行政院原子能委員會

委託研究計畫研究報告

奈米標靶藥物人體最大耐受劑量及安全性臨床試驗

Re-188-liposome Nanoparticle Phase I Study to Determine the Maximum Tolerated Dose and Safety

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目　錄

中文摘要

微脂質體作為化療藥物的輸送系統已被廣泛用於治療癌症。加上藥物的脂質體較易分布於具滲漏性的腫瘤相關血管，通過一個所謂"增強通透性和保留(Enhanced Permeation Retention, EPR)"的過程而達到脂質體藥物累積至腫瘤的優勢，如此可改善常規化療藥物的藥理學特性。核研所發展之脂質體包覆銖-188 藥物(Re188-liposome)已在數個動物癌症模型中顯現療效。根據這些令人振奮的腫瘤與毒性測試實驗數據，核研所已在過去兩年利用脂質體包覆銖-188 藥物進行一個探索性新藥研究以評估其體內分佈、藥物動力學及安全性，並獲得令人振奮的結果。其中 12 例可評估患者中，兩位顯示腫瘤反應。基於此正面的成果，我們將進行第 I 期臨床試驗，以確定脂質體包覆銖-188 藥物最大耐受劑量（MTD）和安全性，受試病人將為傳統治療失敗之轉移性癌症患者。

關鍵詞：銖-188 (Re188);脂質體(liposome); 新藥研究(investigational new drug); 藥物動力學 (pharmacokinetics); 最大耐受劑量（MTD）

Abstract

Liposomes coupled with therapeutics are more easily distributed into leaky tumor-associated blood vessels, through so-called "enhanced permeation retention" (EPR), leading to preferable accumulation of liposomal drugs within tumor microenvironment. ^{188}Re-liposome is a novel liposomal therapeutic coupling radioisotope, ^{188}Re, developed by Institute of Nuclear Energy Research (INER). In preclinical studies, it displayed therapeutic effect on various tumor models. Given the encouraging results of preclinical efficacy and toxicity studies, an exploratory investigational new drug (eIND) study for evaluation of distribution, pharmacokinetics and safety of ^{188}Re-liposome had been conducted in the past two years. The eIND study had generated very encouraging results in the absence of significant toxicity. Among the 12 evaluable patients, two of them showed tumor response. Based on the positive results, a phase I trial to determine the maximum tolerated dose (MTD) and safety of ^{188}Re-liposome is proposed for treatment of metastatic cancer patients who failed or cannot tolerate standard chemotherapy.

Key words: Re188; liposome; investigational new drug; pharmacokinetics; maximum tolerated dose (MTD)

壹、計畫緣起與目的

Nanoscale liposomes as drug delivery systems containing chemotherapy drugs have been widely used for treatment of cancer. Many of the pharmacological properties of conventional chemotherapy drugs can be improved using this drug delivery system, which composed primarily of lipids and/or polymers. These novel therapeutic complexes are designed to improve the pharmacokinetics (PK) and biodistribution (BD) of the coupled chemotherapy drugs. As compared with conventional chemotherapy, circulation of liposome coupled chemodrugs could be prolonged. Moreover, the liposome coupled drugs could be redirected to relatively leaky tumor-associated blood vessels, leading to superior accumulation in tumors via a process often referred to as the "enhanced permeability and retention" (EPR) effect. The most notable examples are the pegylated liposomal doxorubicin, which is approved for cancer treatment with substantial decrease in toxicity as compared to doxorubicin free drug.

