumors (NETs)
  - Utilize FDA approved imaging diagnostics to identify SSTR2 expression
- **PEN-221 positioned to satisfy unmet needs in NETs and SCLC**
  - GI NETs represents the largest NETs population
  - Open treatment landscape - NCCN does not distinguish lines of therapies believing that most patients will receive all forms of approved medicines
  - Potential for long treatment duration
  - Two approved drugs are not curative
  - GI NET patients will likely see all approved drugs during the course of their treatment
  - Effective therapies are needed for treatment of SCLC patients
- **Composition of matter patent issued** with long duration protections



# Phase 1: Early Clinical Benefit Seen From PEN-221 In GI NET And Pancreatic NET Patients And Well Tolerated (8 to 18 mg)

- 23 advanced, heavily treated patients treated in Phase 1 across 7 dose cohorts ranging from 1 mg to 25 mg
- MTD determined at 18 mg as patients experienced DLTs at 25 mg
  - 2 patients with Grade 3 liver enzyme elevation
- Objective RECIST Responses are rarely seen in GI and PNETs. Most responses are minor.
  - Afinitor – 2%/5% (GI NET/PNET)
  - LutATHERA - 13% (GI NET)
  - Sutent – 9% (PNET only)
- 5 of 7 patients with prolonged stable disease exceeding historical controls
- Tumor reductions or stable disease seen in 6 of 7 (86%) GI and PNET patients including 1 partial response\*

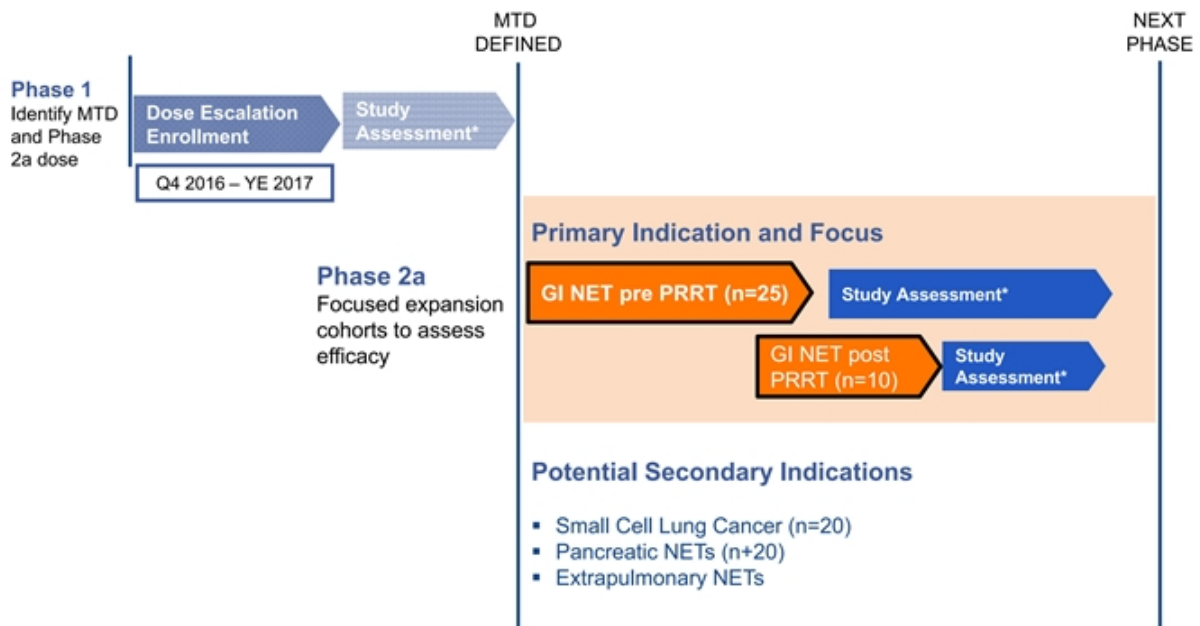
\*This patient expired from causes unrelated to their malignancy or its treatment prior to receiving confirmatory scan



Preliminary Clinical Data. Formal Cleaning To Be Completed. Response data from patients who had at least one on-study scan



# PEN-221 Phase 2a Clinical Trial Progressing



\* Patients will continue on study while benefitting from PEN-221 and consent

## Key Expected 2020 Milestones

- Subject to stockholder approval and satisfaction of closing conditions, close previously-announced transaction with Organovo in 1H 2020
- PEN-866 Program:
  - Presentation of Phase 1 data
  - Initiate single agent Phase 2a cohorts
  - Prepare to initiate combination study(ies)
- PEN-221 Program:
  - Maturation of data for GI neuroendocrine cohort(s) and potential for related presentation
  - Complete enrollment of initial small cell lung cancer cohort
- Develop new conjugate proof of concept in additional miniature conjugate programs with publication/presentation of new data
  - Potential for new conjugate candidate for next clinical program identified
  - Conjugates with new targeted payloads identified for advancement



Thank You

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