

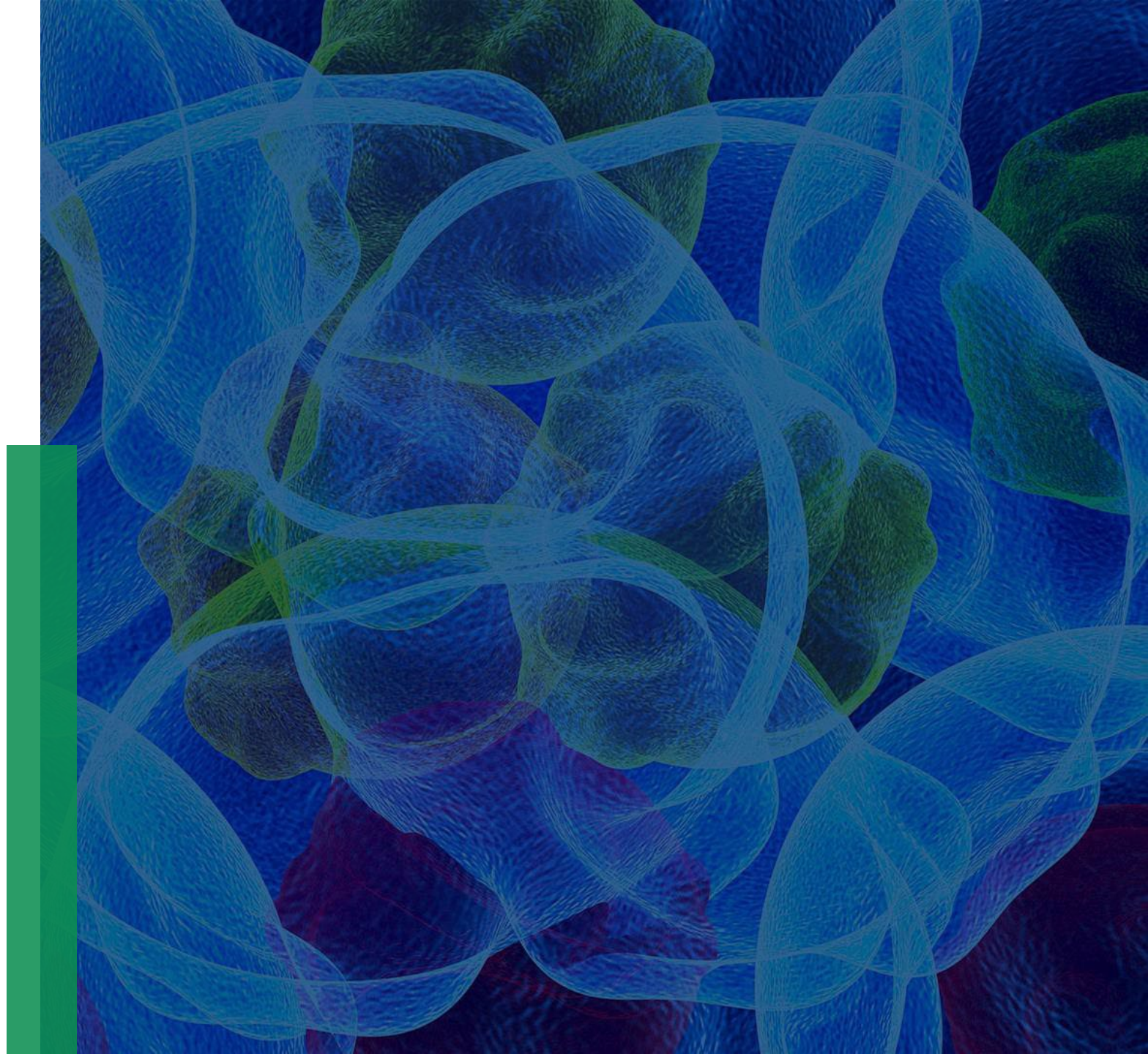


# Moving Beyond Solid Tumors: A Novel Radiotherapy in Hematologic Cancers

Targeted Radiopharmaceutical Summit 2022

July 17, 2022

NASDAQ: CLRБ

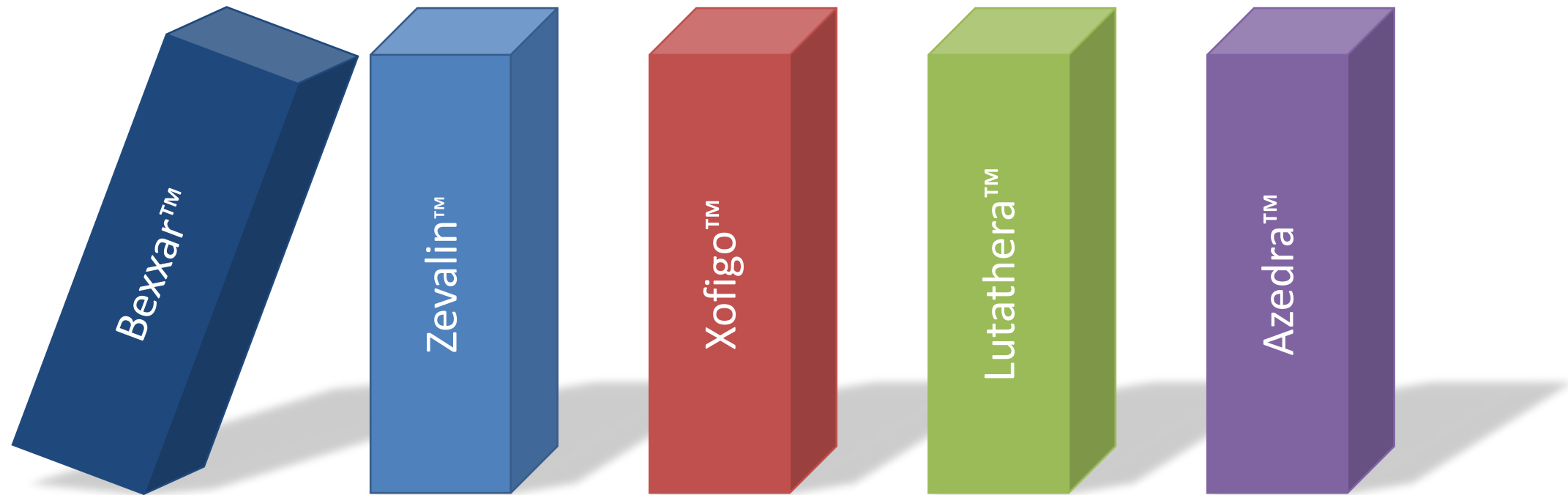


# Forward-Looking Statements

This presentation contains forward-looking statements. Such statements are valid only as of today and we disclaim any obligation to update this information. These statements are only estimates and predictions and are subject to known and unknown risks and uncertainties that may cause actual future experiences and results to differ materially from the statements made. These statements are based on our current beliefs and expectations as to such future outcomes including our expectations of the impact of the COVID-19 pandemic. Drug discovery and development involve a high degree of risk. Factors that might cause such a material difference include, among others, uncertainties related to the ability to raise additional capital, uncertainties related to the disruptions at our sole source supplier of iopofosine, the ability to attract and retain partners for our technologies, the identification of lead compounds, the successful preclinical development thereof, patient enrollment and the completion of clinical studies, the FDA review process and other government regulation, our ability to maintain orphan drug designation in the United States for iopofosine, the volatile market for priority review vouchers, our pharmaceutical collaborators' ability to successfully develop and commercialize drug candidates, competition from other pharmaceutical companies, product pricing and third-party reimbursement. A complete description of risks and uncertainties related to our business is contained in our periodic reports filed with the Securities and Exchange Commission including our Form 10-K for the year ended December 31, 2020 and our Form 10-Q for the quarter ended September 30, 2021.

# Are We Destined to Repeat the Mistakes of Others

*Understanding Bexxar and Zevalin in Order to Move Beyond*



# Cool Sciences & Good Data Success They Do Not Ensure

*Ignore the Market At Your Own Peril*

## Targeted Immuno-radio conjugates

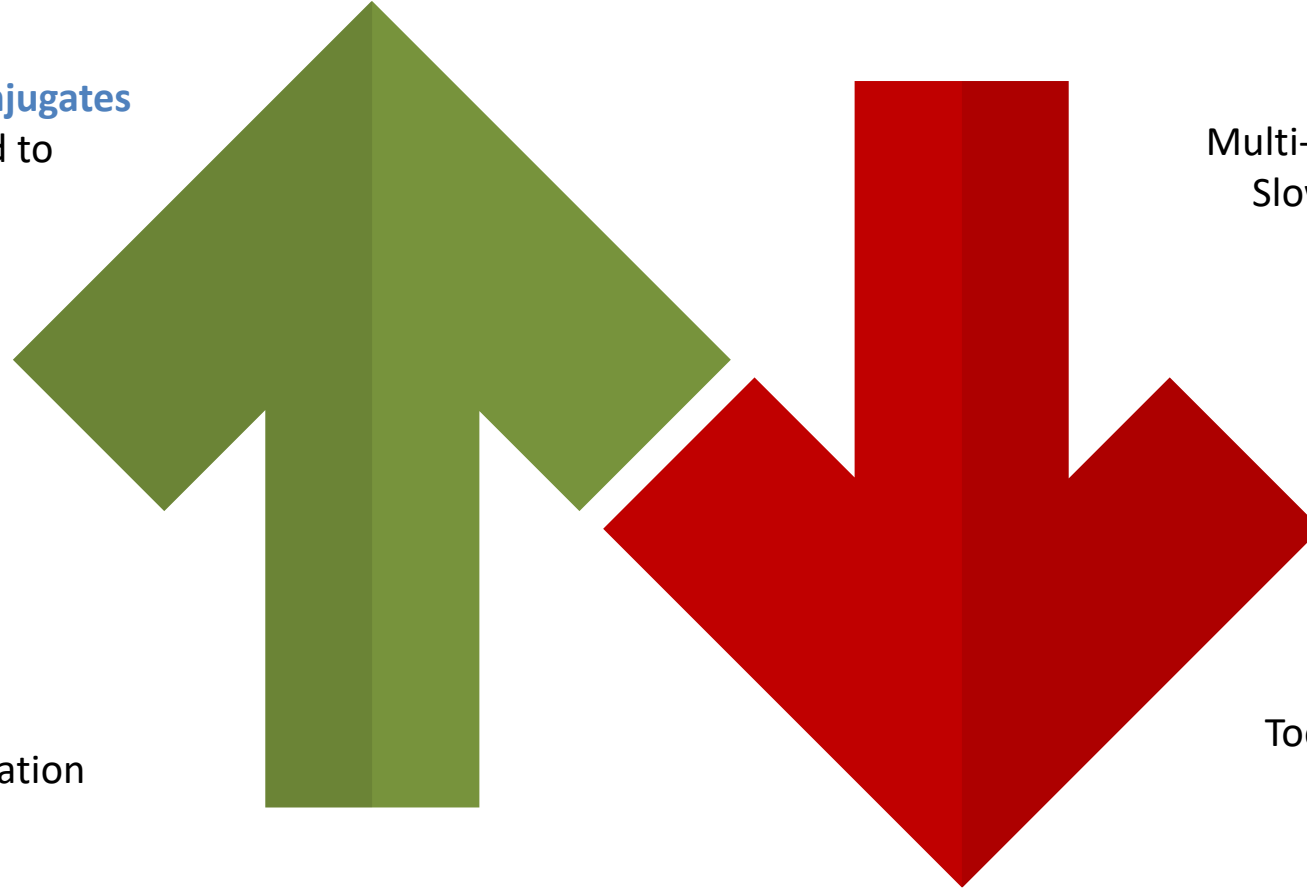
Anti-CD20 Antibodies bound to either Y90 or I131