Although liposomal doxorubicin displayed superior localization of doxorubicin in relatively leaky tumor microenvironment, killing of tumor cells required release of this chemodrug and the coupling to its target, DNA. To take advantage of the EPR effect of liposomal drug

and the cytotoxic effect of radiation even in the absence of internalization of liposome by cancer cells, we had developed a liposomal therapeutics, ^{188}Re-BMEDA-labelled pegylated liposome (^{188}Re-liposome), and examined its biodistribution, pharmacokinetics and cytotoxic effects, compared with unencapsulated ^{188}Re-BMEDA control in a subcutaneous murine C26-colon tumor model. MicroSPECT/CT images were evaluated to characterize the distribution and tumor targeting of ^{188}Re-liposome in mice. The highest uptake of liposome in tumors was 3.62% +/- 0.73% at 24 h after ^{188}Re-liposome administration, and the tumor to muscle ratio of RBLPL was 7.1-fold higher than that of ^{188}Re-BMEDA. The results of the pharmacokinetics revealed that the area under the tissue concentration-time curve (AUC) of ^{188}Re-liposome was 4.7-fold higher than that of unencapsulated ^{188}Re-BMEDA. These results suggested the potential benefit and advantage of ^{188}Re-labeled nanoliposomes for imaging and treatment of malignant diseases.

Similar biodistribution and pharmacokinetics studies were also conducted in a C26 colon carcinoma ascites mouse model. The biodistribution studies indicated that the radioactivity in ascites was 69.96±14.08 percentage injected dose per gram (% ID/g) at 1h to

5.99±1.97% ID/g at 48 h after ip administration of ^{188}Re-liposome. The levels of radioactivity in tumor were progressive accumulation to a maximum of 6.57±1.7% ID/g at 24 h. The radioactivity of ^{188}Re-BMEDA in ascites reached the maximum level of 54.89±5.91% ID/g at 1 h and declined rapidly with time. Pharmacokinetic studies revealed that the terminal half-life, total body clearance and area under the curve of ^{188}Re-liposome were 5.3-, 9.5- and 9.4-fold higher than that of ^{188}Re-BMEDA in blood, respectively. These results suggested that the long circulation, bioavailability and localization of ^{188}Re-liposome in tumor and ascites sites, which also demonstrate that the ip administration of ^{188}Re-liposome is a potential multifunctional nanoradiotherapeutics and imaging agents on a C26 colon carcinoma ascites mouse model.

Most significantly, the therapeutic effects of ^{188}Re-liposome were explored on various tumor models, including subcutaneous inoculated murine CT26 and human LS-174T models as well as C26 colon carcinoma ascites mice model. ^{188}Re-liposome suppressed tumor growth and increased survival time of tumor-bearing mice. While comparing 5-FU with ^{188}Re-liposome, both delivered at 80% of MTD, ^{188}Re-liposome demonstrated superior anticancer effect and prolonged

survival time of either CT26- or LS-174T-bearing mice. Additionally, preclinical toxicity study performed by the research team at INER did not displayed discernible toxicity in both mice and rats. The dosimetry data of ^{188}Re-liposome regarding the distribution and absorbed radiation doses of tumor and normal tissues will be a great indicator for both potential therapeutic and side effects. The OLINDA/EXM program was adopted to calculate mean values of %IA/g for the organs in mice which were extrapolated to uptake in organs and tumor of various sizes of a 70 kg adult. The deduced absorption doses were about 20 mGy/MBq for 40-gram tumor and up to more than 100 mGy/MBq for small tumors (0.5 - 6 grams). Whereas, the deduced absorption doses of normal organs were well below the upper limits.

Based on the encouraging preclinical efficacy and toxicity results as well as favorable dosimetry data, INER had conducted a phase 0 exploratory clinical trial at Taipei Veterans General Hospital in 2012 and 2013. Total 14 patients were recruited and received injection of 3mCi of ^{188}Re-liposome. Two patients could not tolerate the fixed lying down position due to huge axillary mass and ascites, respectively. The remaining 12 evaluable patients did not experience any significant side effect. Quite intriguingly, two of the 12 patients displayed tumor

response. In light of the encouraging results from the phase 0 trial, it will be worthwhile to explore the potential toxicity and benefit of ^{188}Re-liposome in human clinical trial for treatment of patients with multiple metastases. Our team at Taipei Veterans General Hospital (TVGH) is collaborating with INER to develop a phase I trial plan to evaluate this novel therapeutics for determining the maximum tolerated dose (MTD) and safety in a dose-escalating trial. We had completed the trial design of which the protocol was conditionally approved by the IRB of TVGH and Taiwan FDA (TFDA). We are expecting to obtain official approval letter from TFDA soon and initiate the trial.

