

# Safety of $^{188}\text{RE}$ ]Re-Imdendrim in the Treatment of Tumor Indications

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## Abstract

The detection of intraoperative stroke is paramount for enhancing patient outcomes during major vascular surgical procedures. Prior studies have demonstrated that alterations in cerebral blood flow (CBF) resulting from surgical interventions can be identified through a variety of neuromonitoring techniques, including electroencephalography, neurophysiological evoked potential assessments, transcranial Doppler ultrasound, and near-infrared spectroscopy. In this report, we present a case involving an open repair for type B aortic dissection that was complicated by extensive, multifocal cerebral infarctions. A notable intraoperative decline in the Patient State Index (PSI) and a concomitant rise in the Suppression Ratio (SR) were observed immediately following the transition of bypass modalities. This decline in PSI did not recover by the conclusion of the surgical procedure, despite only minor fluctuations in blood pressure and cerebral oximetry. Continuous monitoring of the PSI may facilitate the early detection and differentiation of intraoperative strokes, even in the absence of compromised CBF.

**Kew Words:** autism spectrum disorder; cognitive epileptiform disintegration; evoked cognitive potentials; fractional anisotropy; diffusion tensor MR imaging; standardized psychiatric diagnostic methods

## Introduction

In 2022, the global incidence of cancer reached 20 million cases, with 9.7 million deaths. The escalating global burden of cancer warrants attention worldwide[1]. Thus far, curative resection remains the most effective treatment for tumors[2]. However, due to delayed diagnosis and patient factors such as age, frailty, and comorbidities, the proportion of patients eligible for surgical resection is not high[3-5]. Additionally, the recurrence rate after tumor resection remains high[6]. Conventional chemotherapy and radiotherapy have suboptimal efficacy[7-9]. In recent years, advancements in nuclear technology have led to the emergence of

exciting radioactive drugs, which demonstrate high efficacy in cancer imaging and treatment. These drugs offer a promising therapeutic strategy for challenging-to-operate tumors and tumor resistance issues[10-12].

Early radioactive drugs, such as I-131 potassium iodide compounds (radioiodine therapy, RIT), have been extensively employed in clinical practice, with considerable success in the treatment of thyroid cancer[13-14]. I-131 is the active ingredient in RIT, which employs the specific uptake of iodine by thyroid cancer cells to achieve targeted radiotherapy for thyroid cancer[15]. Nevertheless, with a half-life of 8.05 days[16], I-

131 necessitates a lengthy treatment cycle. The systemic radiation therapy feature of RIT may potentially result in damage to organs and tissues outside the thyroid[17].

[<sup>177</sup>Lu]Lu-PSMA-617, which has been designated as a breakthrough therapy by the FDA in recent years, is a small molecule radiolabeled with PSMA (prostate-specific membrane antigen)[18]. It is designed to target prostate cancer cells that express PSMA. The radiopharmaceutical delivers <sup>177</sup>Lu to prostate cancer cells expressing PSMA, inducing apoptosis through  $\beta$  radiation, thereby achieving targeted radiotherapy[19]. However, [<sup>177</sup>Lu]Lu-PSMA-617 is primarily indicated for the treatment of PSMA-positive prostate cancer, with limited efficacy in PSMA-negative patients. The range of indications is relatively narrow[20].

Radioembolisation is a locally administered arterial route therapy that utilises tumor vascular proliferation to deliver high-dose radiation therapy. This method has been used in hepatocellular carcinoma (HCC) treatment[21-22]. Radioembolisation devices consist of 20-40 $\mu$ m beads, with yttrium-90 (<sup>90</sup>Y) integrated into a glass or resin. <sup>90</sup>Y emits  $\beta$  rays with a physical half-life of 64 hours. Microspheres carrying [<sup>90</sup>Y] (20-40 $\mu$ m) are capable of killing tumor cells through embolisation, but cannot diffuse into other areas of the tumor. Consequently, in cases of a large tumor volume, other tumor regions remain untreated[23-26].

