Debio 0228, Targeted Radiotherapy

May 2023

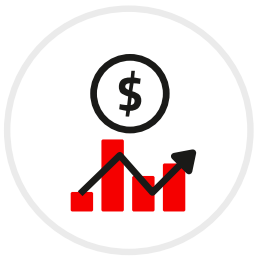
Executive Summary

Radioligand therapy targeting Carbonic Anhydrase 9 (CAIX) Program

- Radioligand therapy is an exciting field in oncology
- Debio 0228 has the potential to be the first-in-class peptide theranostic pair to treat multiple tumor types and **attain blockbuster status**
- CAIX offers a potential target to deliver radiotherapy to the core of the cancer
- Pre-clinical data package is complete
- **First-in-human study was initiated in Q1 2023** with a market exclusivity expected until 2047

Value Drivers

Potential long period of commercial exclusivity in multiple indications



EXPECTED TIME TO MARKET

2030

EXPECTED PATENT PROTECTION

up to 2047

POTENTIAL IN MULTIPLE INDICATIONS

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The Challenge

Take Radiotherapy to the Next Level

Current Issues with Radiotherapy

Radiotherapy is a proven standard of care but important limitations still exist

Toxicity burden

Intrinsic damage to healthy tissues

Administration of multiple fractionated treatment cycles

Dose limiting toxicities

Extended Disease

More efficient when reduced tumor burden

Unfeasible if tumor/nodal volume too extensive

Anatomical imaging

Unfeasible for small lesions or early disease dissemination due to limitations on imaging resolution

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The Target

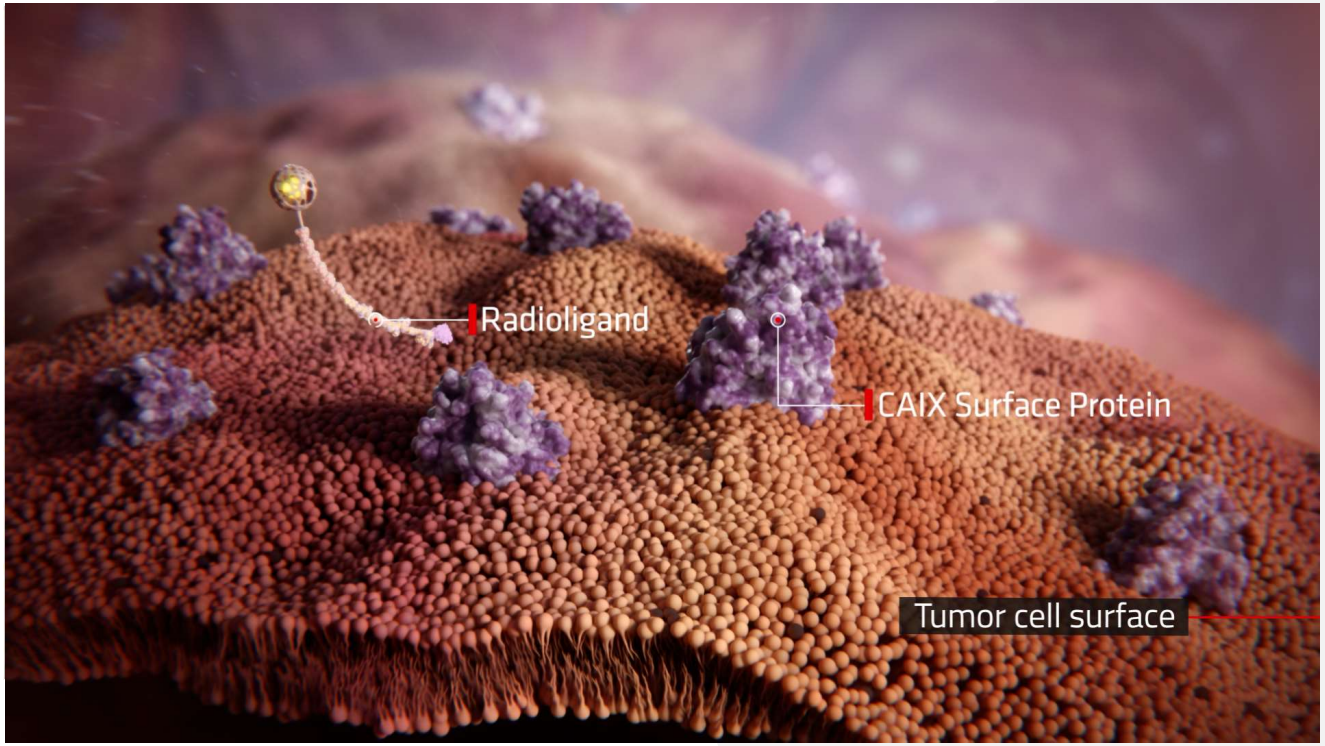
Carbonic Anhydrase 9 (CAIX)