貳、研究方法與過程

This is an open-label, dose-escalation study carrying in the single-center. Patients with histologically confirmed diagnosis of primary solid tumor, and with pathologically or radiologically documented metastases, which are refractory to current standard/available therapies are eligible to participating in this study. Patients may have one or more measurable lesion(s) after resection or who are not suitable for complete curative resection, can be measured for efficacy evaluation.

Initially patients who are eligible to enroll in the study will receive a

low dose (14±1.4 mCi) ^{188}Re-BMEDA-liposome once for imaging analysis (Stage I) to determine tracer biokinetics to tumor and organs. Single-photon emission computed tomography (SPECT) imaging will be performed on 1, 4, 8, 24, 48 and 72hrs time points to observe dosimetry and biodistribution. Computed tomography (CT) scan will be performed in accordance with SPECT scan on the 24hrs post-injection for fusion image. Blood sampling will also be collected on the same time point for pharmacokinetic (before performing SPECT). Once imaging data are obtained, evaluation and calculation will continue and on Day 14, patients will be evaluated based on these imaging data and absorbed dose ratio, and calculate the maximum radiation dosimetry on tumor and critical organs. When the patient is qualified to show Tumor/Non-Tumor organ ratio > 2 on at least one measurable tumor in organ, as well Tu/liver 、Tu/lung ratio > 3, and Tu/red marrow ratio > 5, he/she can be entered to Stage II and receive therapeutic infusion after performing criteria screening, including laboratory tests on Day 21 in Stage I timeline. Patients will require to sign an inform consent form (ICF) and undergo criteria screening on Day 21±3 (Stage I) before receiving the Stage II therapeutic dosages. It has been suggested by TFDA that the administration of ^{188}Re-BMEDA-liposome (between

Stage I and II) must be at least 21 days apart. Once patients are receiving the therapeutic infusion dosage, the day will be counted as Stage II Day 0. On the contrary, if patients are not qualified (Tu/non-Tu ≤ 2, or Tu/liver、Tu/lung ratio ≤ 3, or Tu/red marrow ratio ≤ 5) on the evaluation day (Day 14), patients will continue to follow until Day 30±5 for safety evaluation and exit from the study. There would be no necessary to carry evaluations on Day 21 on patients who are unqualified. In note, the predicted radiation dosimetry for each critical organ (e.g, kidney, lung, liver, spleen, red marrow) will be calculated (please referring to Appendix II). If any critical organ shows tendency of over maximum tolerance radiation dosimetry before introducing the patient to receive therapeutic dosage (Stage II), the patient must be discontinued from the trial for safety concern. Moreover, 3 out of 15 patients will need to pass Stage I requisition (Tu/non-Tu organ ratio > 2 on at least one measurable tumor in organ, as well Tu/liver 、Tu/lung ratio > 3, and Tu/red marrow ratio > 5) successfully to perform each dose level cohort in Stage II in order to proceed the study. Patients who enter Stage II will be enrolled in a cohort of 3 patients for each dose level. Dose escalation will proceed sequentially between each dose. Each patient receives his/her therapeutic dose and observes for 2 weeks

before recruit the next patient. This applies in each dose level (6 dose level). Investigator is responsible to approve and recruit the next dose level patient until the cohort is completed and reviewed by DSMB in order to continue to the next cohort or action.