In this context, to address some of the current issues faced by radiopharmaceuticals, we have developed a liquid, non-embolic, in-situ tumor treatment method using fifth-generation dendritic polylysine (DGL) as a scaffold to transport nitroimidazole complexes chelated with rhenium-188 (<sup>188</sup>Re). By injecting [<sup>188</sup>Re]Re-ImDendrim directly into the tumor, utilizing the high affinity of nitroimidazole for hypoxic tumor cells, <sup>188</sup>Re carried by [<sup>188</sup>Re]Re-ImDendrim is selectively absorbed by hypoxic tumor cells. Subsequently, the nano carrier DGL delivers <sup>188</sup>Re throughout the entire tumor, emitting  $\beta$  rays to kill tumor cells.

This approach represents a departure from the conventional paradigm of single-indication nuclear medicine treatment, with the potential to address the treatment of all hypoxic solid tumors. It offers a new targeted anticancer drug for the in-situ treatment of primary and metastatic tumors.

## Materials And Methods

### Trial Oversight

The multi-center clinical trial of the new technology for targeted cancer therapy, "Nano Gun," is an Investigator-Initiated Trial (IIT) initiated by researchers and conducted in Shanghai, China. The trial design and baseline characteristics of patients were developed by the research committee. The trial was designed and overseen by a steering committee, and received funding support from the Science and Technology Commission of Shanghai Municipality, China (Project name: Multi-center clinical trial of the new technology "Nanogun" for targeted tumor treatment. Project number is: 19411951100). The funder had no role in the design or conduct of the trial, nor did they participate in data collection or analysis, manuscript writing, or the decision to submit for publication. The trial protocol has been approved by the ethics committees of Shanghai East Hospital, Xinhua Hospital, and Fudan University Shanghai Cancer Center in China, and is available on (the Supplementary Appendix1). The trial is conducted in accordance with the principles of the Helsinki Declaration. The authors are responsible for the accuracy and completeness of the data and analysis, as well as the fidelity of the trial and this report to the protocol.

### Sample Population

From June 2023 to February 2024, all patients enrolled in the [<sup>188</sup>Re]Re-Im Dendrim trial were screened at Shanghai East Hospital, Fudan University Affiliated Cancer Hospital, Xinhua Hospital, and Shanghai Sixth People's Hospital in Shanghai, China. Eligible patients were males and females aged 18 years and older with histologically or cytologically

confirmed malignant solid tumors, either primary hepatic or pulmonary malignancies, or metastatic malignancies to the liver or lungs, as determined by CT or MRI, with a single tumor diameter >1.0 cm. Patients who had previously failed standard treatment regimens (defined as standard first- or second-line chemotherapy  $\pm$  targeted therapy) were eligible. These patients had an Eastern Cooperative Oncology Group performance status score of  $\leq 2$  and an expected survival of  $\geq 12$  weeks. Baseline assessments were conducted for all patients prior to treatment.

The decision to treat on compassionate grounds was made by an interdisciplinary tumor board; patients gave written informed consent. This retrospective analysis meets the criteria for retrospective studies of the local ethics committee.

### Preparation of [<sup>188</sup>Re]Re-ImDendrim

[<sup>188</sup>Re]Re-ImDendrim consists of three components: a therapeutic agent utilizing <sup>188</sup>Re's  $\beta$ -radiation, an imidazolic ligand targeting cancer cells, and a nanovector (Dendrimer G5) facilitating localized bioavailability. (the Supplementary Appendix2)

<sup>188</sup>Re is rinsed and labeled in the GMP manufacturing Workshop of radiopharmaceuticals. In the production process, the <sup>188</sup>Re rinsed from the tungsten-rhenium generator is mixed with the acid solution, following this, mixture is introduced into the reducing agent at 72°C for 20 minutes under carbon monoxide. The dendrimer's coupling with <sup>188</sup>Re occurs followed as the content of vial "B" (ligand) is introduced into the mixture, and incubation at 72°C for one hour. Finally, the radiolabelling success is assessed by the radiopharmacist using TLC with radio detection to confirm a labeling percentage of approximately 85% or higher, with any unlabelled compound identified as free reduced Rhenium 188. If the radiolabeling is successful, the final product is inserted into the sealed vial. The 188Re-ImDendrim vial is placed inside a radiation-shielded (the Supplementary Appendix 3).