## Market

Non-Hodgkin's lymphoma – r/r low grade follicular

## Data

Greater than 60% ORR  
~2 years of PFS  
Ability to be used in combination



## You live with your launch

Multi-year delay responding to FDA  
Slow uptake; lack of market prep

## Infrastructure breakdown

Patient referrals  
Complex/Issues with supply

## Science vs treating

Dosimetry  
Dose determination

## Market limitations

Too narrow: restricted to subset  
Single drug – single disease

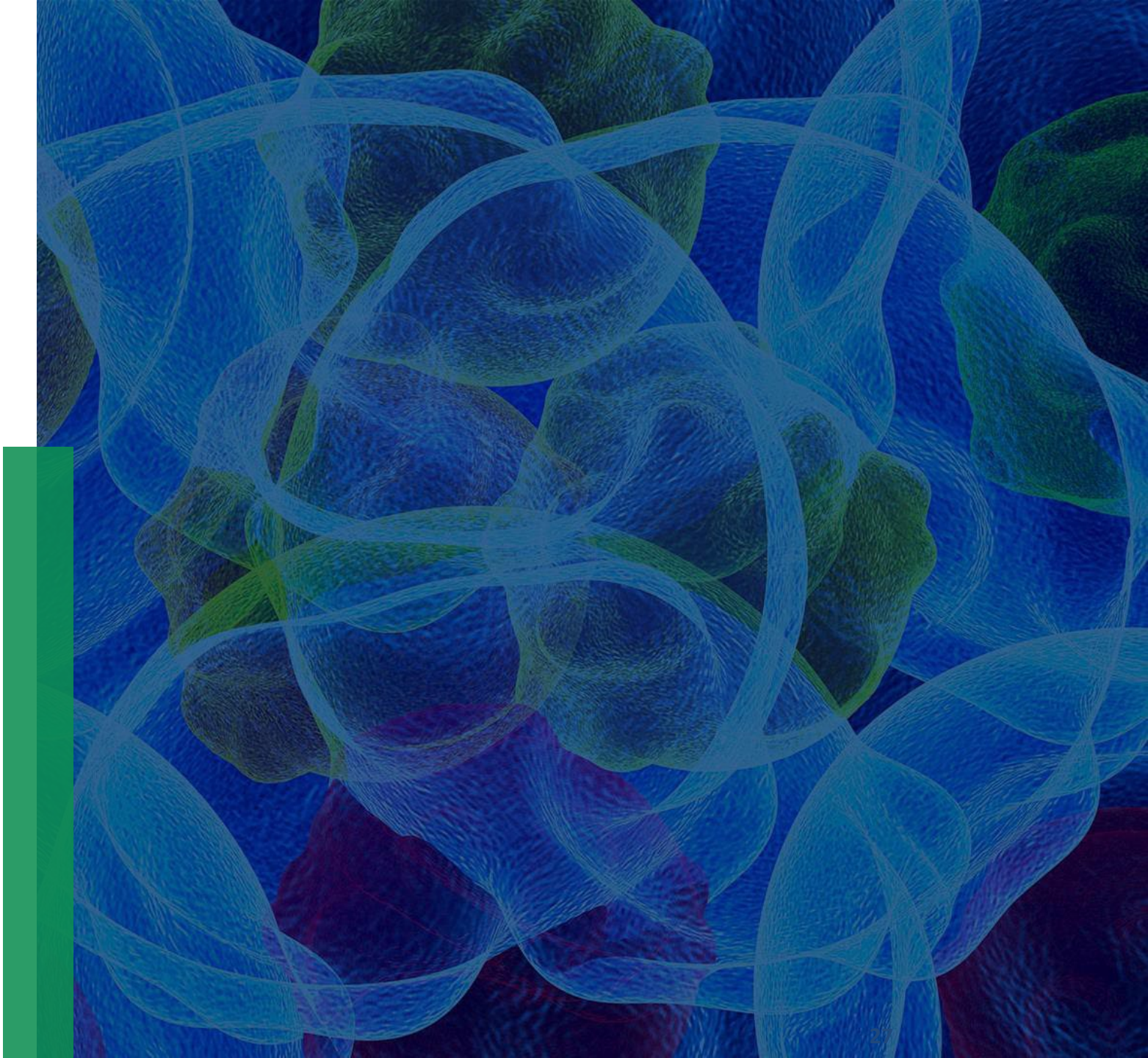
## Keep It Simple

No compounding at the site  
Be careful with your development



# Next Generation TRP

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# Company Highlights

*Proprietary Versatile Drug Conjugate Platform to Target Cancer*




Novel cancer targeting conjugate platform



Lead clinical asset; iopofosine I-131 (formerly known as CLR 131), a targeted radio-conjugate in rare adult and pediatric cancer indications



Ongoing pivotal study of iopofosine in Waldenstrom's macroglobulinemia (WM), top-line data anticipated 2H 2022



Additional clinical studies ongoing, including a Phase 2b study in highly refractory multiple myeloma



Preclinical programs with small molecule drug conjugates, peptide conjugates and nucleic acid conjugates

# PDC Strategy

*Phospholipid Ether Franchises*

**PRC Portfolio**

**PDC Portfolio**

**PPC Portfolio**

**POC Portfolio**

**Radio-conjugates**

**Small Molecule  
Drug Conjugates**

**Peptide and Nanobody  
Drug Conjugates**

**RNAi, siRNA, mRNA  
Drug Conjugates**

## **Radio-conjugate Franchise**

- Ability to provide targeted delivery of any radioisotope
- Currently developing alpha & beta emitters
- Lead beta emitter program iopofosine I-131 in a pivotal study

## **Small Molecule Franchise**

- Demonstrated in vivo safety and efficacy in multiple animal models
- Pico and nanomolar activity

## **Biologics Franchise**

- Targeting intracellular pathways that cannot be targeted with small molecules

## **Nucleic Acid Franchise**

- Intracellular delivery of nucleic acids providing knockdown or knock-in gene control in cancer cells

*Targeted Delivery with a Broad Range of Therapeutic Modalities*

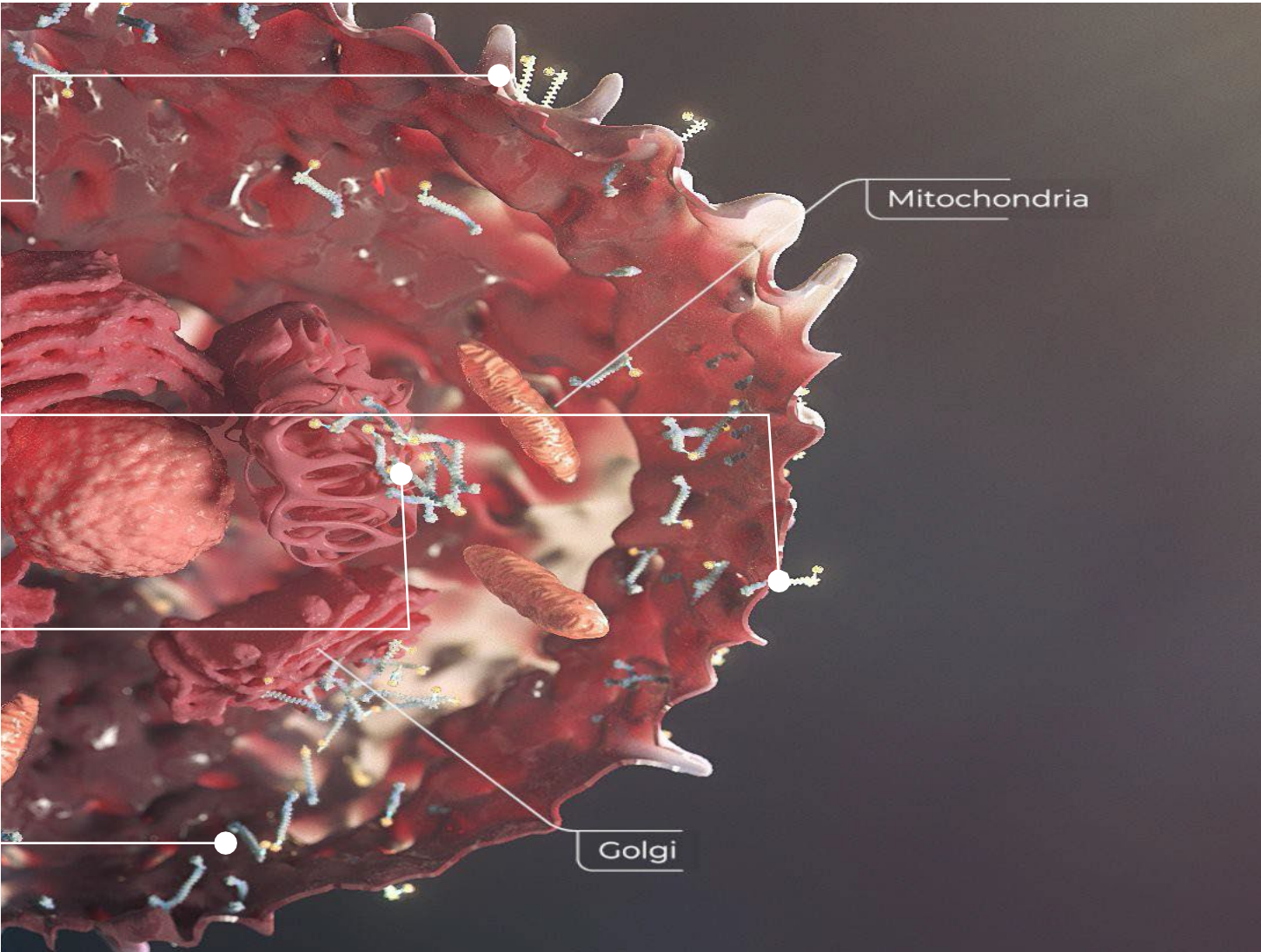
# Targeted Delivery to Tumor Cells

**1** PDC with Cancer targeted payload

**2** Specific Targeting of Cancer

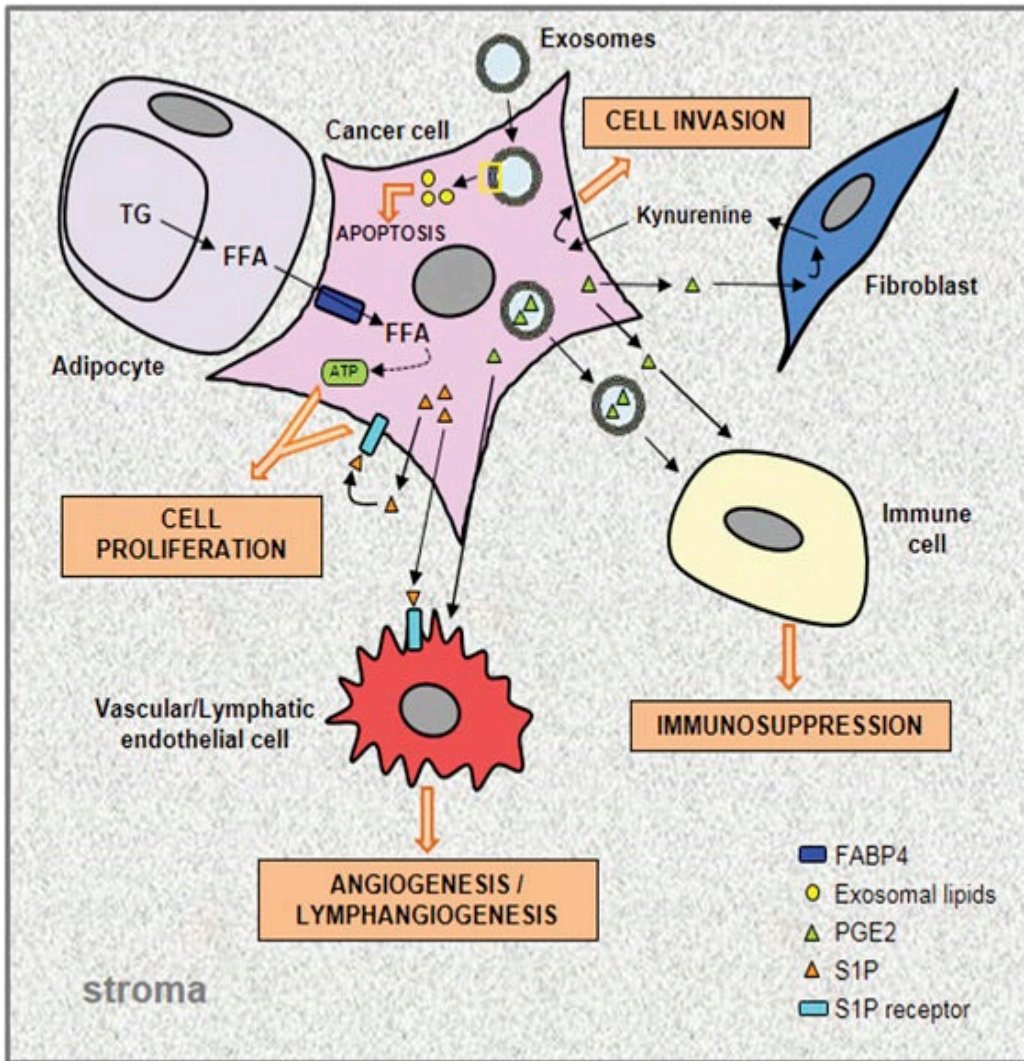
**3** Intracellular Delivery to Cancerous Cells