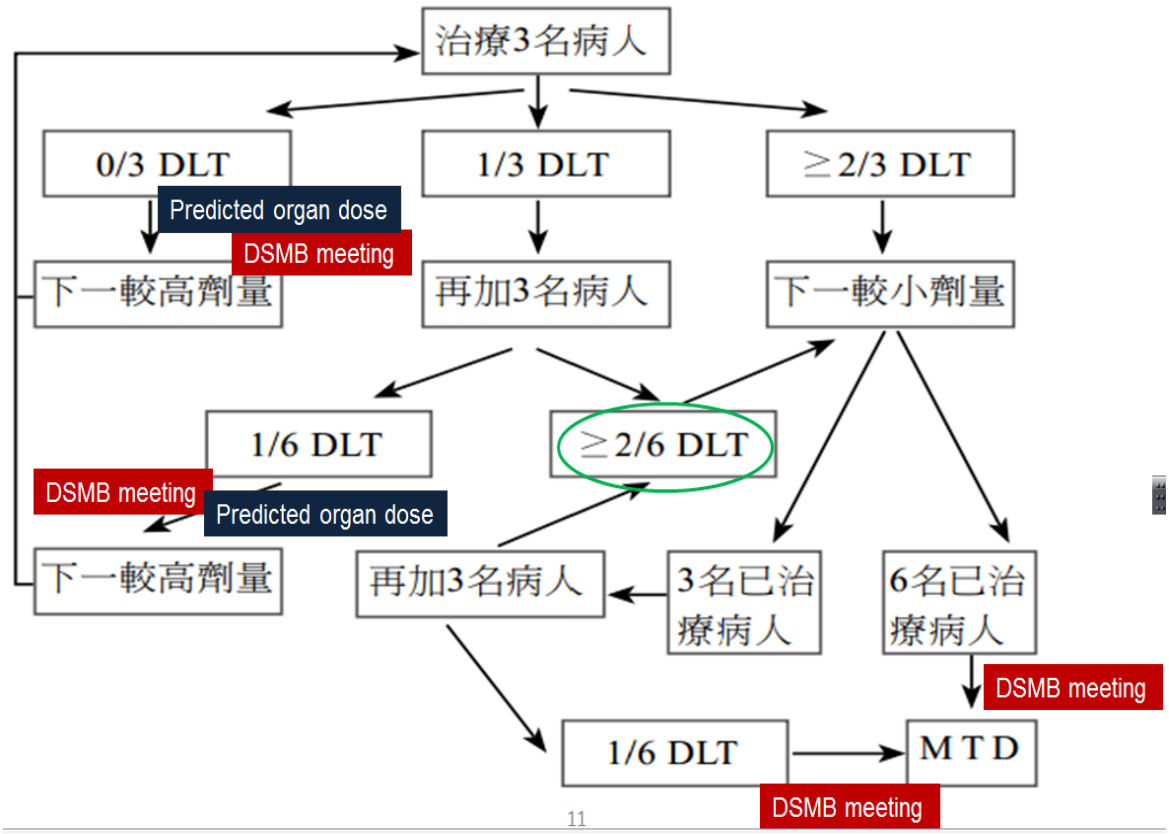
The protocol had been developed and conditionally approved by TFDA, which only requested some revisions. Dose escalation will proceed sequentially between each dose. Each patient receives his/her therapeutic dose and observes for 2 weeks before recruit the next patient.

Dose Level	Dose of ^{188}Re-BMEDA-liposome
Dose 1	0.42±0.04 mCi/kg
Dose 2	0.63±0.06 mCi/kg
Dose 3	0.84±0.08 mCi/kg
Dose 4	1.05±0.11 mCi/kg
Dose 5	1.26±0.13 mCi/kg
Dose 6	1.47±0.15 mCi/kg

After patient is qualified to show Tu/non-Tu > 2, , as well Tu/liver 、Tu/lung ratio > 3, and Tu/red marrow ratio > 5 on at least one measurable tumor at pre-treatment stage (Stage I), patient will enter Stage II and receive therapeutic dose, giving by a single administration by intravenous infusion less than 20 minutes (infusion pump rate: 30 ml/hr).

Dose limiting toxicity (DLT), defined as any of the following drug-related AEs (according to CTCAE v 4.03) which occur from the start of study (Stage I) till the end of study visit:

- Grade 4 neutropenia (defined as ANC <500mm3) present for more than 5 days or accompanied with fever (≥38.3˚C)
- Grade 4 thrombocytopenia (defined as platelet <25,000mm3) or grade 3 thrombocytopenia (platelet 25,000~ 50,000mm3) with significant bleeding.
- ≥ Grade 3 non-hematologic toxicity lasting over 24 hours, despite standard prophylaxis and/or treatment has performed (excluding alopecia and depilation)
- Grade 4 nausea and/or vomiting that lasts over 24 hours despite supportive treatment.