### Data Analysis

The administration of the [<sup>188</sup>Re]Re-ImDendrim drug was conducted via percutaneous puncture under CT navigation. To mitigate radiation exposure to medical personnel, radiation-proof syringes were utilized, and patients were required to wear lead clothing. For whole-body SPECT using [<sup>188</sup>Re]Re-ImDendrim, data acquisition started 60 minutes after treatment. Sequential SPECT scans were conducted at 1h, 6h, 24h, 48h, 72h, and 96h post-administration to assess the uptake and retention of [<sup>188</sup>Re]Re-ImDendrim within the tumor and its systemic distribution within the patient. Image reconstruction and image analysis were performed using software provided by the Siemens. (Model: Siemens healthineers Symbia Intevo ® 16).

Throughout the course of clinical trials, surveillance was conducted to monitor and document adverse events (AEs) and serious adverse events (SAEs). The Eastern Cooperative Oncology Group Score (ECOG) Performance Status was assessed prior to each treatment session to gauge the patient's functional status. Each patient enrolled in the study received either all available medications or lacked alternative treatment options for their particularly challenging medical condition.

### Statistical Analysis

Safety was assessed through descriptive analysis. Statistical analysis was performed using SPSS (IBM SPSS Statistics 22.0).

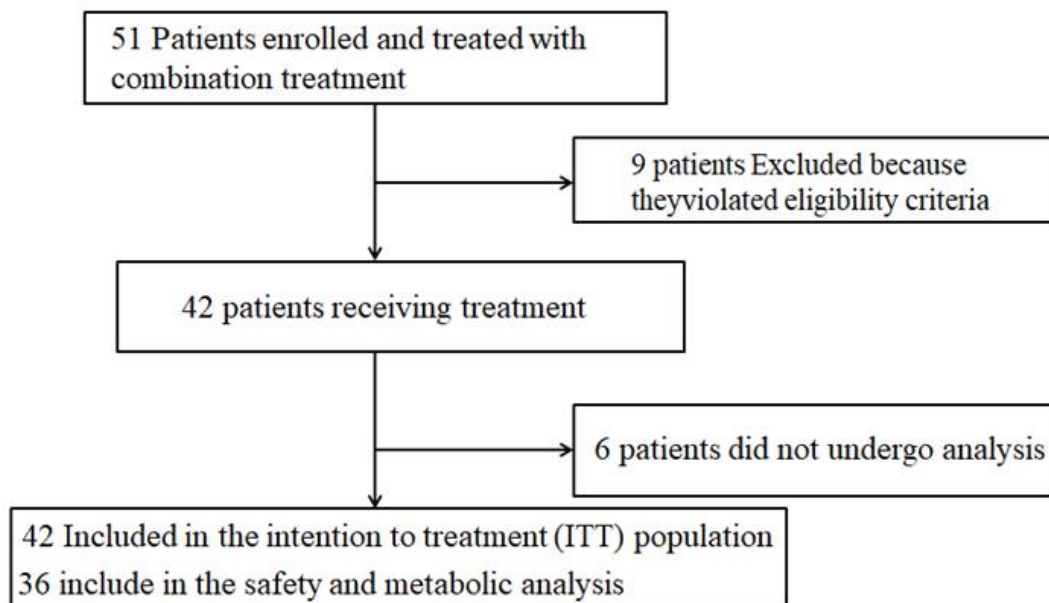
## Result

### Demographic and clinical characteristics

A cohort of 51 patients were screened for participation in the study at Shanghai East Hospital, Fudan University Affiliated Cancer Hospital, and Shanghai Sixth People's Hospital in Shanghai China. 42 patients were successfully screened and enrolled, while the remaining 9 patients failed to be screened for the following reasons: no appropriate treatment lesions

(4 cases), ineligible examination results (4 cases), and withdrawal of informed consent by family members (1 case). Among the 42 treated patients, 4 patients were lost to follow-up and returned to their local hospitals for treatment, and 2 patients refused subsequent treatment, resulting in a total of 42 patients included in the intention-to-treat (mITT) population analysis. This group of 36 patients underwent safety analysis (Figure 1). The ECOG score of these patients did not exceed 2 points, with only one case exhibiting an ECOG score of 3. 83.3% of patients had

experienced treatment failure with prior standard protocols (defined as third line or above of chemotherapy±targeted therapy). Among the 36 cases of efficacy analysis, the treatment target lesions were mainly liver and lung tumors, accounting for 83.3% of the population. The median age was 59 years, with an age range of 26-78 years, 74% of patients are male (Table 1). Baseline assessments were conducted for all patients prior to treatment.



