ASX Announcement

DEP® presentation at SNMMI radiopharmaceuticals conference

Melbourne, Australia; 11 June 2024: Starpharma (ASX: SPL, OTCQX: SPHRY) today provides a copy of the DEP® radiotheranostics scientific poster presented at the Society of Nuclear Medicine and Molecular Imaging (SNMMI) Annual Meeting in Toronto, Canada, overnight. The scientific poster presents data from Starpharma's DEP® HER2 radiotheranostics program, demonstrating the promising utility of DEP® dendrimers in precision radiotheranostics for cancer imaging and therapeutic applications.

The SNMMI Annual Meeting is a leading scientific research event in nuclear medicine and molecular imaging, where developments in radiopharmaceuticals are a key focus. The conference offered Starpharma a valuable opportunity to present data on its radiotheranostics program and to network with interested companies.

Building on Starpharma's previously reported preclinical results, the scientific poster presents new dosimetry analyses, showing that DEP® HER2 achieved significant tumour accumulation, with 20-30% of the injected dose per gram localising in tumour from day 1 to 5. This is comparable to trastuzumab, a monoclonal antibody marketed under the brand name Herceptin®. DEP® HER2 was distributed more rapidly to tumour than trastuzumab and was cleared more rapidly from the blood, resulting in less exposure to radiosensitive organs/tissue such as bone marrow, heart, and lungs. Due to its lower biodistribution in bone marrow, DEP® HER2 could potentially deliver 1.7 times more radioactivity to the tumour than the trastuzumab antibody, demonstrating the ability of DEP® dendrimers to enhance tumour targeting in drug delivery.

Overall, the results from Starpharma's radiotheranostics program continue to demonstrate that DEP® dendrimers are a promising, versatile, and multifunctional platform for customising precision radiotheranostics for cancer imaging and therapeutic applications, bridging the gap between small molecules and large antibodies. DEP® HER2 is a priority program for Starpharma.

The DEP® radiotheranostics scientific poster presentation is appended. Co-authors on the poster were Professor Kris Thurecht and his team from The University of Queensland's Centre for Advanced Imaging, Australian Institute for Bioengineering and Nanotechnology, ARC Research Hub for Advanced Manufacture of Targeted Radiopharmaceuticals (AMTAR Hub).

About Starpharma

Starpharma (ASX: SPL, OTCQX: SPHRY) is dedicated to helping patients with significant illnesses, such as cancer, achieve improved health outcomes and quality of life through the application of our unique dendrimer technology.

Dendrimers are precise, synthetically manufactured, nanoscale molecules. Their unique properties—including their size, structure, high degree of branching, polyvalency, and water solubility—are advantageous in medical and pharmaceutical applications.

Starpharma uses its dendrimer technology to develop novel therapeutics and to enhance the performance of existing pharmaceuticals. The Company's portfolio includes multiple clinical-stage oncology products, which utilise its Dendrimer Enhanced Product ('DEP®') drug delivery technology, as well as marketed products, including VIRALEZE™ and VivaGel® BV, which utilise SPL7013, a proprietary dendrimer with antimicrobial properties. Starpharma's DEP® drug delivery platform is being used to enhance the effectiveness of existing and novel therapies and to reduce drug-related toxicities through controlled and specified drug delivery.

For more information about Starpharma, visit www.starpharma.com or connect with Starpharma on LinkedIn.

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Disclosure
This ASX Announcement was authorised for release by Chair, Mr Rob Thomas.