During the trial, we will assemble a DSMB(資料安全監測委員會)，composed of the experts who can objectively review the interim trial results and monitor any side effects associated with this trial. The meeting will be held at least two times during the trial.

We will work closely with the CRO designated by INER to monitor and record any side effects induced by this experimental drug. We will also continue analyzing the data and statistics regarding the dosimetry and pharmacokinetics. Moreover, we will hire a study nurse to be in charge of the logistics of this trial on a daily basis.

參、主要發現與結論

The proposal of this study was approved by TFDA on 103/07/13. The proposal was submitted for review by Taipei Veterans General Hospital IRB, Taipei Veterans General Hospital approved this study protocol on 103/9/1. We received the approval letter on 103/9/29. A start meeting was organized by CRO, and initialed visit and PI meeting was proceeded.

The first study case was enrolled on 103/10/28, this case was admitted for study on 103/10/31. For now, we completed a clinical trial of three cases.

Three cancer patients were recruited for this study. Re-188 liposome images were acquired at 1, 4, 8, 24, 48, 72 hr after injection by SPECT. There was reveal accumulation of radioactivity in the liver and spleen at 1 hr after injection. Uptakes of radioactivity were accumulated obviously in liver and spleen in each time point. All of the patients did not experience a serious adverse event related to the Re-188 liposome.

Biodistribution of Re-188 liposome in tumor in patient no.1-1-001

Re188-liposome (mCi/kg)	1 h	4h	8 h	24 h	48 h	72 h	org wt.(kg)	org wt.(g)
Lungs	1.6222	1.4242	1.4316	1.3234	1.0315	0.3532	0.6946	694.5983
Heart contents	0.7246	0.6020	0.6181	0.4859	0.3629	0.1582	0.3131	313.0817
Liver	2.1635	2.1962	2.2120	2.1457	2.0014	1.4031	1.3139	1313.949
Spleen	2.9972	3.3467	3.4774	3.2986	2.9433	2.0338	0.1260	125.9513
Kidneys	0.8393	0.9227	0.9436	1.0384	1.1596	0.7501	0.1844	184.4377
Upper large intestine	0.2941	0.3354	0.4529	0.7895	0.3127	0.1004	0.1659	165.8745
Tumor-abdomen	0.5692	0.5448	0.6141	0.6216	0.5814	0.2955	0.2592	259.2222

Dosimetry of Re-188 liposome in tumor in patient no.1-1-001 (ULI)

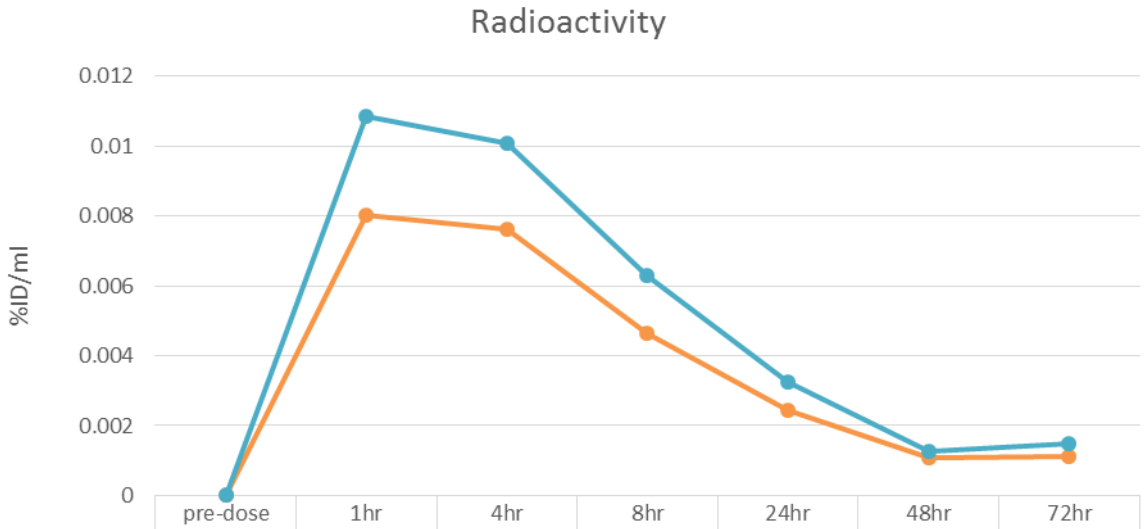
Target Organ	Total (mGy/MBq)
Adrenals	0.121
Brain	0.116
Breasts	0.116
Gallbladder Wall	0.123
LLI Wall	0.117
Small Intestine	0.118
Stomach Wall	0.119
ULI Wall	0.258
Heart Wall	0.261
Kidneys	0.481
Liver	1.3
Lungs	0.818
Muscle	0.117
Ovaries	0.118

