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# RADIOPHARMACEUTICALS – THERAGNOSTIC PAIRINGS

- July 26, 2022

# SUCCESS AND FAILURE

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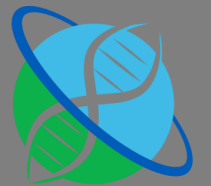
**Zevalin**  
**Bexxar**

> \$20 mUSD



**Xofigo**  
**Lutathera**  
**Pluvicto**

\$415 mUSD  
> \$400 mUSD  
> \$500 mUSD?

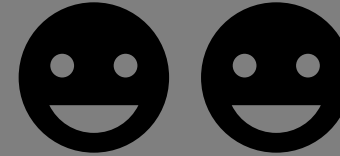


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# HOW CAN RPS BECOME BLOCKBUSTERS?



> 1,000 mUSD ?



**Zevalin**  
**Bexxar**

> \$20 mUSD

**Xofigo**  
**Lutathera**  
**Pluvicto**

\$415 mUSD  
> \$400 mUSD  
> \$500 mUSD?



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# LEVERAGE POINTS

Case in  
point:  
PSMA-617

Case in  
point:  
Lutathera

Case in  
point:  
Iomab-B

- Targets not druggable by ADCs and other agents
  - Low level of target expression
  - Non internalizing non-oncogenic targets
  - Small targeting moieties
  - Chemo resistance
- Leverage unique safety / efficacy profile
- Abscopal effect / synergy



# WHERE RPS ARE TODAY CLINICALLY

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- Single agent
- Last or late line
- Palliative
- Conventional alternatives limiting commercial success



# WHERE WE NEED TO GO

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- Early lines of therapy (1L, 2L)
  - Combinations with conventional drugs
  - Maintenance, Adjuvant
  - MRD positivity
- “Cures” or long term CRs
- Leverage specific advantages of Radiopharmaceutical



# HOW RADIOPHARMACEUTICALS CAN WIN BIG

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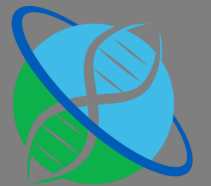
Potential upfront settings

Part of combination therapies

- Replace chemo
- Replace EBRT
- Leverage potential synergies
  - PD-(L)1, PARP etc.
  - Leverage abscopal effect
- Additive effect with different safety profile

MRD paradigm: adjuvant / maintenance

- “Surgical kill” (α-emitters)



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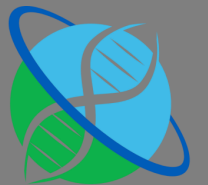
# A SIMPLE TRUTH

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Case in point:  
Zevalin vs  
Rituximab

When directly competing with conventional therapies, radiopharmaceuticals will lose

- Radiopharmaceuticals need to be clearly superior to conventional therapy
  - Efficacy
  - Safety



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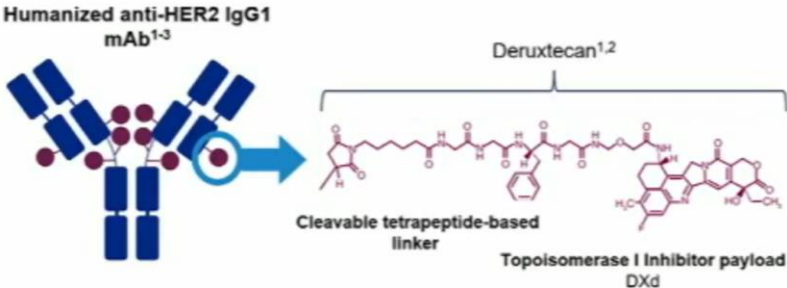


# A WARNING: ADCS MAKING PROGRESS

- T-DXd's (Enhertu) profile is like a RPs'
- ADCs remain key competitors
- Their safety profile mimics that of the payload
- Tolerability is a positive differentiator for RPs

## T-DXd Was Designed With 7 Key Attributes...

**T-DXd is an ADC composed of 3 components<sup>1,2</sup>**  
A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab, covalently linked to:  
A topoisomerase I inhibitor payload, an exatecan derivative, via  
A tetrapeptide-based cleavable linker

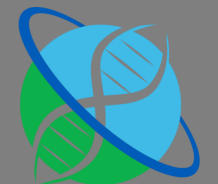


**Humanized anti-HER2 IgG1 mAb<sup>1-3</sup>**  
**Deruxtecan<sup>1,2</sup>**  
**Cleavable tetrapeptide-based linker**  
**Topoisomerase I Inhibitor payload DXd**

|   |
|---|
| Payload mechanism of action: topoisomerase I inhibitor <sup>a,1,2</sup> |
| High potency of payload <sup>a,1,2</sup>                                |
| High drug-to-antibody ratio, ≈8 <sup>a,1,2</sup>                        |
| Payload with short systemic half-life <sup>a,1,2</sup>                  |
| Stable linker-payload <sup>a,1,2</sup>                                  |
| Tumor-selective cleavable linker <sup>a,1,2</sup>                       |
| Bystander antitumor effect <sup>a,1,4</sup>                             |