Targeted Radiopharmaceuticals

Targeting the CAIX surface protein and delivering radioactive particles directly to the tumor

When injected into the patient's bloodstream, the targeting agent:

- Attaches to cancer cells by binding to the CAIX target
- Delivers high-dose radiation to tumor
- Spares normal tissues, where CAIX expression is very limited



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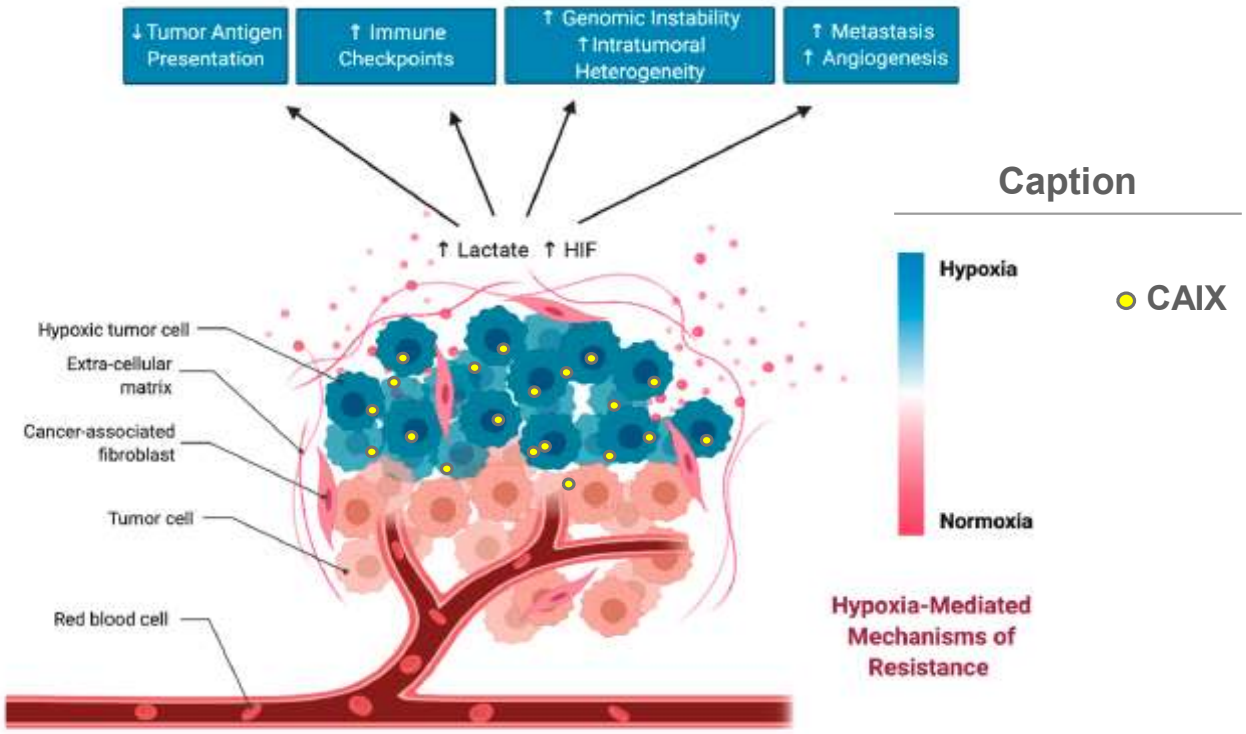
CAIX & Hypoxia

CAIX expression is induced by hypoxia and is a hallmark of tumor aggressiveness & resistance to treatments



CAIX expression is also a hallmark of resistance to common antineoplastic therapies