Forward-Looking Statements
This document contains certain forward-looking statements, relating to Starpharma's business, which can be identified by the use of forward-looking terminology such as "promising", "plans", "anticipated", "will", "project", "believe", "forecast", "expected", "estimated", "targeting", "aiming", "set to", "potential", "seeking to", "goal", "could provide", "intends", "is being developed", "could be", "on track", or similar expressions, or by express or implied discussions regarding potential filings or marketing approvals, or potential future sales of product candidates. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no assurance that any existing or future regulatory filings will satisfy the FDA's and other authorities' requirements regarding any one or more product candidates, nor can there be any assurance that such product candidates will be approved by any authorities for sale in any market or that they will reach any particular level of sales. In particular, management's expectations regarding the approval and commercialization of the product candidates could be affected by, among other things, unexpected trial results, including additional analysis of existing data, and new data; unexpected regulatory actions or delays, or government regulation generally; our ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry, and general public pricing pressures; and additional factors that involve significant risks and uncertainties about our products, product candidates, financial results and business prospects. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated, or expected. Starpharma is providing this information as of the date of this document and does not assume any obligation to update any forward-looking statements contained in this document as a result of new information, future events or developments or otherwise. Clinical case studies and other clinical information given in this document are given for illustrative purposes only and are not necessarily a guide to product performance and no representation or warranty is made by any person as to the likelihood of achievement or reasonableness of future results. Nothing contained in this document, nor any information made available to you is, or shall be relied upon as, a promise, representation, warranty or guarantee as to the past, present or the future performance of any Starpharma product.

Dendrimer nanoparticles (DEP) enable targeted precision delivery and customized biodistribution for cancer radiotheranostics

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PURPOSE AND BACKGROUND

- DEP dendrimers:
  - a **clinically validated** drug delivery platform technology
  - successfully used in humans to **deliver**, **modify PK** of, and **improve the safety profile** of multiple classes of chemotherapeutic drugs.
- Radiotheranostics using antibodies, antibody fragments or peptides for targeting are limited by factors including off-target toxicity and accumulation of radioactivity in radio-sensitive organs (e.g., dose limiting myelosuppression and nephrotoxicity).
- To address such limitations, DEP dendrimers have been conjugated to both receptor-specific targeting moieties and radionuclide chelators for radiotheranostic applications.
- We assessed DEP dendrimers as targeted radiotheranostics with optimized biodistribution profiles, enhanced tumor killing and improved therapeutic indices.

MATERIALS AND METHODS

- Radio-imaging, *ex vivo* biodistribution and dosimetry studies conducted in tumor-bearing female BALB/c mice.
- A HER2-targeted VHH (single domain antibody, sdAb) was covalently linked to a 4th generation poly-lysine dendrimer with 16 deferoxamine (DFO) chelating sites (DEP-HER2) (**Figure 1**).
- Control: Trastuzumab with 2 covalently linked DFO chelating groups.
- DEP-HER2 and trastuzumab were labeled with ^{89}Zr → high specific activity.
- Mice inoculated SC with BT474 HER2+ breast cancer cells.
- Tumor growth >150 mm^3 → single IV dose of DEP-HER2-^{89}Zr or trastuzumab-^{89}Zr (3 MBq).
- Biodistribution evaluated in tumor and normal tissues at serial timepoints *ex vivo* by gamma counting for up to 12 days, and *in vivo* via PET-CT imaging for up to 5 days (**Table 1**).
- Biodistribution data were used to conduct dosimetry analyses.

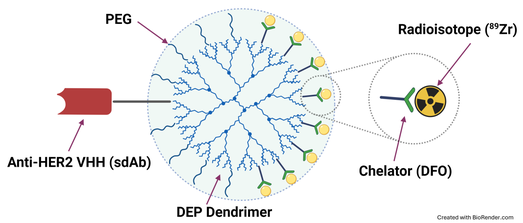
Table 1: Study schedule

Group	Total mice dosed (3 MBq)	Number of mice assessed at each timepoint *(ex vivo / PET-CT)*						
		4 hr	24 hr	2 days	3 days	4 days	5 days	12 days
DEP-HER2	25	3 / 4	3 / 4	3 / 4	3 / 4	3 / 4	3 / 4	3 / 0
Trastuzumab	25	3 / 4	3 / 4	3 / 4	3 / 4	3 / 4	3 / 4	3 / 0