**4** Selective Release of Payload inside Cell





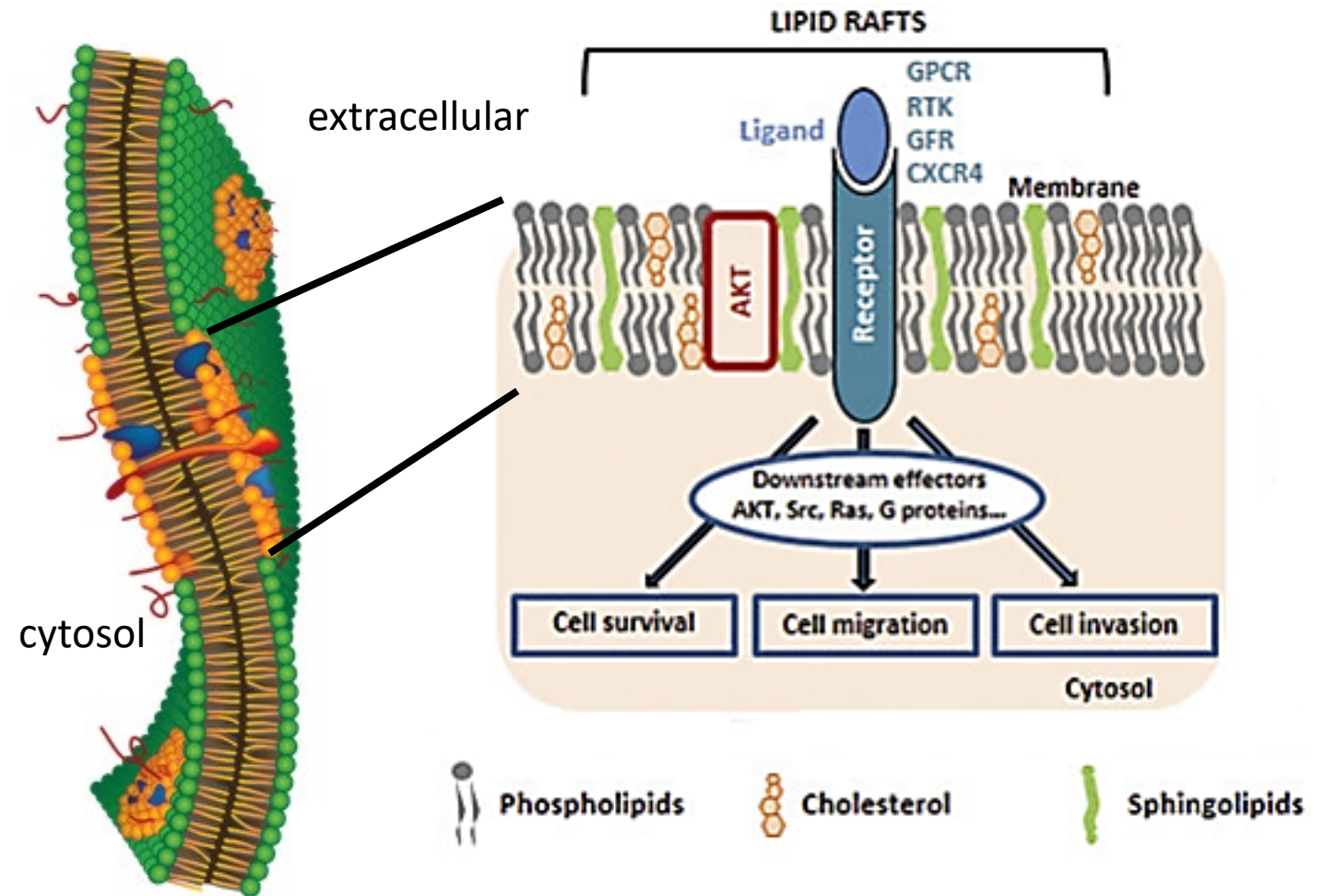
# Cancers Microenvironment Communication Network



- Lipids are required in tumor cells for:
  - Energy/ATP production – beta-oxidative pathway
  - Membrane production
  - Signaling molecules (PGE2, S1P)
- Normal cells utilize endogenous produced lipids predominately; cancer cell require exogenous lipids
- Cancer cells acquire lipids from the extracellular environment and adipocytes
- Utilization of lipids by cancer cells is often related to increased survival and an aggressiveness
- Primary uptake of lipid in cancer via lipid rafts (both caveolae lipid rafts and flat lipid rafts)
  - Lipid rafts are the predominate point of lipid uptake in tumors

# Lipid Rafts: Novel Approach to Targeting Cancer

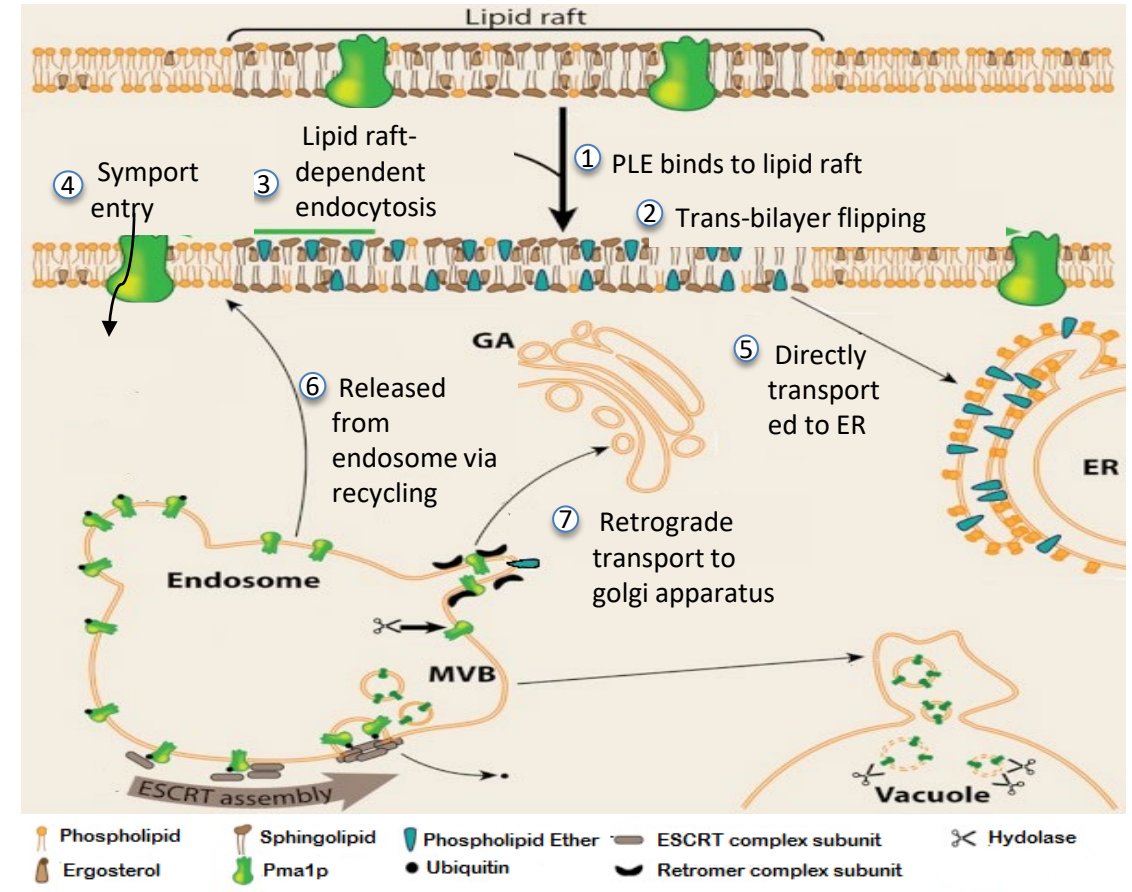
- Highly ordered, tightly packed, microdomains, enriched in cholesterol and sphingolipids
- Act as signaling hubs; coalesce GPI-anchored proteins, signaling proteins and receptors (src, GPCR, RTK, including growth factor receptors), chemokine receptors (CXCR4 and others) and integrins
- Why are they targetable in cancer
  - Increased in concentration in cancer
  - Increased size of rafts
    - Normal cells = nanostructures (~25nm)
    - Cancer cells = Coalesced raft (100uM)
  - Stabilized (days vs nanoseconds)

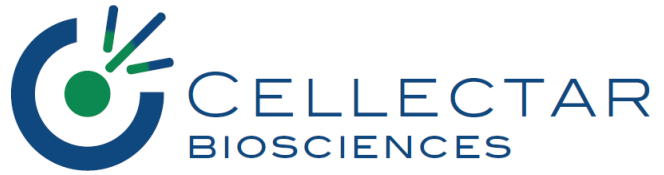


# Phospholipid ether Mechanism of Entry

*Validated In Vitro and In Vivo*

- PLEs entry mechanisms
  - Bind to lipid rafts
  - Lipid raft dependent endocytosis
  - Active transport
- Majority of PLEs enter via transmembrane flipping; directly into cytoplasm
- Destiny post internalization
  - Transit along golgi apparatus network to ER (beta oxidation)
  - Endosome for recycling into membrane or signaling molecule
- Able to cross blood brain barrier
- Validated delivery with
  - Radio-isotopes (diagnostic CLR 124 & therapeutic CLR 131)
  - Fluorescent molecules (CLR 1500 series)
  - Small molecule therapeutics (CLR SM series)