**Figure 1:** Flowchart of investigations study of 188Re-ImDendrim

Patient No.	Age, y	Gender	Primary tumor	Treatment lesion	ECOG Performance Status
1	60	Female	Colon cancer	Lung	1
2	58	Male	hepatic carcinoma	liver	1
3	78	Male	Lung cancer	Lung	2
4	68	Male	Gastric cancer	liver	1
5	69	Male	Gastric cancer	Inguinal lymph node	1
6	62	Male	Rectal cancer	Lung	2
7	52	Female	Lung cancer	adrenal gland	1
8	36	Male	osteosarcoma	Iliac soft tissue	1
9	43	Male	Colon cancer	liver	1
10	75	Female	Intrahepatic cholangiocarcinoma	liver	1
11	70	Male	Colon cancer	Lung	1
12	58	Female	ampulla cancer	liver	1
13	26	Male	Synovial sarcoma	chest wall	1
14	65	Female	Lung cancer	liver	2
15	42	Male	Colon cancer	liver	1
16	67	Male	Rectal cancer	liver	1
17	50	Male	Intrahepatic cholangiocarcinoma	Lung	1
18	35	Male	renal carcinoma	Left hip	1

19	76	Male	Lung cancer	Lung	3
20	52	Female	Lung cancer	adrenal gland	1
21	61	Male	Rectal cancer	liver	1
22	53	Female	Rectal cancer	Lung	1
23	53	Female	Rectal cancer	Lung	1
24	69	Male	Rectal cancer	Lung	1
25	53	Male	Lung cancer	Lung	1
26	65	Male	Rectal cancer	liver	1
27	47	Male	Gastric cancer	liver	1
28	74	Male	breast cancer	Lung	1
29	74	Male	Lung cancer	Lung	1
30	59	Male	hepatic carcinoma	liver	1
31	70	Male	Colon cancer	liver	1
32	61	Male	renal carcinoma	Lung	1
33	55	Female	Colon cancer	liver	1
34	45	Male	Rectal cancer	liver	1
35	55	Male	Colon cancer	liver	1
36	74	Female	Lung cancer	Lung	2

**Table 1:** Patient Characteristics**[<sup>188</sup>Re]Re-ImDendrim production and quality inspection**

Following the radiolabeling of the [<sup>188</sup>Re]Re-ImDendrim with <sup>188</sup>Re via elution from a tungsten-rhenium generator in a GMP pharmaceutical factory, the labeling efficiency of the [<sup>188</sup>Re]Re-ImDendrim was evaluated using thin-layer chromatography (TLC). The results demonstrated a labeling efficiency of over 85% and the relative fluorescence value (RF) was found to be between 0.1 and 0.9. A comprehensive physical and chemical identification, as well as microbial testing, of [<sup>188</sup>Re]Re-ImDendrim was conducted in accordance with the established quality control manual. (Supplementary Data).

**Treatment safety**

All 36 efficacy-evaluated patients experienced at least one treatment-related adverse event (TRAE); the most common TRAEs were fatigue

(47.2%, n=17), pain (44.4%, n=16), and nausea (30.6%, n=11), most of which were deemed related to invasive treatment. Grade 3 TRAEs occurred in 2 cases (5.6%), one of which was hematemesis during treatment, and postoperative gastroscopy confirmed it to be esophageal variceal bleeding, which was a past medical history of the patient. The other case was pneumothorax during follow-up after local treatment of pulmonary metastases, which improved following closed chest drainage and was related to the puncture process. No TRAEs of grade 4 or higher were observed in the population (Table 2).

The study indicates the absence of typical radionuclide therapy-related toxicities, such as hematologic toxicity, skin and mucosal damage, and organ function impairment. Some atypical manifestations associated with radiopharma treatment include fatigue, nausea, dizziness, etc., which typically resolve within 1-2 days of observation.