Adapted from Vito & al., *Cells*, 2020

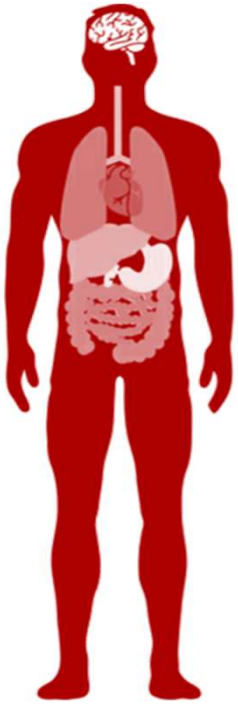
Indications

Our first development targets: renal, pancreatic & colorectal cancers

Renal Cancer

15’000 deaths in US

→ CAIX expression:
85% - estimated[1]



Pancreatic Cancer

48’000 deaths in US

→ CAIX expression:
50% - estimated[2]

Colorectal Cancer

53’000 deaths in US

→ CAIX expression:
30% - estimated

Additional potential in many different indications

- Lung cancer
- Breast cancer
- Brain cancer
- Thyroid cancer
- Head & Neck cancer
- Mesothelioma
- Cholangiocarcinoma
- Bladder cancer

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Notes: 1: Histology= clear cell; 2: Histology= Adenocarcinoma of the Ductal Epithelium. Source: Globocan (2020) for epidemiology of the disease in US (all histological subtypes, no biomarker)

Why Targeted Radiotherapeutics?

Precision nuclear medicine

- **Validated yet emerging approach**
  - Innovative technologies successfully launched in the past 5 years (Lutathera, Pluvicto)
  - Physicians are excited by this new targeted treatment approach in oncology
- **Sizable market opportunity**
  - Market is expected **to grow to $30b by 2030[1] worldwide**
  - Recent deals confirm growing interest of Pharmas
- **Patient centric**
  - Only treating patients who have a chance to benefit (Treat what you see)
  - Targeting radiation directly to the cancer cell allowing a potentially better safety, tolerability profile and quality of life
- **Long Life cycle**
  - Complex supply chain coupled with manufacturing know-how may facilitate protection against generics and competitor erosion

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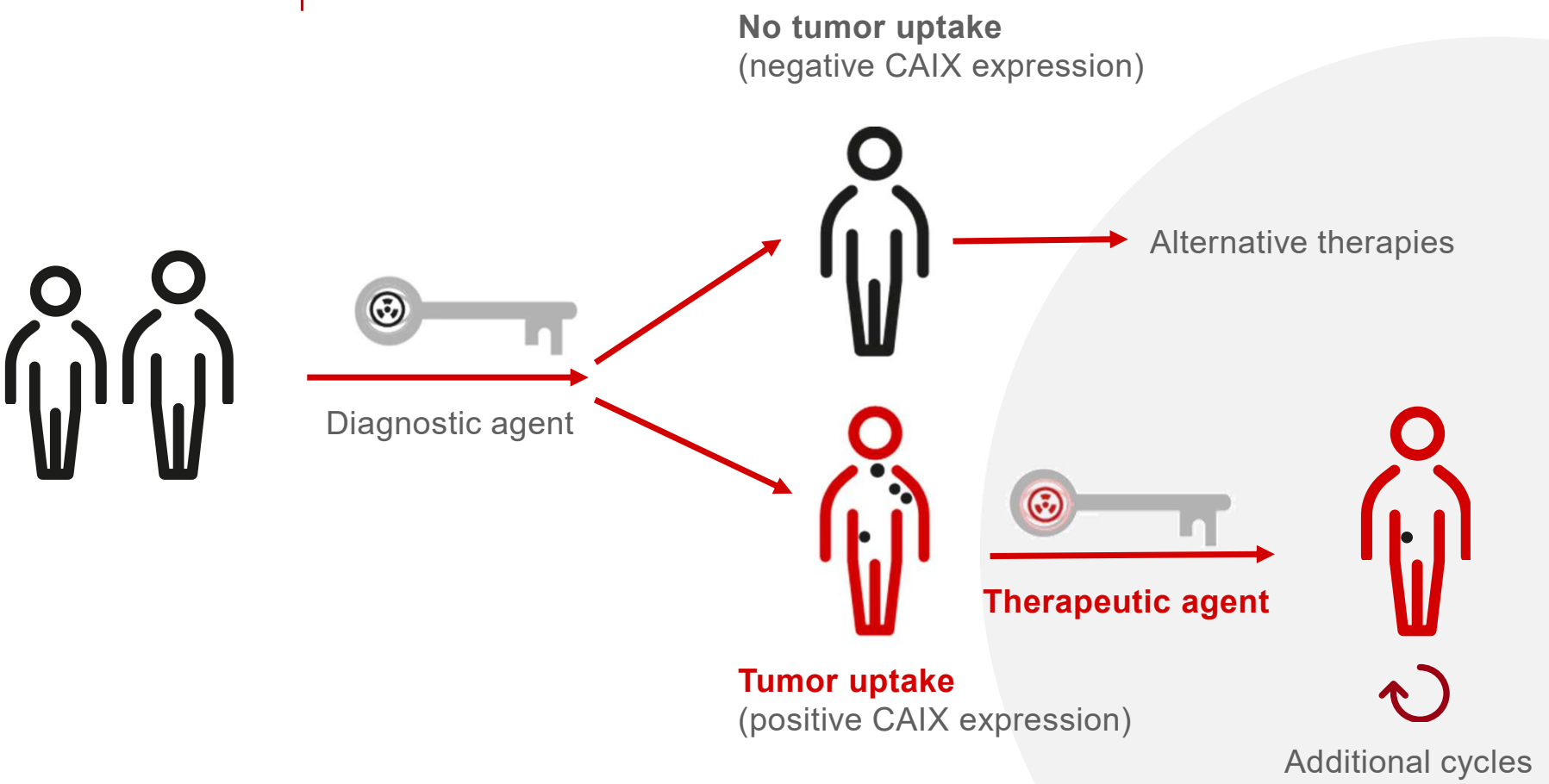
Source: [1]MEDraysintell Nuclear Medicine (2020)