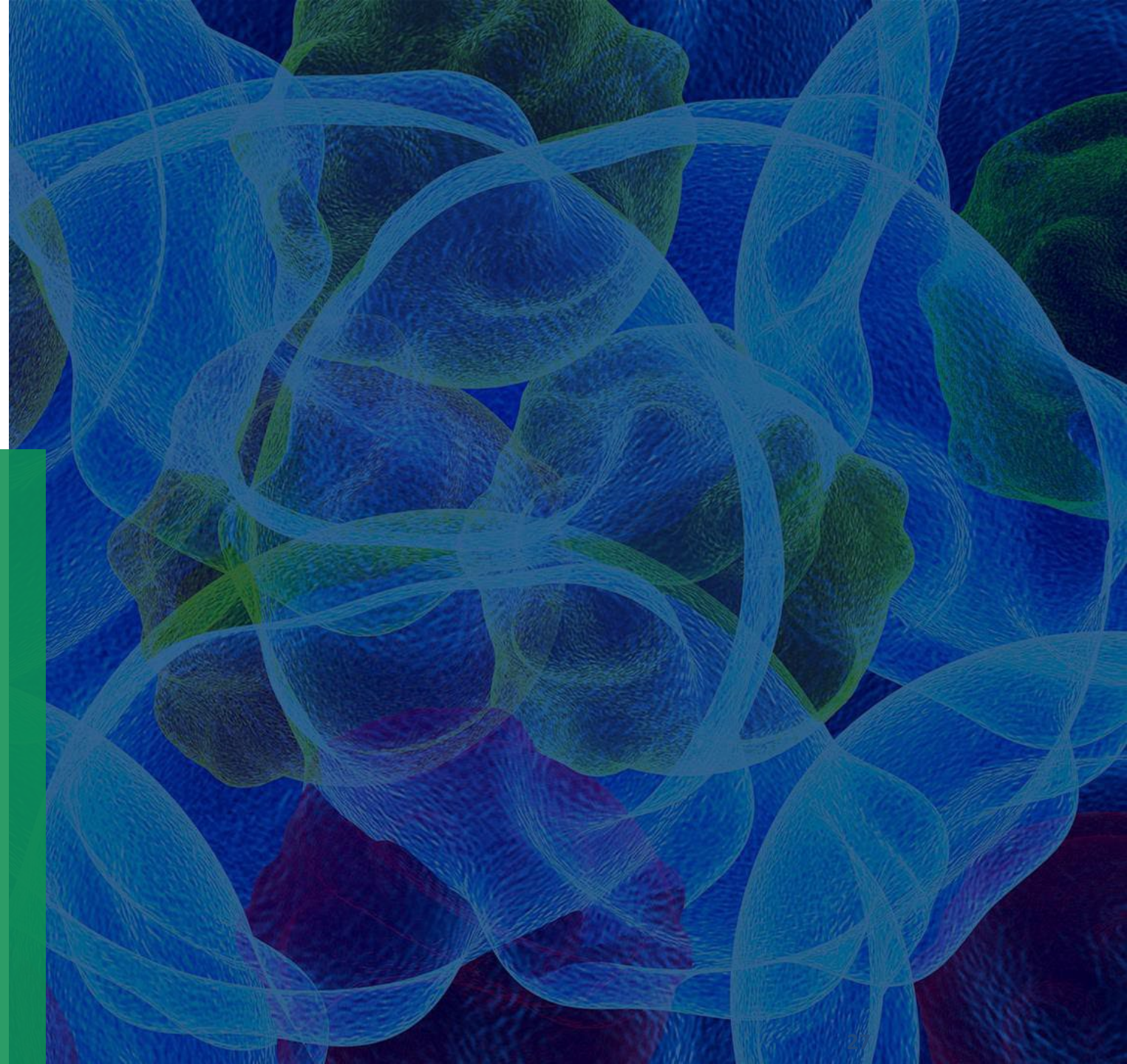




# Next Generation TRP

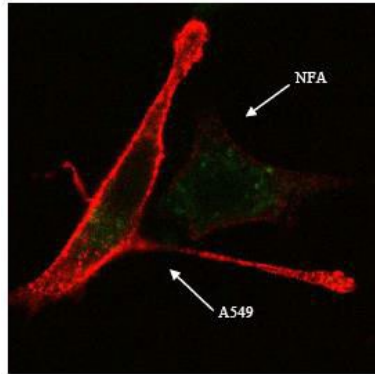
*Preclinical*

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# Lipid Rafts Mediate Entry of PLE into Tumors

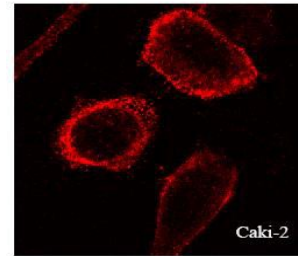
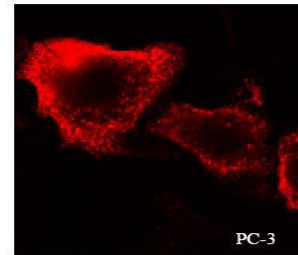
*(red = lipid rafts)*



**Co-cultured  
Fibroblast vs A549**

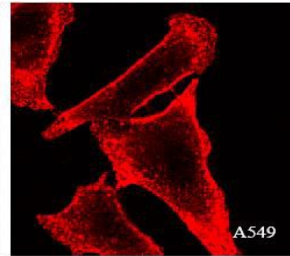
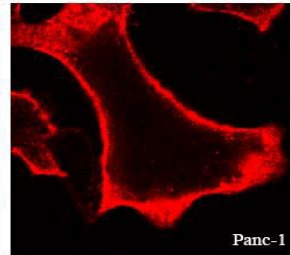
*(fluorescent-labeled cholera toxin  
subunit B binds to lipid raft)*

**Prostate**



**Kidney**

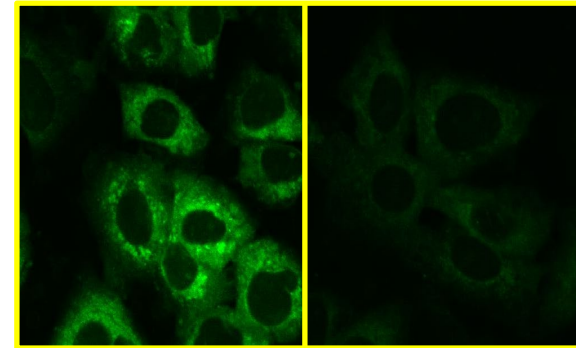
**Pancreatic**



**Lung**

*(red = CLR 1502)*

**A549 NSCLC**



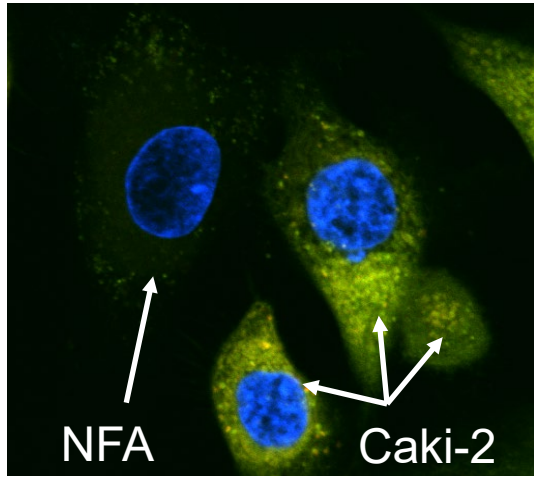
**Intact Rafts**

**MBCD  
Pretreatment  
Decreased 1501  
uptake 60%**

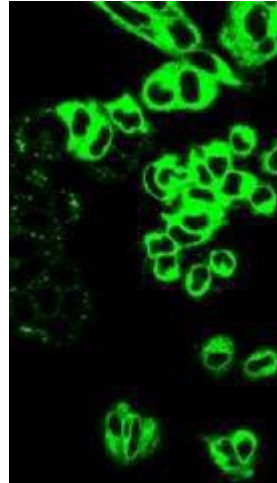
*Methyl- $\beta$ -cyclodextrin selectively disrupts  
lipid rafts.*

***CLR1501 is taken up by cells via lipid rafts***

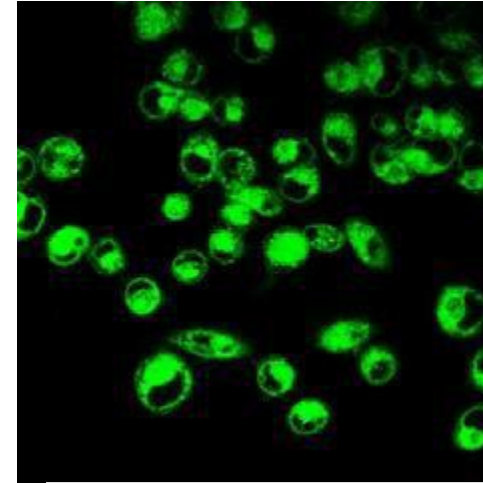
# PLE Uptake Validated Across Most Tumors Tested