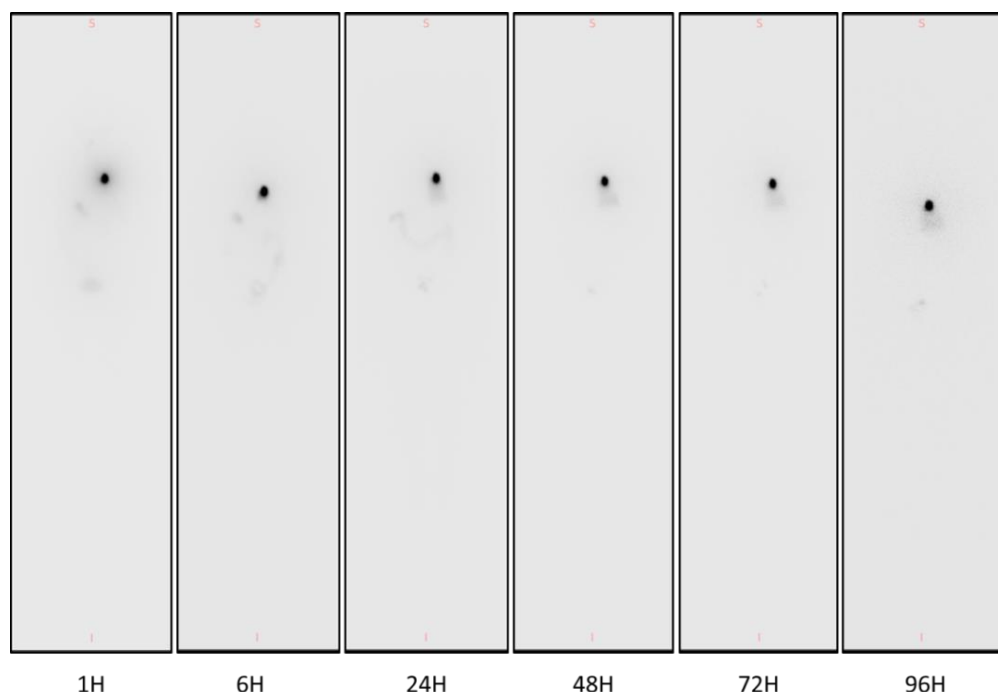
NO. (%) (N=36)			
TRAES	All grades	Grade 1-2	Grade ≥3
Fatigue	17(47.2)	17(47.2)	0
Pain	16(44.4)	16(44.4)	0
Nausea	11(30.6)	11(30.6)	0
dizziness	9(25)	9(25)	0
bleeding from different parts of the body	8(22.2)	7(19.4)	1(2.8)
hypertension	7(19.4)	7(19.4)	0
pneumothorax	4(11.1)	3(8.3)	1(2.8)
fever	3(8.3)	3(8.3)	0
hypotension	2(5.6)	2(5.6)	0
electrolyte imbalance	2(5.6)	2(5.6)	0
vomiting	2(5.6)	2(5.6)	0

**Table 2:** Summary of treatment-related adverse events

### Biodistribution and metabolism

The biodistribution of [ $^{188}\text{Re}$ ]Re-ImDendrim within the patient's body post-treatment was preliminarily assessed. Whole-body SPECT scans were conducted on the patients. Imaging was Captured at 1, 6, 24, 48, 72, and 96 hours post-administration, indicating predominant distribution within the treatment lesions with minimal imaging observed in other

tissues. Given the renal excretion of  $^{188}\text{Re}$ , trace amounts accumulated in the intestines and bladder. At 1h, 6h, and 24h, small quantities of  $^{188}\text{Re}$  were detected in the intestines and bladder; however, by 48h, all nuclides were observed to be concentrated within the treatment lesions (Figure 2). This underscores the high uptake of [ $^{188}\text{Re}$ ] Re-ImDendrim by treatment lesions, while normal organs such as the brain, heart, liver, spleen, and muscle exhibited extremely low uptake rates.