Our approach

A new ligand radioconjugate,
targeting CAIX positive tumors

Theranostic Concept



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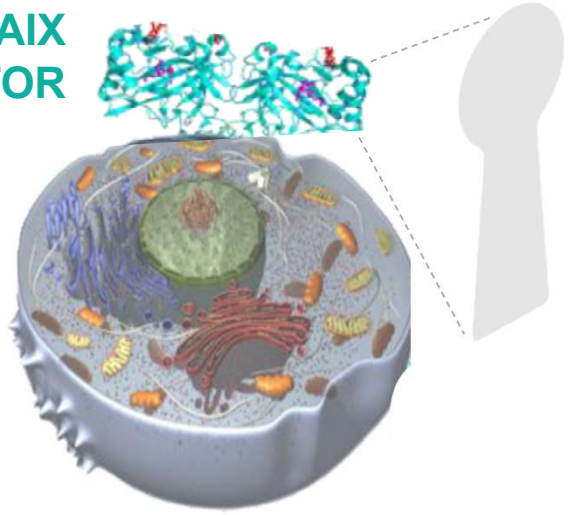
Theranostic Pair

Debio 0228 (^{177}Lu) and Debio 0328 (^{68}Ga) are a new radiopeptide tandem targeting CAIX

CAIX RECEPTOR



HYPOXIC CANCER CELL

Debio 0228

177Lu

- as a β-emitting radionuclide, for treatment
- maximum penetration of 2.2 mm in tissue

→ **Sufficient to kill targeted tumor cells with a limited effect on neighbouring normal cells/tissues**

Debio 0328

68Ga

- as a γ-emitting radionuclide, for patient selection or diagnosis
- convenient $t_{1/2}$=68 min

→ **Various PET imaging applications**

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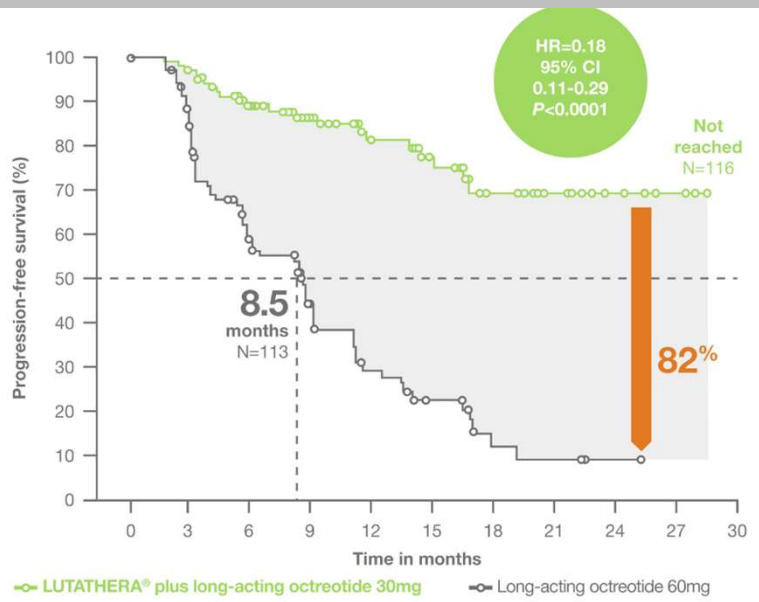
Validated Concepts (1/2)