ADC, antibody-drug conjugate; DXd, DX-8951f derivative; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; mAb, monoclonal antibody; T-DXd, trastuzumab deruxtecan.  
\*The clinical relevance of these features is under investigation.  
1. Nakada T et al. Chem Pharm Bull (Tokyo). 2019;57:173-185. 2. Ogtani Y et al. Clin Cancer Res. 2016;22:5097-5108. 3. Trail PA et al. Pharmacol Ther. 2018;181:126-142. 4. Ogtani Y et al. Cancer Sci. 2016;107:1039-1048.

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# ALPHA VS BETA

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## Criteria:

- |                           |                     |
|---------------------------|---------------------|
| • Target expression level | Low: $\alpha$       |
| • Cross-fire              | long range: $\beta$ |
| • Abscopal effect         | $\beta$             |
| • Radiation resistance    | $\alpha$            |
| • MRD setting             | $\alpha$            |
| • Community use           | $\alpha, (\beta)$   |

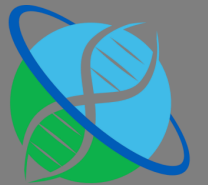


# CAN TRACERS SUPPORT BROADER USE...

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- ... as RPs are used more upfront and in larger indications?
- ... and in cancers that may have many actionable mutations?

➤ Yes, but...



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# IMAGING TRACERS - CLINICALLY COMPELLING

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- Dosimetry – “image twin”
- Target expression - patient selection
- Cancer heterogeneity
- Early response marker
- Tracking: AI opportunity



# IMAGING TRACERS - CLINICALLY COMPELLING

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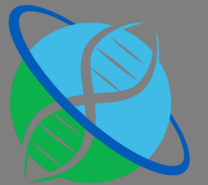
- Dosimetry – “image twin”
- Target expression - patient selection
- Cancer heterogeneity
- Early response marker
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# POURING WATER IN YOUR WINE...

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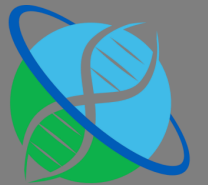
- Only few tracers have potential relevance beyond being a companion
  - PSMA is the exception!
- PET tracers are not great for screening
  - High “hit ratio” needed (say 1 : <3)
- PET companion tracers are not necessarily an advantage if they are required to use the therapeutic
  - Access
  - Stakeholder economics



# COMPANION TRACER FOR PATIENT SELECTION?

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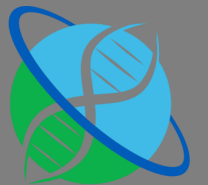
- Standard approaches to analyze target expression
  - Biopsy, CTC, ctDNA, ctRNA
  - IHC, PCR, NGS etc.
- Many options
- Established as companion tests for conventional therapies
- Broad set of data often available



# COMPANION TRACER STRATEGIES

Case in  
point:  
Lutathera

- Leverage in vitro tests combined with imaging, where appropriate
  - Pre-select patients with existing data on mutations
- Create treatment algorithms driven by tracers
  - Move beyond excluding low expressers
- Dosimetry based individual dosing as a post approval option, if possible
- AI-driven response predictions
  - Combine imaging and clinical data



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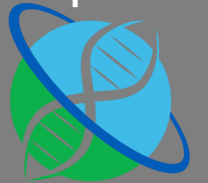


# TRACER-DRIVEN ALGORITHMS

Ideally, companion tracers should drive comprehensive treatment choices rather than just excluding a subset of patients

Case in point:  
Keytruda vs  
Lutathera

- E.g. PD-(L)1 – TPS > 1%, NSCLC
  - High expression level – single agent therapy
  - Low expression level CPI + chemo
- Adaptive: Quick, well-defined early response, if not combination



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# COMPANION TRACERS NEED TO DRIVE VALUE

Case in  
point:  
Lutathera

Case in  
point:  
PSMA

- How competitive is the therapeutic?
- Is the data generated unique and useful?
- Do data gate a specific treatment, or have broader use?
- Do they change patient management and improve outcomes?
- Is it the best option?
- Is it cost-effective?



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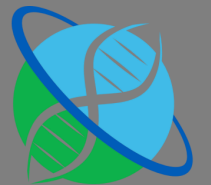
# WHERE DOES THIS LEAVE US?

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Companion tracers need to create unique clinical value to support a product

- Think about companion diagnostics more broadly
  - Avoid companion tracer requirement unless there is a compelling use case
  - Leverage existing in-vitro data
  - Consider in vitro-tests combined with PET tracers in particular for screening
- Expand the tracer use case beyond binary patient selection
- Leverage tracers to drive a comprehensive treatment algorithm

Be bold - think long-term CR and cure!



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# COMMENTS - QUESTIONS?

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