**Figure 2:** Biodistribution of nuclide after [ $^{188}\text{Re}$ ] Re-ImDendrim treatment

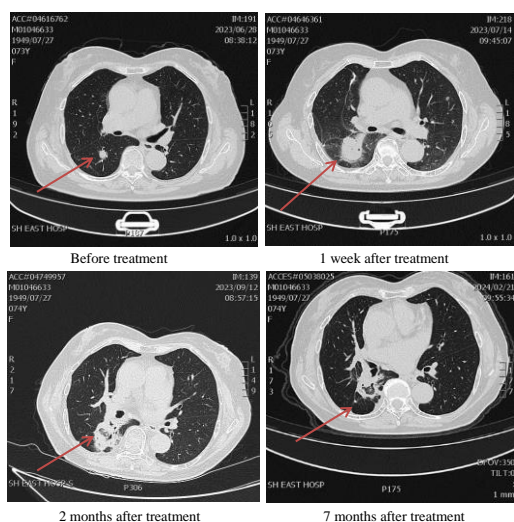
### Treatment efficacy

As of the data cutoff date, among the two patients with partial remission, one had lung metastasis from lung cancer, and despite disease progression in lung lesions during targeted treatment, consolidation was observed in the treated target lesion area following [ $^{188}\text{Re}$ ]Re-ImDendrim therapy. Subsequent 7-weeks follow-up demonstrated gradual lesion reduction, leading to partial remission (Figure 3A). The other patient with partial remission of the target lesion had liver metastasis from colorectal cancer. After standard first-line and second-line treatments, two liver lesions

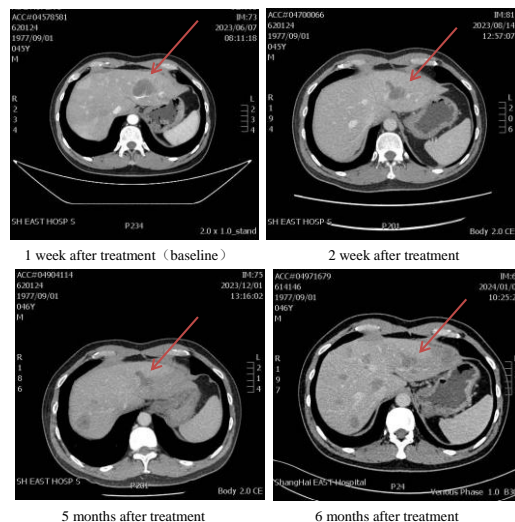
progressed compared to baseline. However, one lesion showed reduced size during follow-up at 2 months [ $^{188}\text{Re}$ ]Re-ImDendrim post-treatment, resulting in partial remission (PR). Subsequent follow-up at 5 months revealed progression in other liver lesions and appearance of new lesions, while the target lesion remained stable (Figure 3B).

In other efficacy evaluation instances, significant reduction in blood supply was observed in target lesions treated with the [ $^{188}\text{Re}$ ] Re-ImDendrim, displaying low-density shadows within the tumor, indicating reduced tumor activity (Figure 3C).

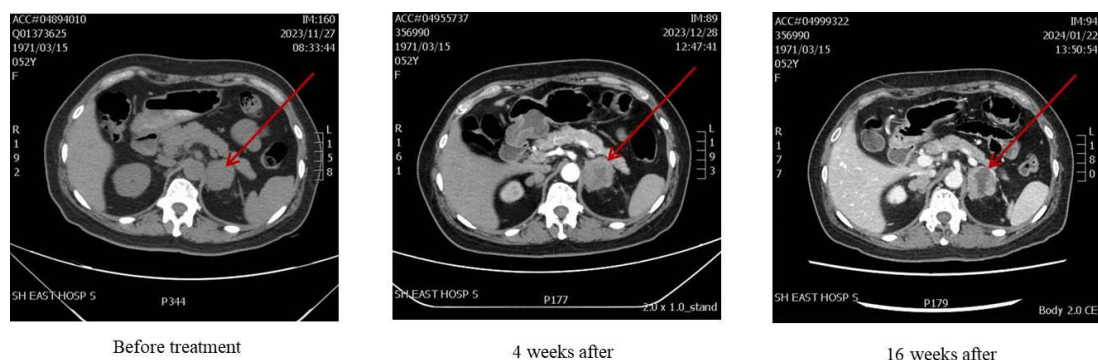
A



B







**Figure 3:** Changes in lesions after  $[^{188}\text{Re}]\text{Re-ImDendrim}$  treatment in typical cases. The red arrow indicates the injection site