DOSIMETRY ANALYSES

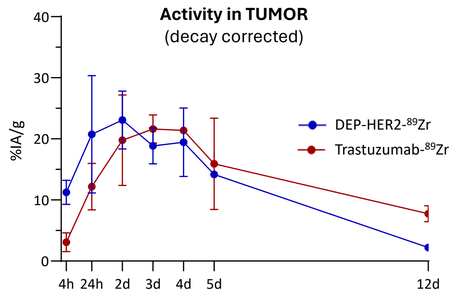
- Biodistribution data from mice were subjected to allometric conversion to estimate human biodistribution.
- Following conversion, time-activity curves, representing the percentage of injected activity per gram of tissue (%IA/g) over time, were constructed. These curves were derived by extrapolating activity data from ^{89}Zr-labeled DEP-HER2 and trastuzumab, to simulate the activity that would have been observed if the therapeutic radioisotope, ^{177}Lu, had been used as the labeling isotope.
- Derived curves were used to calculate time-integrated activity coefficients (TIACs) for ^{177}Lu, which were then used to estimate therapeutic doses that would have been delivered to tumor and each relevant tissue in humans in mGy/MBq.
- Dose to the red bone marrow estimated based on activity measured in blood (Wessels et al., *J Nucl Med* 2004;45:1725–33).

Figure 1: Schematic representation of DEP-HER2-^{89}Zr

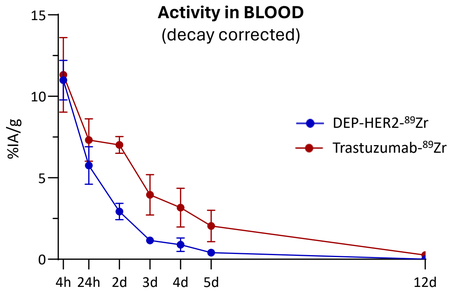


RESULTS

- **DEP-HER2 achieved significant tumor accumulation** comparable to trastuzumab, with 20-30% of the injected dose per gram (IA/g) localizing in tumor from day 1 to day 5.
- **DEP-HER2 distributed more rapidly to tumor** than trastuzumab, achieving a higher percentage of IA/g up to day 2.



- **DEP-HER2 was cleared rapidly from blood, exhibiting "fast in/fast out" kinetics.** In contrast, trastuzumab showed longer retention in blood, resulting in higher doses delivered to lungs, heart, and kidneys – all highly perfused organs.



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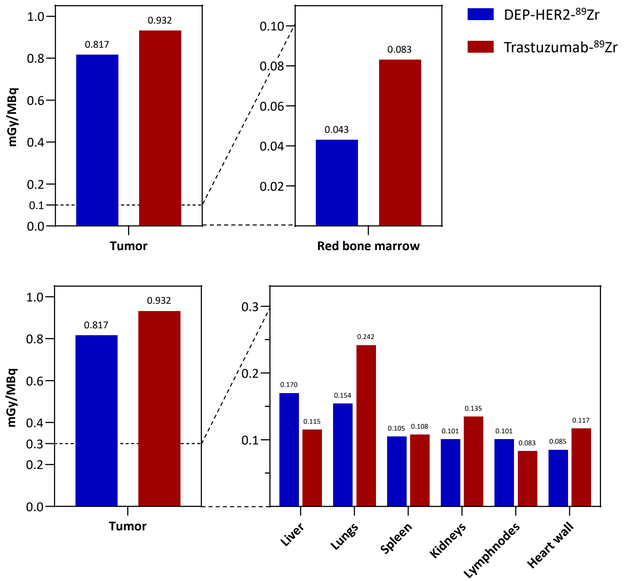
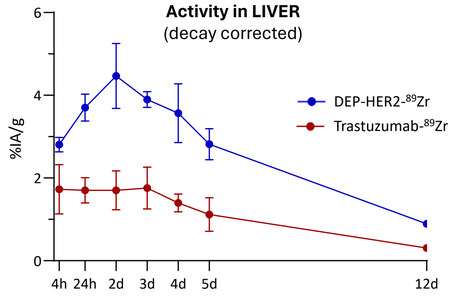
Prolonged residence time of trastuzumab in blood leads to almost double the radiation dose to red bone marrow vs. DEP-HER2