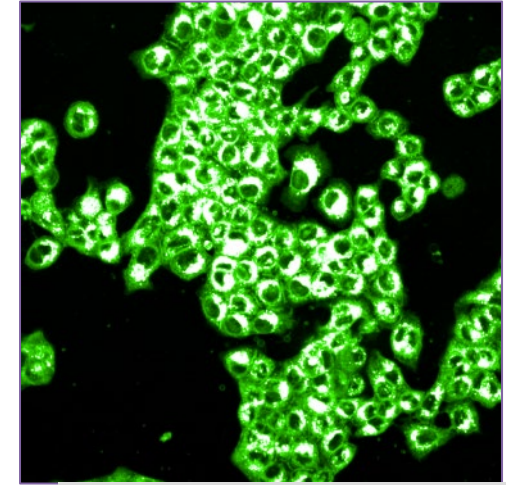
*Caki vs Fibroblast (24 hrs)*



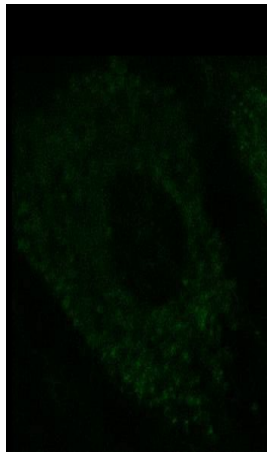
MES SA/Dx5 Uterine



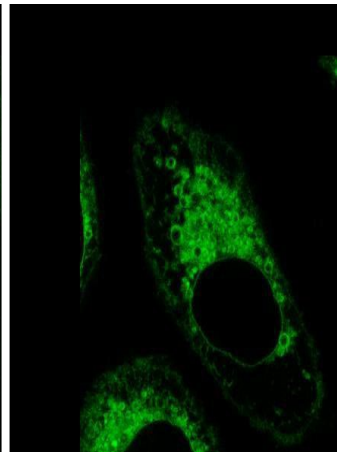
Mia Paca-2 Pancreatic



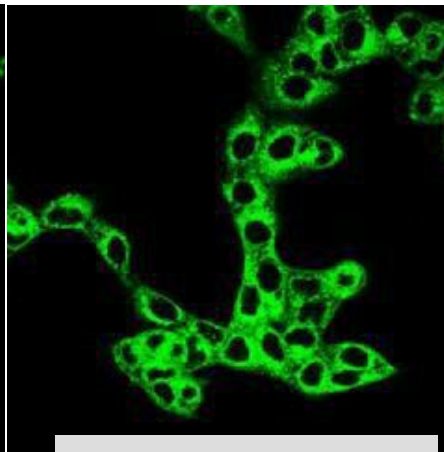
HT-29 colorectal



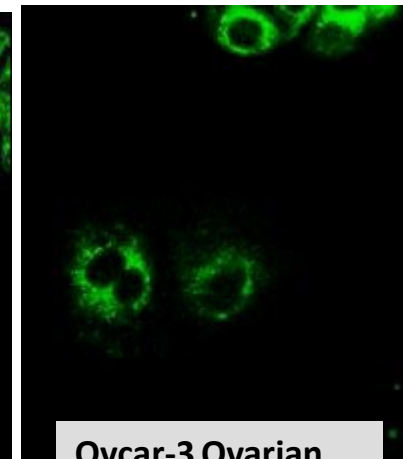
SK704-skin



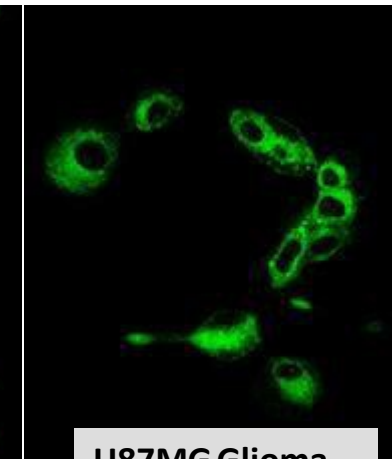
A375 Melanoma



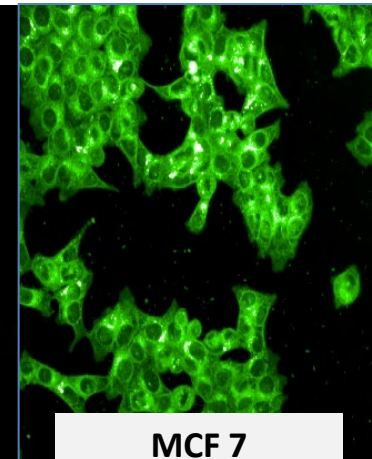
HCT-116 Colorectal



Ovc3 Ovarian



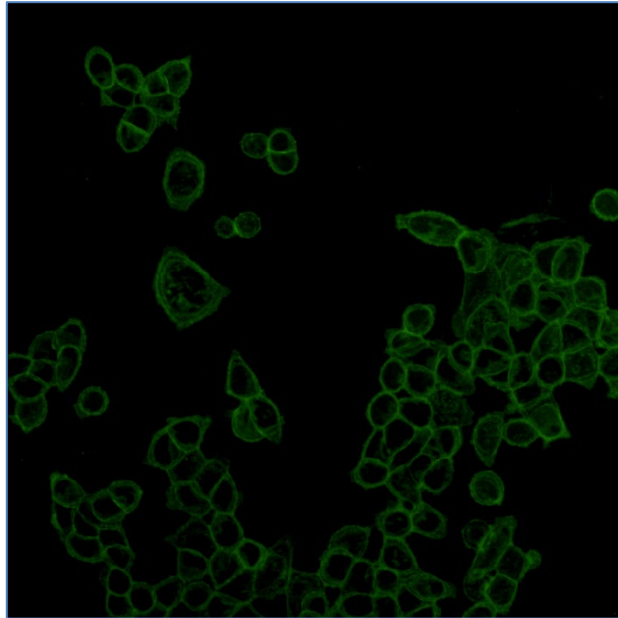
U87MG Glioma



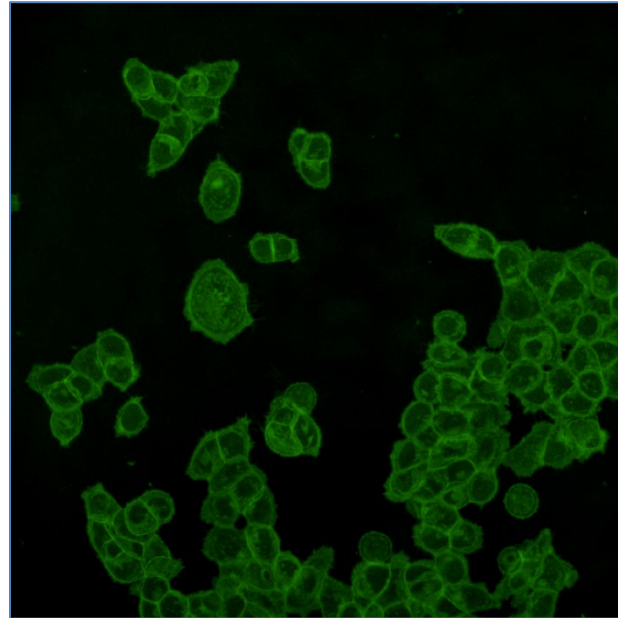
MCF 7

*Even in co-culture CLR 1501 selectively enters tumor cells*

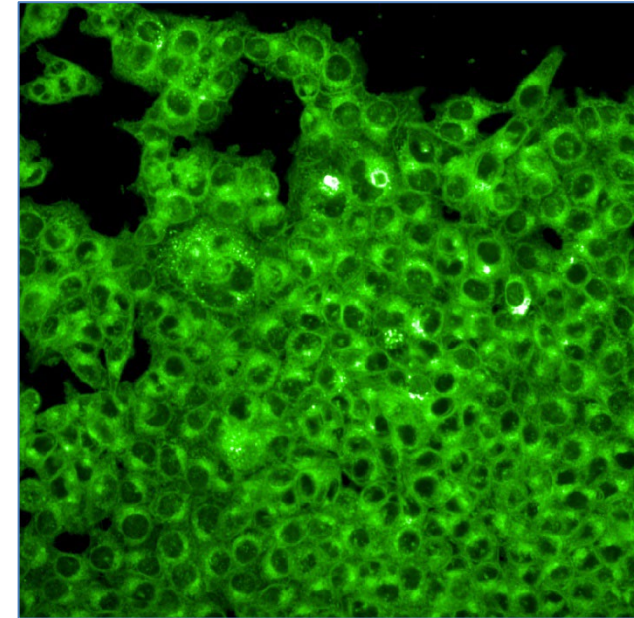
## PLE Uptake Time Course (MCF 7 cells)



10 mins



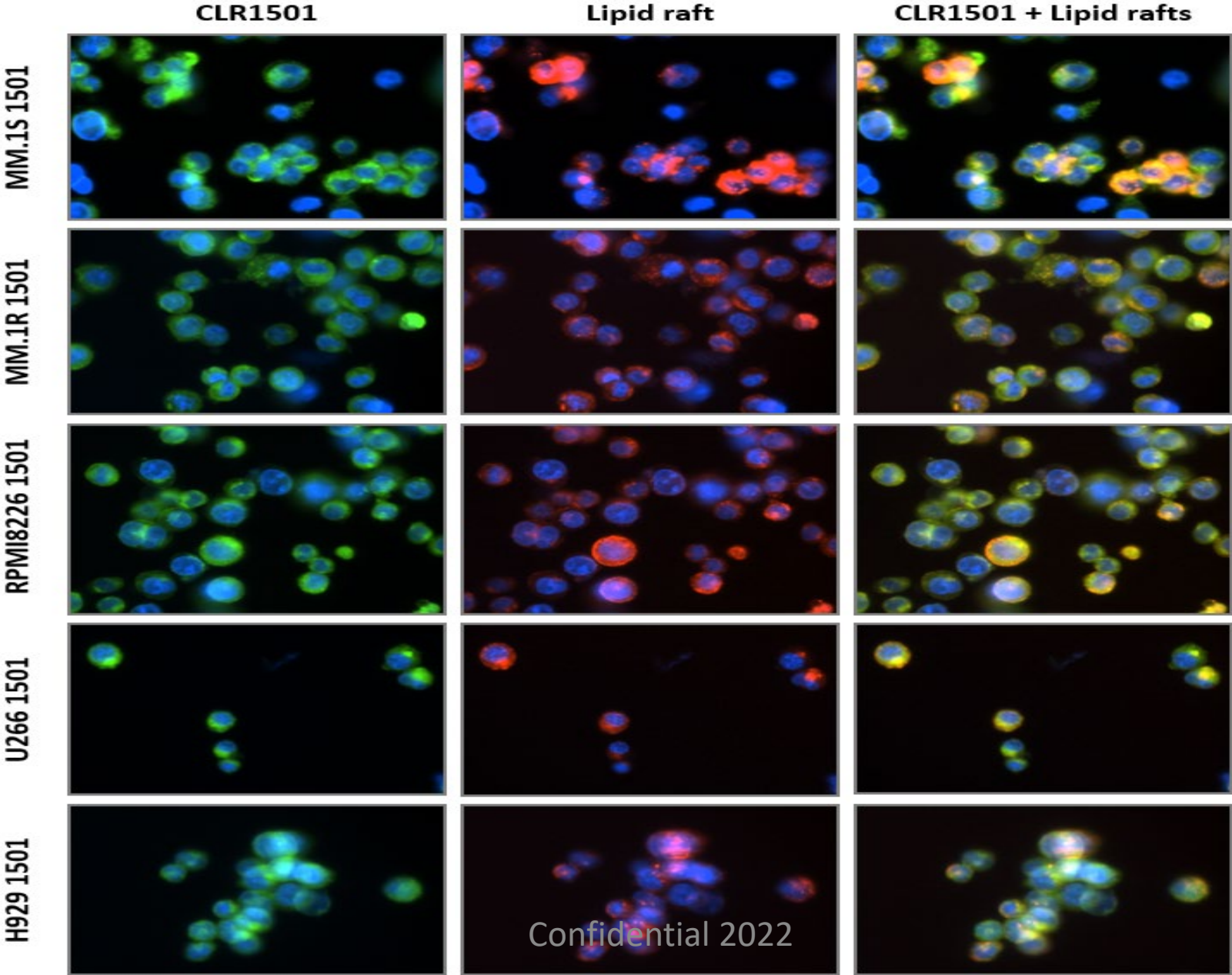
1 hr



24 hrs

*Uptake by cells is rapid post exposure with increased accumulation over 72 – 96 hours*

# CLR 1501 Uptake Confirmed in Multiple Myeloma Cells



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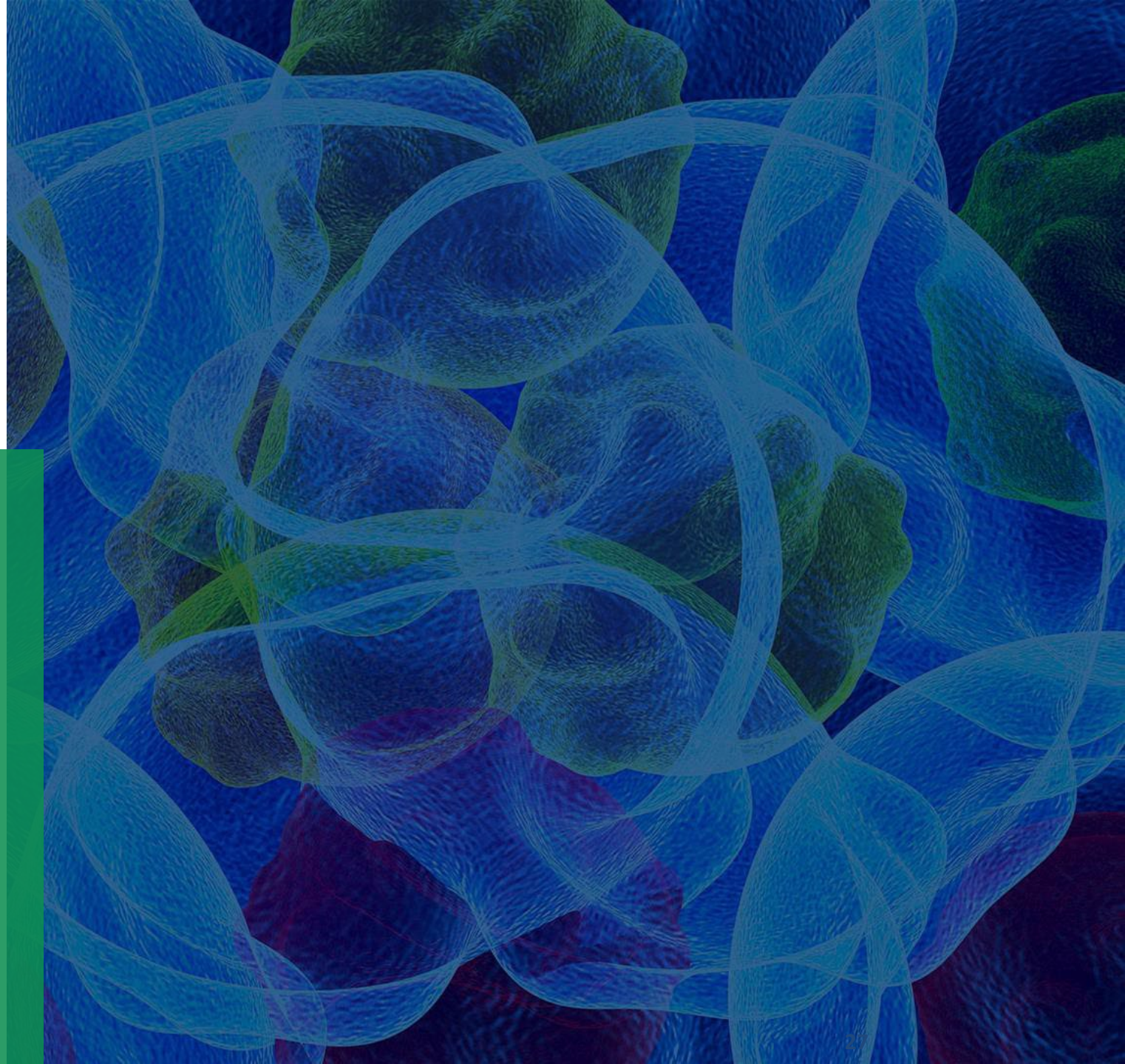