## Discussion

The global attention being directed towards radiopharmaceuticals for cancer treatment is a noteworthy phenomenon. In this study, researchers completed the preparation and labelling of  $[^{188}\text{Re}]\text{Re-ImDendrim}$  within two hours and injected it directly into the patient's tumor through in situ puncture. The procedure is straightforward and relatively rapid. Following the direct injection of  $[^{188}\text{Re}]\text{Re-ImDendrim}$  into the tumor through puncture, the radioactive drug is almost concentrated in the target lesion throughout the entire energy delivery period. This is consistent with the results of our previous preclinical study[27]. The patients enrolled included a variety of solid tumors, including colorectal cancer, lung cancer, liver cancer, breast cancer, and soft tissue sarcoma. Following the administration of the  $[^{188}\text{Re}]\text{Re-ImDendrim}$  treatment, the safety of the patients was evaluated, and no adverse event (AE) of grade 4 or higher was identified. The actual analysis of the adverse events (AEs) that occurred during treatment demonstrated that they were not related to the  $[^{188}\text{Re}]\text{Re-ImDendrim}$  treatment.

Due to the half-life characteristics of radioactive drugs, it is important to shorten the preparation and injection time. QuiremSpheres™ is an excellent internal radiation therapy for liver cancer. It can be imaged not only by SPECT but also by MRI. However, the preparation process is too complicated, which limits its universal use[28-29].  $[^{188}\text{Re}]\text{Re-ImDendrim}$  uses a labelling kit to label within 2 hours. The steps are simple and suitable for wide application in nuclear medicine departments of different hospitals.  $[^{188}\text{Re}]$  Rhenium is an isotope with a half-life of 16.9 h. Compared to  $[^{90}\text{Y}]$  Yttrium, its short half-life ensures high dose rate delivery. At the same time, its  $\beta$  ray energy is higher, which is more conducive to disrupting the DNA chain of tumor cells[30]. Currently, the more commonly used  $[^{90}\text{Y}]$ -Spheres is used to deliver embolic internal radiotherapy for liver cancer via angiography. After treatment, whether it is bremsstrahlung SPECT/CT imaging or PET/CT imaging, its clinical application still faces many challenges[31-32]. The  $[^{188}\text{Re}]$  emits low-abundance  $\gamma$  rays of 155KeV (15%), which is very effective for imaging and dose calculation. It can provide additional diagnostic information, monitor and evaluate radiation dose in real time, and predict treatment effects, making it easy to achieve integrated diagnosis and treatment of cancer patients during the treatment process[33-34].  $[^{188}\text{Re}]$ -complexed nitroimidazole has the ability to target hypoxic cells[35], so local treatment of liver cancer does not require vascular embolization and can be injected directly into the tumor. Solid tumors are highly hypoxic and the nitroimidazole property of targeting hypoxic cells opens up the possibility of  $[^{188}\text{Re}]\text{Re-ImDendrim}$  for local treatment of other solid tumors. It exhibited good targeting in the various indications included in this study. SPECT showed that small amounts of  $[^{188}\text{Re}]\text{Re-ImDendrim}$  were distributed in the intestine and bladder at 1h, 6h and 24h; at 48h all nuclides were found to concentrate in the treatment lesions. The treatment effect of 3 typical patients was demonstrated that the blood supply in the target lesions was significantly reduced, low density shadows in the tumor body and reduced tumor activity were observed, and the treatment effect was evident. In addition to the powerful  $\beta$ -radiation energy of the  $[^{188}\text{Re}]$ ,