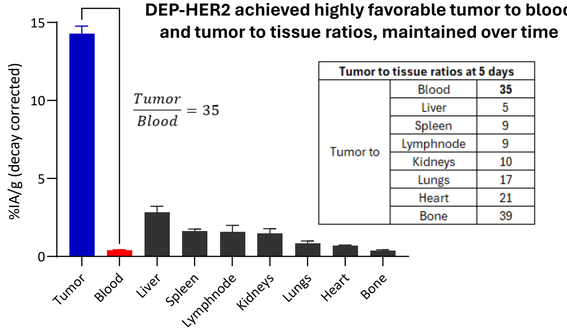


- Due to lower biodistribution in bone marrow, **DEP-HER2 could deliver a 1.7-fold higher dose of radiation to the tumor** when clinical dose limits to bone marrow – the most radiosensitive tissue – are considered.
- This increased dose to bone marrow significantly offsets trastuzumab's marginal advantage in tumor dosing.
- Biodistribution to liver and spleen was higher for DEP-HER2 (approximately 5% and 2% IA/g, respectively) than for trastuzumab (2% and 1% IA/g, respectively). This distribution is attributed to DEP-HER2 being cleared by the mononuclear phagocyte system (MPS), predominantly by liver Kupffer cells and splenic macrophages.



- Involvement of the MPS in DEP-HER2 metabolism likely contributes to its marginally higher dose to lymph nodes.
- **Neither DEP-HER2 or trastuzumab is excreted via urine**, resulting in biodistribution (<5% IA/g) and corresponding radiation doses to kidneys that are much lower than for small compounds (e.g., antibody fragments, small peptides), which are excreted in urine.

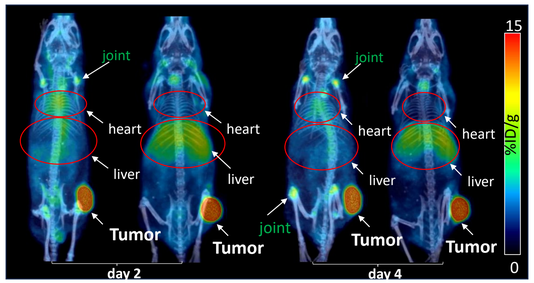
DEP-HER2 achieved highly favorable tumor to blood and tumor to tissue ratios, maintained over time



Tumor to tissue ratios at 5 days		
Tumor to	Blood	**35**
	Liver	5
	Spleen	9
	Lymphnode	9
	Kidneys	10
	Lungs	17
	Heart	21
	Bone	39

DEP-HER2 achieved excellent imaging contrast between tumor and normal tissue, similar to trastuzumab (PET/CT, Day 2 & Day 4)

Trastuzumab-^{89}Zr DEP-HER2-^{89}Zr Trastuzumab-^{89}Zr DEP-HER2-^{89}Zr



- Higher levels of activity observed in heart for trastuzumab, consistent with longer residence time in blood.
- DEP-HER2 uptake in liver, consistent with MPS-related clearance described for nanoparticles in DEP-HER2 size range.
- Deposition in shoulder and hip joints prominent for trastuzumab but not for DEP-HER2.

CONCLUSION

- **DEP-HER2 achieved an optimal biodistribution profile vs. trastuzumab**, with high levels of accumulation in tumor, low uptake in radio-sensitive organs, and fast clearance from circulation.
- **Results support DEP-HER2 as a radiodiagnostic and as a radiotherapeutic** using high energy radioisotopes, e.g., ^{177}Lu.
- **DEP dendrimers are a promising, versatile, multifunctional platform for customization of precision radiotheranostics** for cancer imaging and therapeutic applications, bridging the gap between small molecules and large antibodies.
- **DEP dendrimers can be employed with a wide range of targeting moieties and radiotherapeutic payloads to achieve customized biodistribution and excretion profiles.**