Improved patient outcomes in both rare diseases and highly prevalent cancers

82% reduction in the risk of progression

was shown in the randomized, controlled trial evaluating the efficacy and safety of 177Lu–DOTATE in combination with SOC in patients with advanced, progressive, SSTR–positive midgut NETs

Lutathera (GEP-NET)



2017 - Ph3 NETTER-1

Strosberg J et al. N Engl J Med. 2017 Jan 12;376(2):125-135

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Validated Concepts (2/2)

Improved patient outcomes in both rare diseases and highly prevalent cancers

38% reduction in the risk of death

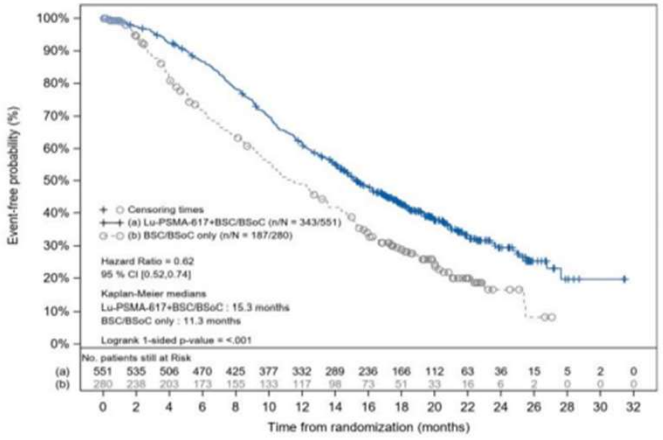
60% reduction in the risk of progression

in combination with SOC

Pluvicto (mCRPC)

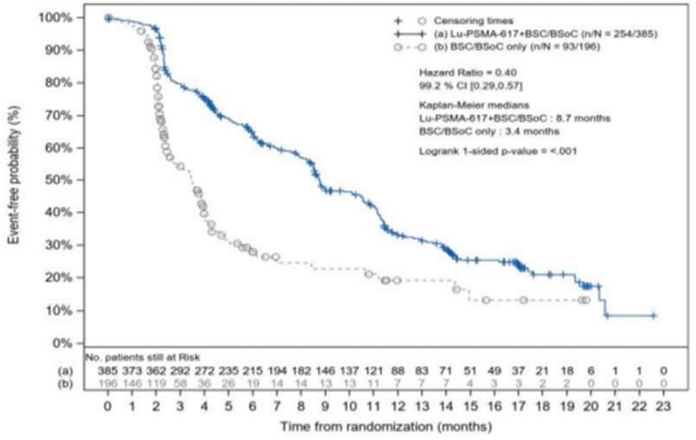
^{177}Lu-PSMA-617 significantly reduced the risk of death by 38%

OS HR[1]: 0.62 (95%CI: 0.52, 0.74)
Median OS: 15.3 months (14.2, 16.9)[3] vs. **11.3** (9.8, 13.5)[3]



^{177}Lu-PSMA-617 significantly reduced the risk of radiographic progression or death by 60%

rPFS HR[1]: 0.40 (99.2%CI: 0.29, 0.57)
Median rPFS: 8.7 months (7.9, 10.8)[2] vs. **3.4** (2.4, 4.0)[2]



1. p<0.001, stratified log-rank test 1-sided 2. 99.2% CI, in line with hypothesis testing strategy 3. 95% CI

2021 - Ph3 VISION

N Engl J Med 2021; 385:1091-1103

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Our asset

Debio 0228/0328

Potentially first and best in class peptide-based RLT targeting carbonic anhydrase 9

Opportunity

- Treatment of **multiple tumor types**
- As **monotherapy** and in **combination**
- **Blockbuster** potential
- Enabling chelation with **beta and alpha**-emitters
- Potential for **long exclusivity** period (up to 2047)

