MagSense® HER2 Imaging Agent: Molecular MRI for the Detection of Axillary Nodal Metastasis in Subjects with HER2+ Breast Cancer

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Introduction

Breast cancer remains the most commonly diagnosed and second-most deadly cancer amongst women in the U.S. Timely and accurate disease staging is crucial to optimizing medical and surgical management, conferring opportunities to improve prognosis and quality of life of afflicted patients. Axillary ultrasound (AxUS)-guided lymph node sampling remains standard of care for primary breast cancer staging, though results are highly operator-dependent with sensitivity and specificity reported as low as 49% and 55%, respectively (Beenken 2003, Choi 2017). Given the significance of accurate nodal assessment, and locoregional disease burden generally, AxUS limitations present an immense opportunity to improve outcomes for patients.

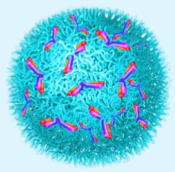
The MagSense® HER2 Imaging Agent (MSH2IA) has been developed as a molecular imaging agent to detect nodal metastases in patients with HER2+ breast cancer. Superparamagnetic iron oxide nanoparticles (SPIONs) have been used in preclinical and clinical research as imaging agents for decades. MSH2IA is the next generation, incorporating an anti-HER2 antibody covalently conjugated to a SPION to provide specific, targeted binding of the imaging agent to HER2 expressing tumor cells. MRI is less operator-dependent and provides a view of the entire nodal region. Molecular MRI with MSH2IA provides noninvasive, non-ionizing, molecularly targeted, tumor-specific contrast enhanced nodal staging, leveraging nearly ubiquitous MRI installed base instruments. Here we present the clinical results from the first MSH2IA phase 1 clinical trial in four sites in Australia (ACTRN1262100126819).

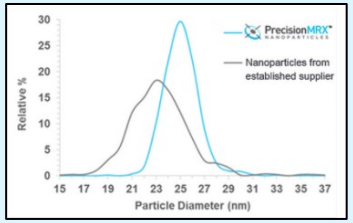
Study Objective

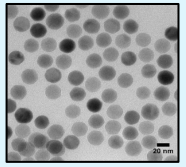
- Primary endpoint: MSH2IA Safety and tolerability
- Secondary endpoint: Confirm MSH2IA LN distribution
- Exploratory endpoint: MRI clinical utility – patient-level concordance with pathology
- 13 participants enrolled. No drug-related safety concerns were noted. Safety results available from these subjects have not identified any significant or unexpected toxicity or tolerability issues. Adverse events related to the drug were limited infusion site reactions.

MagSense® HER2 Imaging Agent

- The MagSense® HER2 Imaging Agent is designed for use with Magnetic Resonance Imaging as a contrast imaging agent for spatial detection of metastatic nodal disease in HER2+ Breast Cancer.







Surface	Diameter	PDI	# of Ab/NP	% of free Ab
PEG + anti-Her2	70-80 nm	<0.10	3-5	<10%

Superparamagnetic magnetite (Fe_3O_4) cores are made with high magnetic relaxivity (r_2 = 180 mM^{-1} s^{-1} at 3 T and 590 mM^{-1} s^{-1} at 7 T) providing excellent Néel relaxation and T2 contrast. Particles are monodispersed with narrow size distribution and exhibit high magnetic saturation. To make a molecular imaging agent, cores are encapsulated with a polymer and then functionalized with carboxylate (COO^-) surface. Polyethylene Glycol (PEG) and an anti-HER2 antibody are conjugated onto the polymer surface.

Acknowledgements: We are very grateful to all the patients for their selfless participation in the study. Our sincere thanks to the investigators, the site staff and the entire study team for their efforts.

Study Design

Patient Eligibility

- Newly diagnosed HER2-positive breast cancer patients prior to treatment
- Suspicion of nodal disease by clinical evaluation

Study Protocol

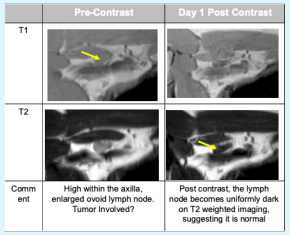
- Breast MRI on Day 1 prior to MagSense® HER2 administration (pre-dose)
- Subcutaneous injection (peri-tumoral or areolar) of 30mg dose of MagSense® HER2
- Breast MRI on Day 2 (~ 24 hours post-dose)
- Breast MRI on Day 4 (~ 72 hours post dose) for patients 1-6 only
- Following last MRI, either dissected nodes if surgery planned before systemic therapy or biopsy (core needle) of a clinically "suspicious" lymph node obtained
- Dissected nodes or biopsied tissue(s) analyzed *ex vivo* for magnetic relaxometry and histology
- Day 7 safety follow up and Day 28 study completion

Safety & Tolerability

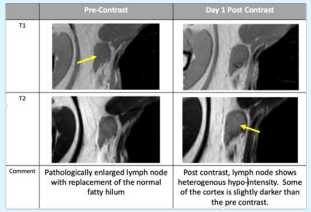
- A Safety Review Committee (SRC) reviewed safety data following enrollment of patients (N=13)
- No dose-limiting toxicities reported.
- Injection Site Reactions (ISR) – majority reported as mild or moderate, mostly discoloration at the injection site.
- No imaging agent or procedure related adverse events (Aes) reported.