the nanomaterial DGL also helps to enhance the efficacy of radioactive drugs. As a carrier of  $[^{188}\text{Re}]$  and nitroimidazole complex, DGL has been shown to have excellent cell transfection function and is widely used to deliver DNA and RNA to tumor cells and other cells[36-37]. The  $[^{188}\text{Re}]\text{Re-ImDendrim}$  is injected into the tumor through puncture, and the nitroimidazole it carries targets hypoxic tumor cells. The nanocarrier DGL then exerts its delivery ability to deliver  $[^{188}\text{Re}]$  into the tumor cells, and uses the high-energy  $\beta$  rays of  $[^{188}\text{Re}]$  to interrupt the DNA chain of tumor cells, continuously killing the tumor. The cell transfection function of DGL not only delivers the nuclide  $[^{188}\text{Re}]$  deep into the tumor, resulting in the optimisation of the radiotoxicity effect of local treatment, which is beneficial for the killing of larger tumors, but also its transfection function may promote the targeting of  $[^{188}\text{Re}]\text{Re-ImDendrim}$  and increase safety[38-39]. The distribution of  $[^{188}\text{Re}]$  in the body, as observed by SPECT imaging, may be related to the transfection of  $[^{188}\text{Re}]$  into tumor cells by DGL. Another notable feature of DGL is that it is non-immunogenic, which provides a favourable safety profile for  $[^{188}\text{Re}]\text{Re-ImDendrim}$ [40]. No adverse event (AE) of grade  $\geq 4$  was observed in this clinical study, and the actual analysis of AEs that occurred during treatment demonstrated that they were not related to  $[^{188}\text{Re}]\text{Re-ImDendrim}$ .  $[^{188}\text{Re}]$  is gaining increasing attention as a potential excellent medical nuclide. There have been numerous clinical studies on  $[^{188}\text{Re}]$  conducted globally[41-42]. Nitroimidazole has been extensively utilized as an antibacterial drug in clinical settings[43-44]. Consequently, the safety of the  $[^{188}\text{Re}]\text{Re-ImDendrim}$  radiopharmaceutical employed in this project has been demonstrated to be consistent in both preclinical animal and clinical studies[27].

In this research we conducted a clinical trial of  $[^{188}\text{Re}]\text{Re-ImDendrim}$  in 36 patients who had failed standard treatment protocols, assessing its biodistribution and safety in patients. It has been demonstrated to possess three key advantages:

The  $[^{188}\text{Re}]\text{Re-ImDendrim}$  is directly injected into the tumor, where the  $[^{188}\text{Re}]$  complexes with the nitroimidazole ligand carrier, which is preferentially absorbed by hypoxic cells without embolisation.

The  $[^{188}\text{Re}]\text{Re-ImDendrim}$  targets and remains at the site, thereby optimising the effects of radiation toxicity, while demonstrating good safety.

$[^{188}\text{Re}]$  is an isotope with a half-life of 16.9 hours, exhibiting greater  $\beta$  radiation energy compared to  $[^{90}\text{Y}]$ , with gamma radiation at 155-KeV (15%). This facilitates the seamless integration of diagnosis and treatment.

It should be noted that this study is subject to certain limitations. The clinical study protocol defines the patient flow, including the baseline assessment and dosimetry. However, the actual application process may vary according to the individual patient's condition. This study initially assesses the safety and distribution of  $[^{188}\text{Re}]\text{Re-ImDendrim}$ . The principal challenges facing future studies include the definition and validation of the dose threshold for  $[^{188}\text{Re}]\text{Re-ImDendrim}$ , the

recruitment of a larger number of patients and the inclusion of additional tumor indications in order to further evaluate the safety and efficacy of the treatment. Of the 3 patients on high doses, 1 was PR and the rest were SD, and none had adverse reactions. This provides a basis for dose exploration in future clinical trials.

## Conclusion

The [188Re]Re-ImDendrim represents a significant departure from the prevailing paradigm of single-indication treatment in targeted radionuclide therapy. The treatment process is straightforward, conducive to clinical treatment, safe, and effective. This new targeted anticancer drug will provide a new treatment option for in situ treatment of primary and metastatic tumors, as well as multiple tumor indications. It is a complement to the existing radioactive drug treatment of tumors. Clinical studies have demonstrated the safety and therapeutic potential of this promising local therapeutic radiopharmaceutical.

## Disclosure

This work was supported by the Science and Technology Commission of Shanghai Municipality, China (Project name: Multi-center clinical trial of the new technology “Nanogun” for targeted tumor treatment. Project number is: 19411951100). No other potential conflict of interest relevant to this article was reported.

## Statement

Informed consent was obtained for experimentation with human subjects.

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