# Next Generation TRP

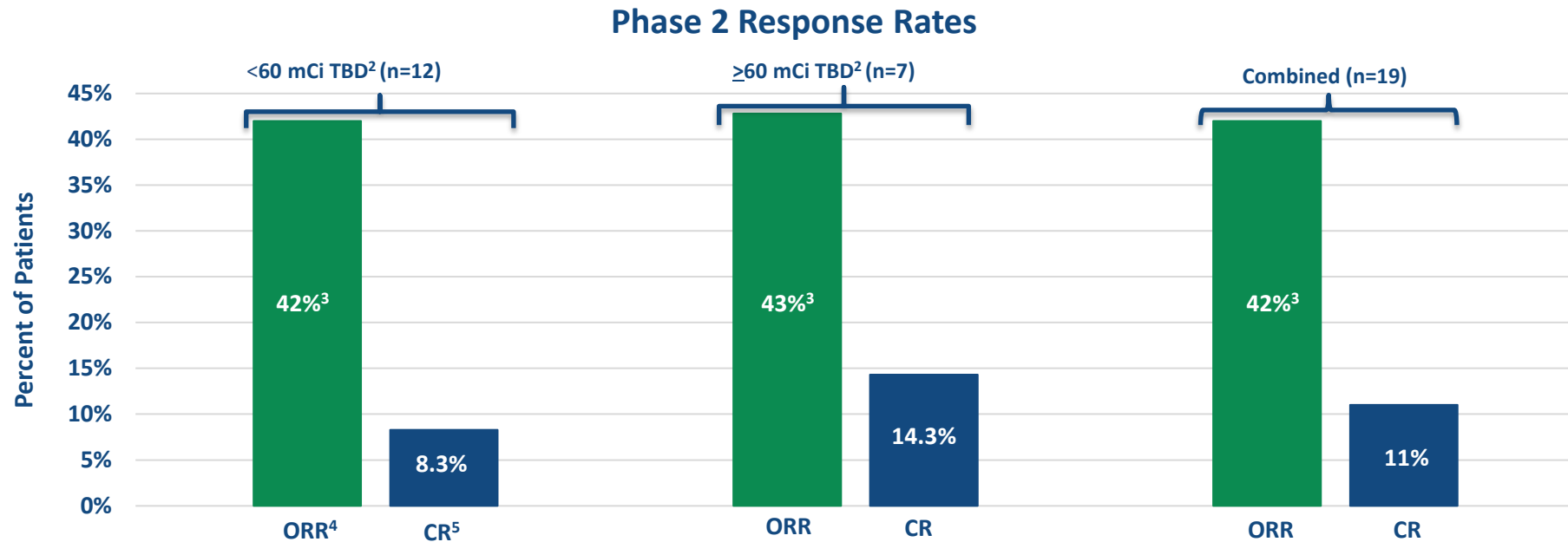
*Iopofosine I 131  
Clinical Program*

NASDAQ: CLRB



# Iopofosine r/r NHL

## Efficacy in Heavily Pretreated Patients



- Diverse, advanced and heavily pretreated patient population
  - Multiple r/r B-cell lymphoma histologies: DLBCL, transformed DLBCL, CLL/SLL, MZL, MCL, LPL/WM
  - Median 3 prior lines of systemic therapy
  - ~47% of patients were refractory to prior therapy
  - ~53% of patients were refractory to rituximab
- Differentiated safety profile

**Both Doses Demonstrate Efficacy in r/r non-Hodgkin's Lymphoma**

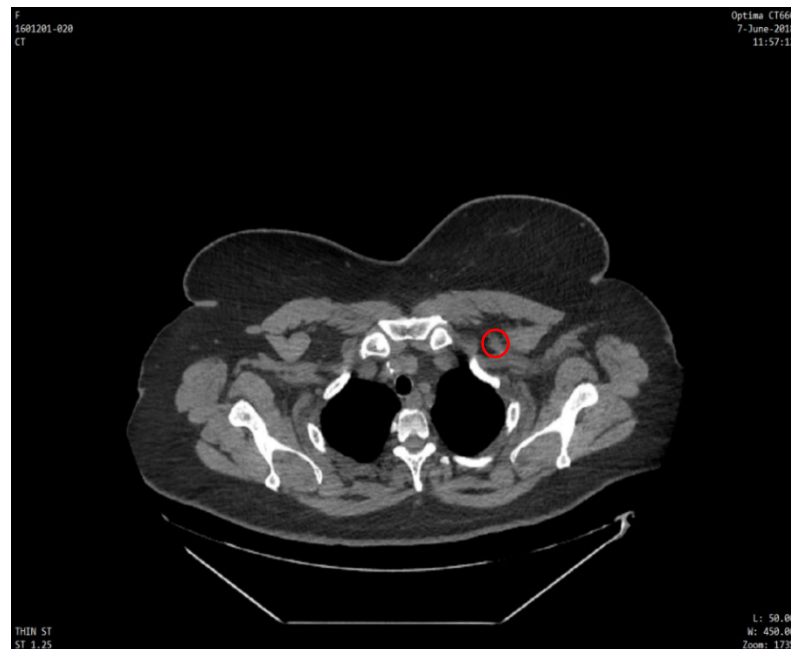
# Iopofosine r/r DLBCL

## Patient Case Study - Complete Response

- Female, 52 years old with subpectoral lymph node mass
  - Germinal cell DLBCL
  - Single hit: MYC positive; BCL-2 negative
- 3 prior lines of treatment - R-CHOP, RICE and chemotherapeutic combination
- Relapse within 10 months of 1<sup>st</sup> line treatment, refractory to 2<sup>nd</sup> and 3<sup>rd</sup> line TRX
- Patient continues to be a complete responder; 570+ days post treatment



Scan Day 1



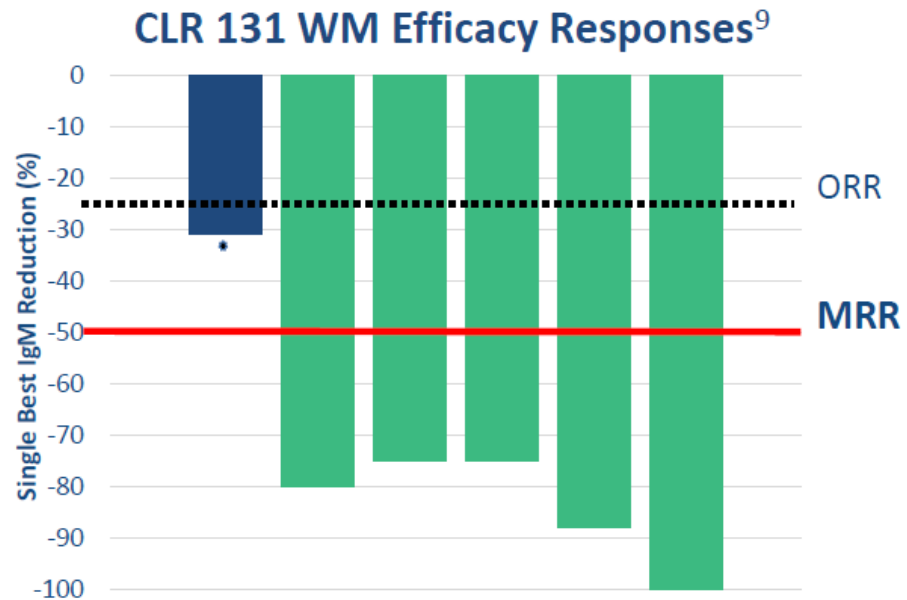
Scan Day 90

# Iopofosine – r/r Waldenstrom’s and Multiple myeloma

*Efficacy in Ongoing Adult Trials*

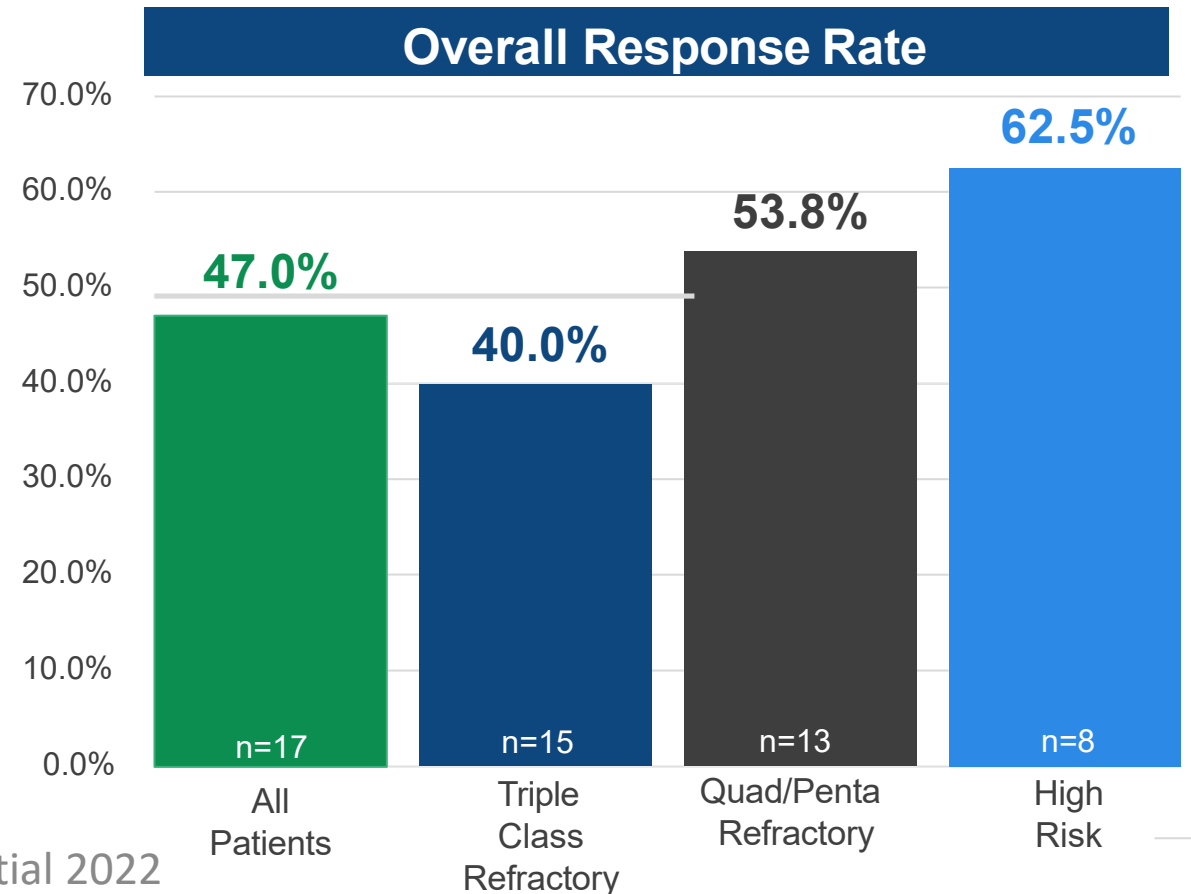
## Waldenstrom’s Macroglobulinemia

- 100% ORR
- 83.3% MRR
- 100% of high-risk patients achieved a MRR with one CR



## Multiple Myeloma

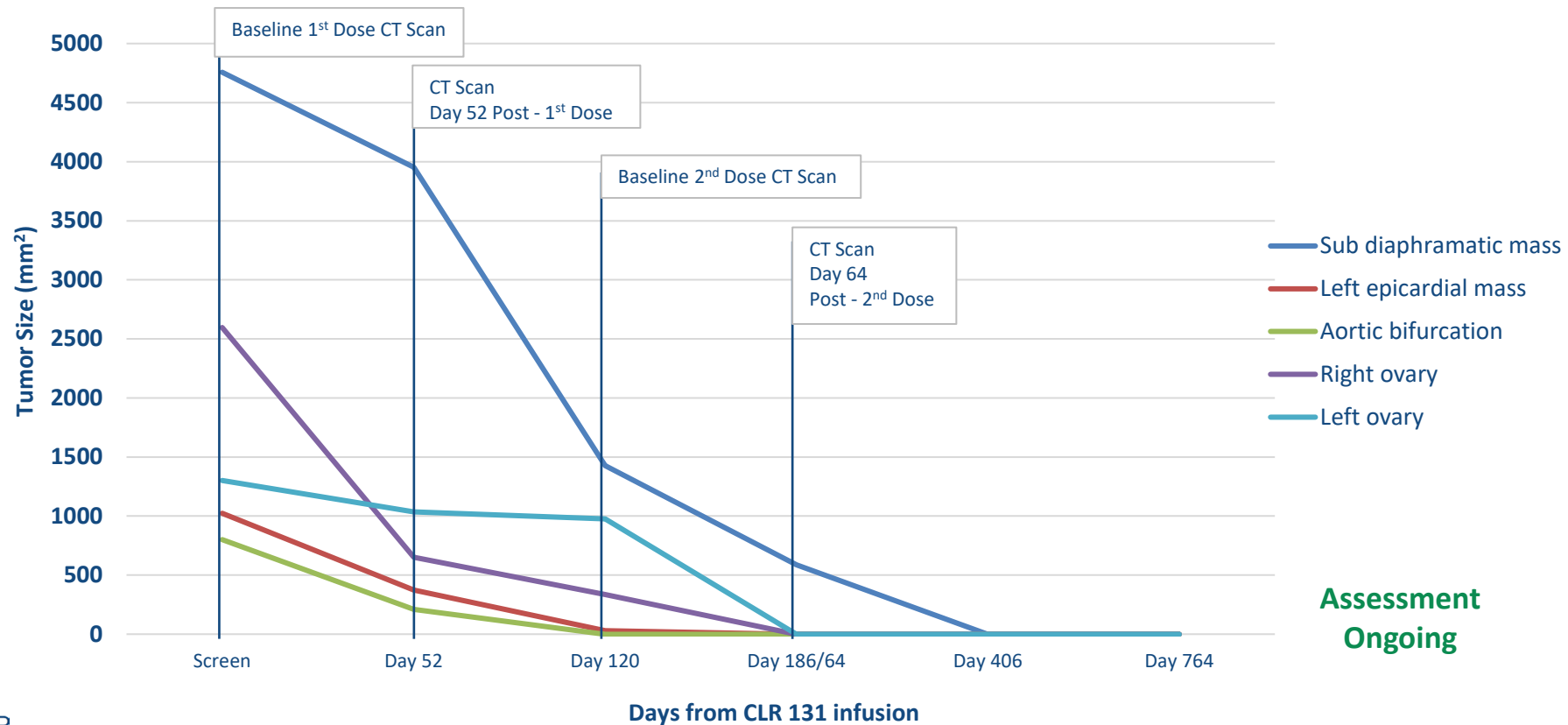
- Triple class refractory mPFS = 3.4m
- 50% ORR in post 5<sup>th</sup> line – any approved drug