MRI Imaging Results

- MRI measurements were conducted using a 1.5T or 3T clinical scanner with a standardized 20-minute breast imaging protocol of the ipsilateral axillary region.*
- A central radiology group was used to evaluate all patient images and compare pre-dose images to post-dose images. Nodes were assessed by both conventional radiological measures such as size and morphology as well as for changes in contrast intensity. A 30% change in contrast intensity (as observed by the radiologist) between pre- and post-dose images was considered sufficient to have observable presence of nanoparticles.
- Nodes were scored as "suspicious", or "normal" or "indeterminate" both pre-dose and post-dose.



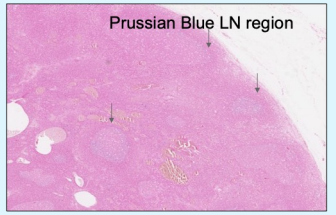
- Central Radiologists reported interpretable contrast change in post dose images for both normal and enlarged nodes vs. pre-dose images in eight (8) of thirteen (13) subjects.
- Post-dose normal nodes displayed a uniformly dark contrast (right panel) whereas post-dose enlarged metastatic nodes (below panel) showed a central heterogeneous hypointensity.
- There was no intensity change from post-dose Day 2 to Day 4

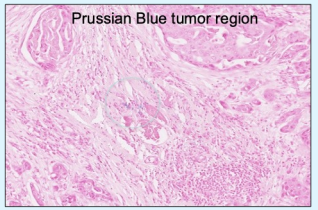


- In three (3) subjects, radiologists utilized pre-dose vs. post-dose contrast as an aid in resolving nodal status of "indeterminate" nodes (ex.: above panel)
- In 5 subjects, post-dose images were not interpretable - excess susceptibility in two (2) and lymphatic invasive tumors limiting particle drainage in three (3) others.

Tissue Specimens

Biopsy extraction of nodal tissue was possible in 12 out of the 13 patients in the study. HER2, IHC and Prussian Blue staining were performed on available tissue samples. Out of the 12 patients, malignant nodes were identified in pathology in 10 patients. HER2 and IHC staining results were positive in all tested samples. Prussian blue stain, which is sensitive for Fe, was positive for uptake of the agent in 11 out of the 12 patients' sample. Based on the pathologist's assessment, the Prussian blue stain's association of iron with tumor cells was negligible in 10 out of these 11 patients and minimal in 1 patient, making the interpretation of agent binding to tumor cells challenging.





Histology slides from Subject 2 showing Prussian blue stains in the lymph region (left panel marked by arrows) and in the tumor region (right panel marked by a blue circle).

Clinical Concordance

In eight (8) out of thirteen (13) patients, MRI-based assessment of pre- vs. post-MSH2IA injection was possible. There were image artifact issues or imaging agent uptake issues in the remaining 5 patients. On a direct comparison between standard of care (SOC) axillary ultrasound imaging, MRI assessment of post-dose imaging performed similar or better in all 8 patients. While comparing the post-dose images with the pre-dose images (equivalent to conventional MR imaging), the administration of MSH2IA provided better clarity in resolving indeterminate nodes, falsely called normal, and suspicious nodes.

Patient	SOC Nodal Imaging History (AxUS)	Pre-MSH2IA Assessment	Post-MSH2IA Assessment	Pathology Assessment
1	2 Suspicious Nodes	4 Suspicious Nodes	3 Suspicious 1 Normal	Positive
2	3 Suspicious Nodes	2 Suspicious Nodes 2 Indeterminate Nodes	2 Suspicious Nodes 2 Normal Nodes	Positive
3	1 Suspicious Node	2 Suspicious Nodes	2 Suspicious Nodes	Positivize
4	0 Suspicious Nodes	1 Suspicious Node 1 Normal Node	2 Suspicious Nodes 1 Normal Node	Negative
5	1 Suspicious Node	1 Suspicious Node 1 Normal Node	1 Suspicious Node 1 Normal Node	Positive
6	1 Suspicious Node	1 Suspicious Node	1 Suspicious Node	Positive
7	2 Suspicious Nodes	4 Suspicious Nodes	4 Suspicious Nodes	Positive
8	2 Suspicious Nodes	1 Suspicious 1 Intermediate; 1 Normal	3 Suspicious Nodes	Positive

Conclusions

On a comparison of post-MSH2IA imaging data with pathology, 7 out of the 8 patients with suspicious nodes were also positive by pathology. Based on these comparisons between SoC Axillary Ultrasound (AxUS) imaging and pre-dose imaging along with patient-level concordance with pathology, there is enough data to qualitatively conclude that MSH2IA aids in the identification of axillary lymph nodes and the discrimination of tumor containing lymph nodes from normal lymph nodes, without any safety concerns for the patients.