Complete preclinical package

- **Cyclic peptide** that binds with a **high affinity and selectivity** to CAIX
- **Better or similar** biodistribution profile in animals compared to the **marketed products**
- **Compelling in-vivo efficacy** results in animal models
- **No identified safety issues** in the preclinical toxicology studies

Clinical stage

- Development initiated in indications with **high unmet need**
- **First-in-human** started in **Q1** 2023
- Anticipated **market entry 2030**

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^{177}Lu-DPI-4452 (Debio 0228)

DPI-4452 is a DOTA cyclic peptide which targets CAIX with high affinity and high selectivity

DPI-4452 binding to recombinant human CAIX assessed by Surface Plasmon Resonance (SPR)

Compound	K_D (nM)	$T_{1/2}$ (min)
DPI-4452	**0.25**	**99**
^{nat}Lu-DPI-4452	**0.16**	**123**
^{nat}Ga-DPI-4452	**0.20**	**112**

DPI-4452 binds human CAIX with high affinity and long residence time, independent of the conjugation with ^{nat}Lu or ^{nat}Ga

^{Nat}Lu-DPI-4452 binding to recombinant human CAs by Surface Plasmon Resonance (SPR)

Target	K_D (nM)	$T_{1/2}$ (min)
hCAIX	**0.32**	**76**
hCAIV	> 2'000	n.d
hCAXII	> 2'000	n.d
hCAXIV	> 2'000	n.d

n.d : not defined

DPI-4452 is highly selective for CAIX

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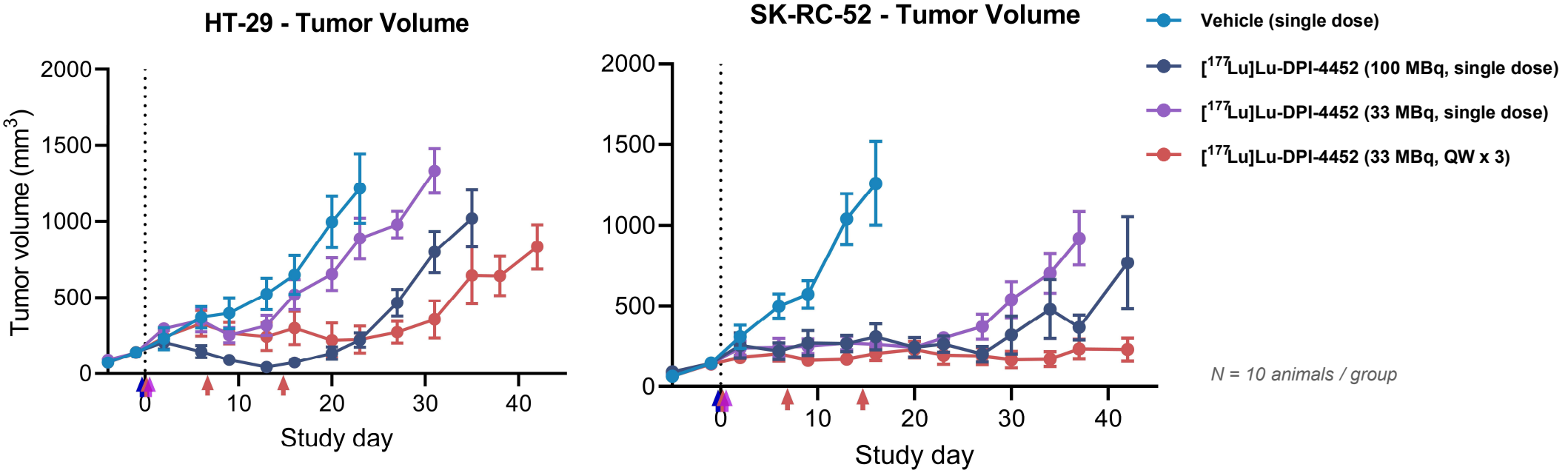
^{177}Lu-DPI-4452 (Debio 0228)

^{177}Lu-DPI-4452 shows *in vivo* anti-tumoral activity in xenograft mouse models



- **Marked Tumor Growth inhibition in both models**
- **Higher efficacy with 3x 33 MBq compared to the 100 MBq group → Fractionation seems beneficial**

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Interested in discussing further?

Contact informations

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