# Iopofosine r/r Waldenstrom's Macroglobulinemia

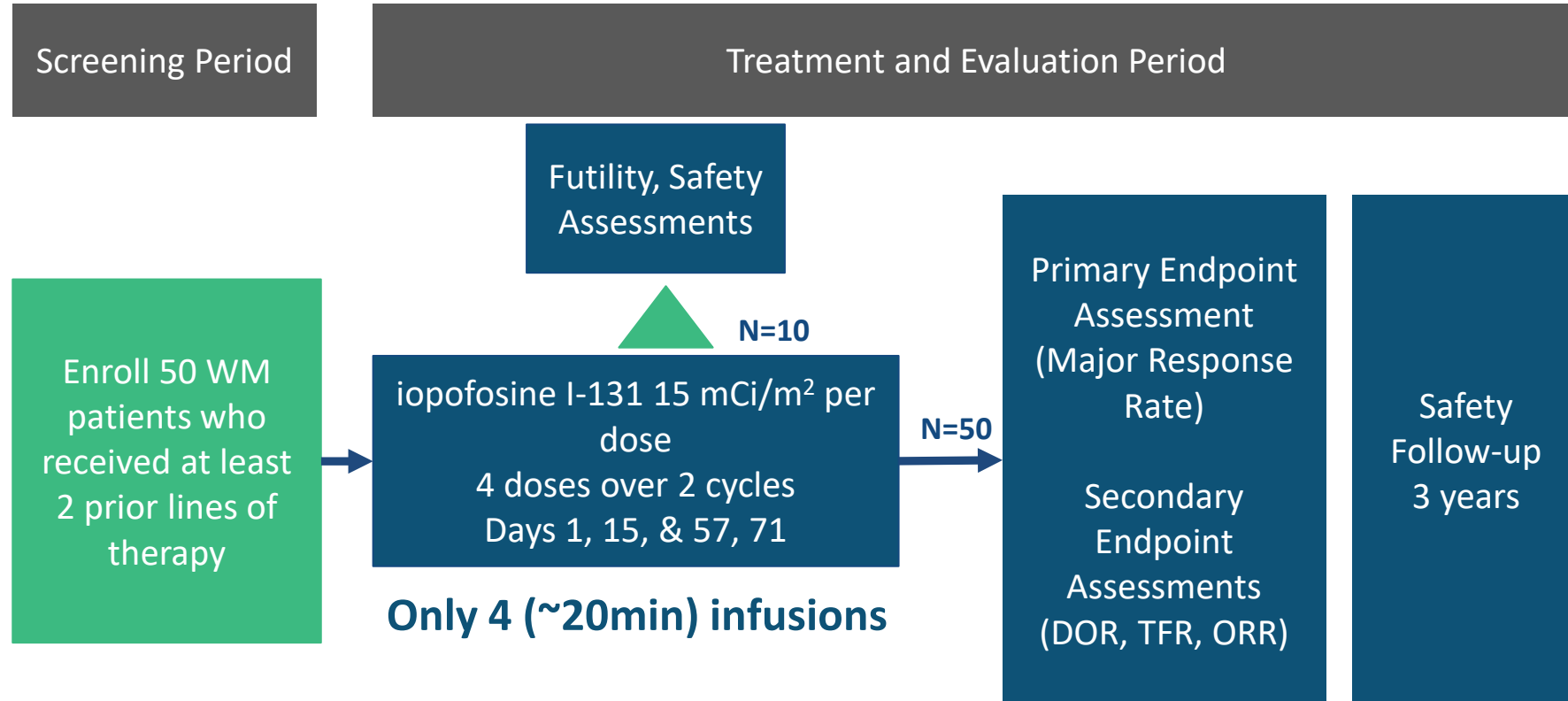
## Patient Case Study - Complete Response

- Baseline pleural effusion & multiple large tumor nodules; third line treatment
  - Patient was refractory to all previous treatments
- Day 187 CT: 100% overall tumor burden reduction & complete resolution of 5/5 tumors
- Day 406 CT: Confirmed Complete Response ongoing as of day 764 (DOR >25 months)



# Iopofosine I-131 WM Global Pivotal Study

Open Label, Single Arm Registration Clinical Study



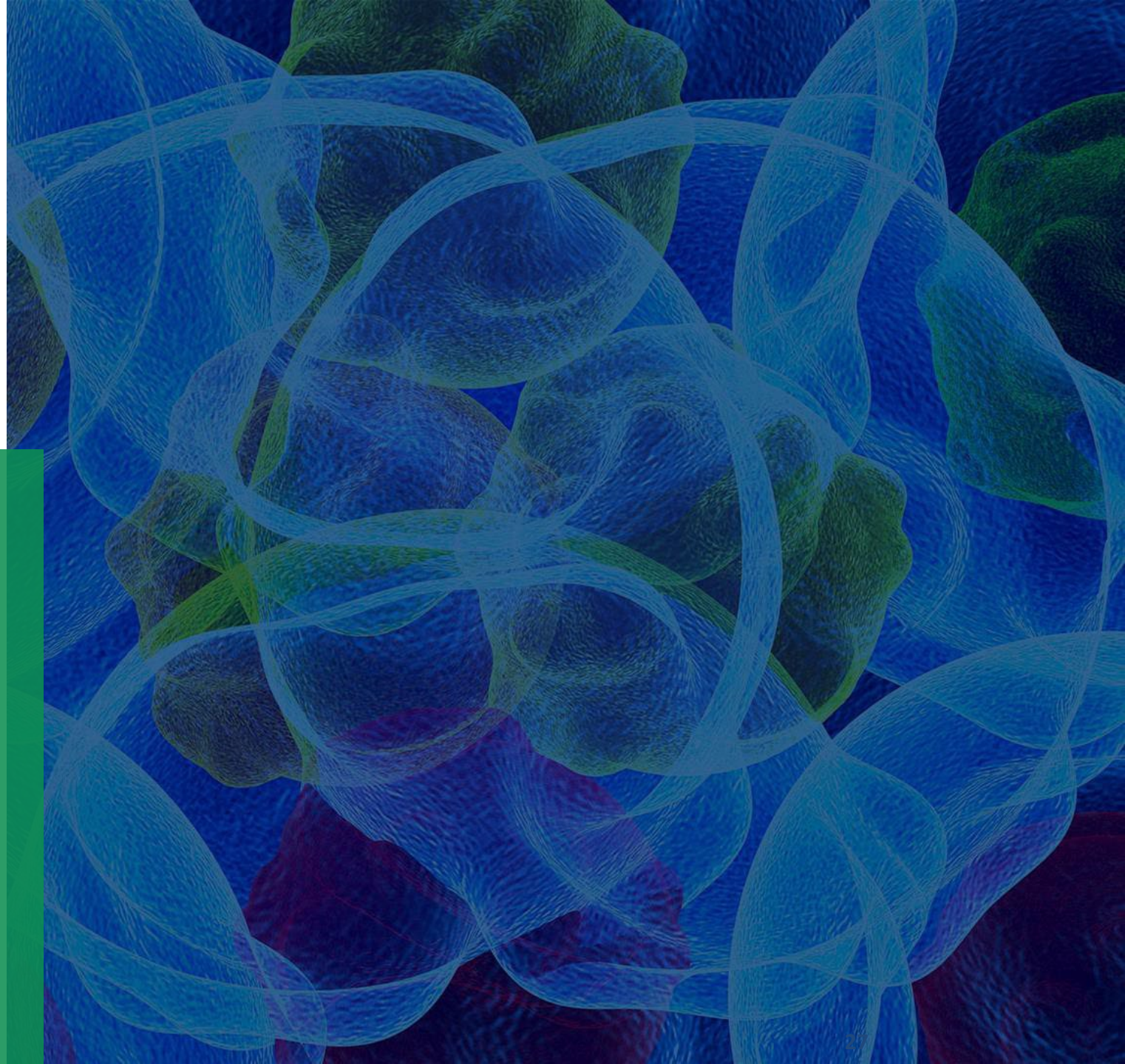
- Prior treatment with a BTKi is encouraged, but not required
- All genotypes eligible
- Includes **Bing-Neel** patients (CNS involvement)
- **No restriction on amount of bone marrow involvement**



# Next Generation TRP

*Beyond I 131*

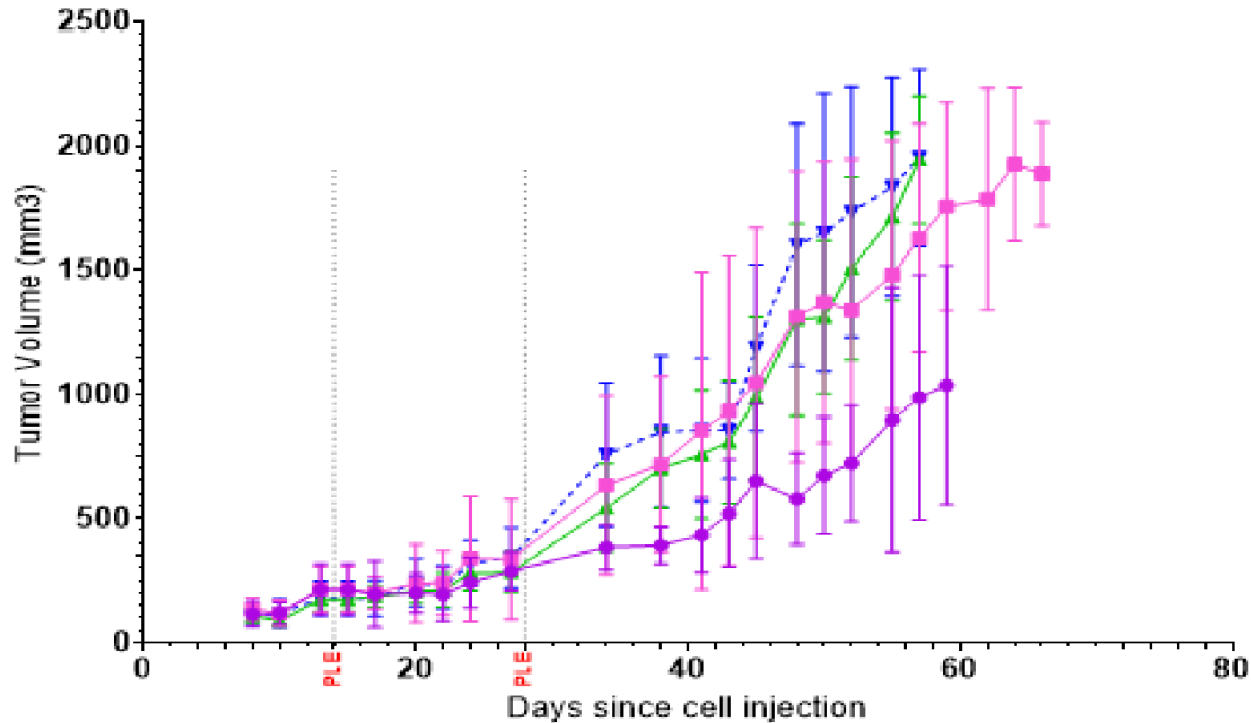
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# Moving Beyond I 131: Efficacy with Alpha emitters

## Actinium 225-PLE in Pancreatic Cancer Model (BxPC3)

Pancreatic Cancer (BxPC3) Model



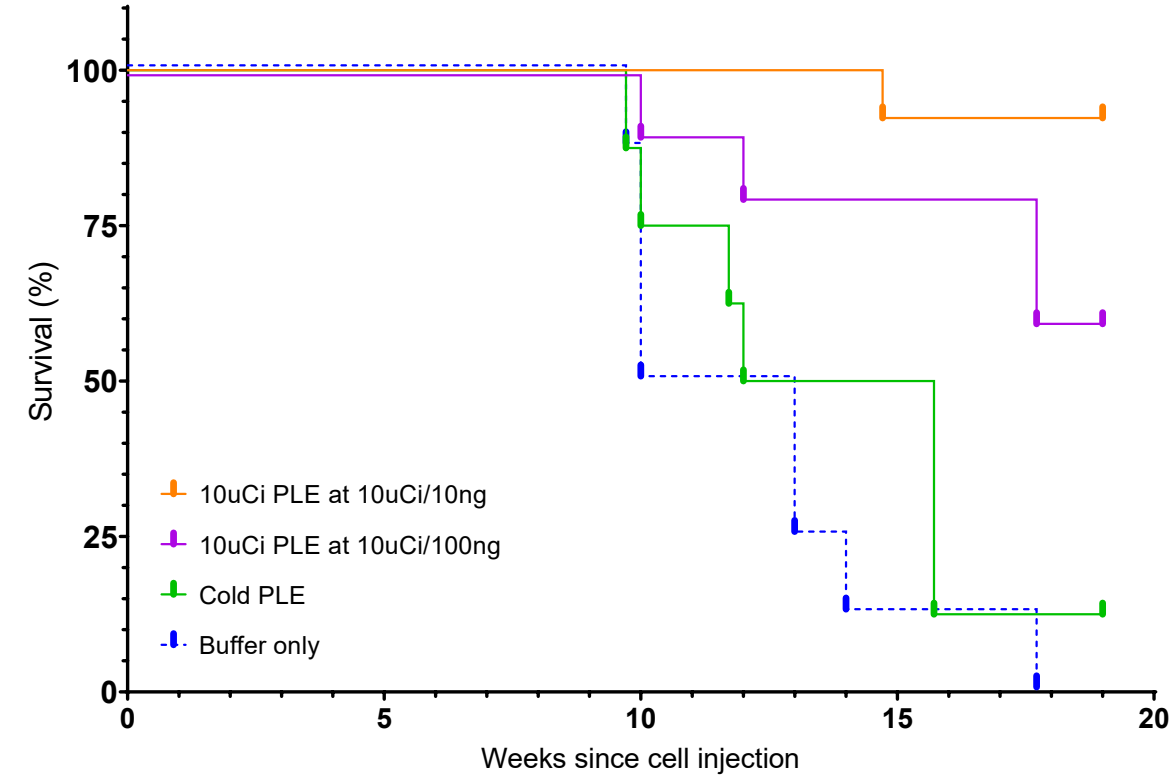
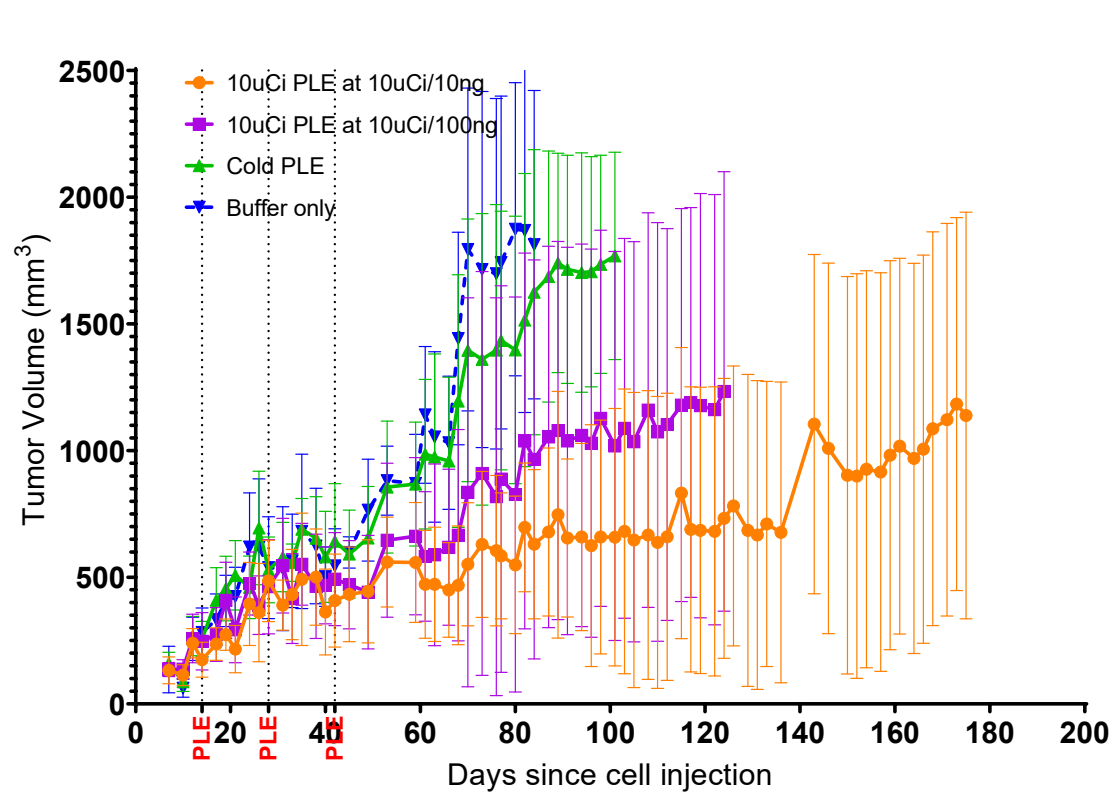
- ▼ Vehicle control
- Cold PLE control
- Single dose Ac-225-PLE 0.1uCi (Day 14)
- Two dose Ac-225-PLE 0.1uCi (Day 14 & 28)

- Mice received either a single infusion of Ac225-PLE or 2 infusions
- Tumor volume at dosing ~150mm<sup>3</sup>
- Two doses showed tolerability, growth delay and survival benefit (not shown)
- Use of PLE with alpha emitters demonstrates efficacy and tolerability in multiple solid tumor models
- Dosing optimization for radioisotope and tumor type



# Moving Beyond I 131: Efficacy with Alpha emitters

## Lead-212-PLN in Triple Negative Breast Cancer Model (HCC70)



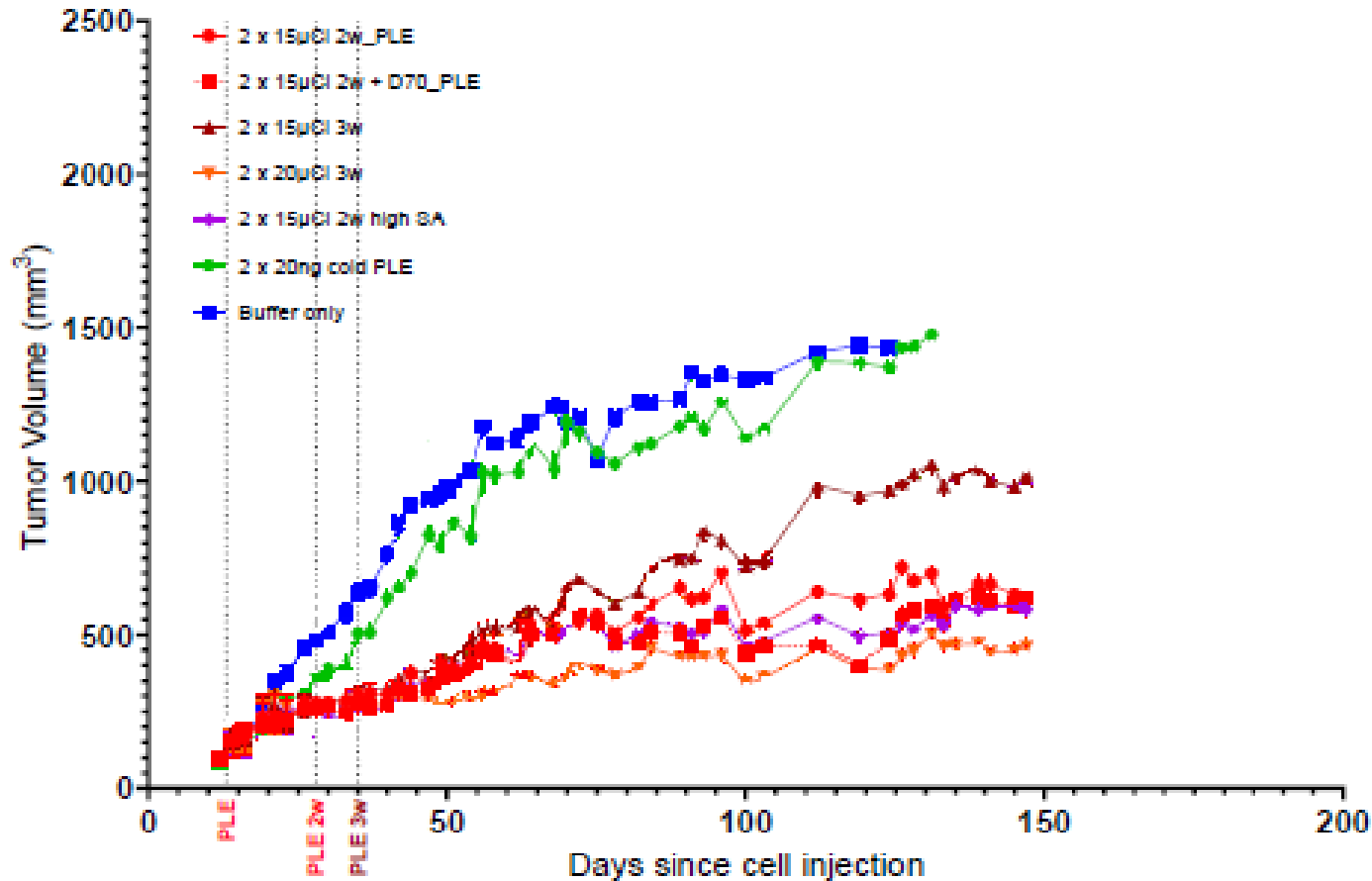
- Tumor volume at dosing ~150mm<sup>3</sup>
- Three doses (Day 14, 28 & 42) with either low or high specific activity
- Tumor volume reduction was seen with both doses post second dose; rebound occurs once drug is removed

	10uCi PLE at 10uCi/10ng	10uCi PLE at 10uCi/100ng	Cold PLE	Buffer only
Median Survival (weeks)	Undefined	Undefined	13,8571	11,5

**Both Doses Demonstrate Efficacy and Survival Benefit**

# Moving Beyond I 131: Efficacy with Alpha emitters

Astatine-211-PLE in Triple Negative Breast Cancer Model (HCC70)



- A variety of doses and dosing regimens tested
- Tumor volume at dosing  $\sim 150\text{mm}^3$
- All treatment doses show some tumor volume reduction and growth delay
- Optimum response achieved with 2 doses given 3 weeks apart (20 $\mu$ Ci) or high specific activity at 15 $\mu$ Ci given 2 weeks apart
- Dosing optimization continues

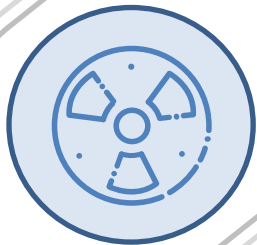
***PLE Demonstrates Ability to Provide Targeted Delivery of Key Therapeutic Alpha Emitters to Various Solid Tumors***

# Learning from the Past

*Building with Patients and the Market in Mind*

## Manufacturing

We utilize multiple finished product manufacturers



## Radioisotope Supply

All drug components are multi-sourced to provide uninterrupted supplies



## Radiopharmacy

Utilize a multi-layered approach with commercial and non-commercial radiopharmacy networks



## Logistics & Stability

Created partnerships with shippers and agents to be able to deliver finished product anywhere within 72 hours. Develop a formulation with 14-day room temp stability



## Patient

Focus drug for disease/patient. Ease of dosing/peripheral infusion. Focus on patients with no alternative treatment.



**THANK YOU**

NASDAQ: CLRB

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