Target Organ	Total (mGy/MBq)
Pancreas	0.122
Red Marrow	0.0786
Osteogenic Cells	0.205
Skin	0.115
Spleen	1.79
Testes	
Thymus	0.118
Thyroid	0.116
Urinary Bladder Wall	0.117
Uterus	0.117
Total Body	0.169
Effective Dose	0.294
Tumor	
Tumor-abdomen	0.434

Tumor sum	0.434

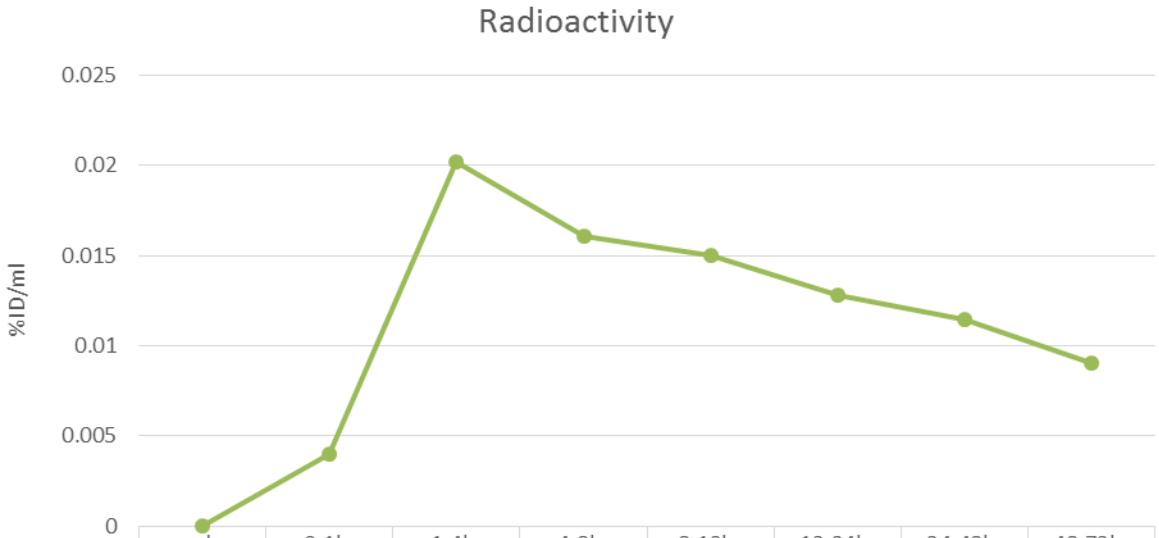
Ratio	
Tumor / Non-tumor	1.68
Tumor / Liver	0.33
Tumor / Lung	0.53
Tumor / Red marrow	5.53

Radioactivity of Re-188 liposome in blood in patient no.1-1-001



	pre-dose	1hr	4hr	8hr	24hr	48hr	72hr
Blood	0	0.008017	0.007615	0.004649	0.002434	0.001067	0.00113
Plasma	0	0.010847	0.010064	0.006291	0.003254	0.001264	0.001478

Radioactivity of Re-188 liposome in urine in patient no.1-1-001



	pre-dose	0-1hr	1-4hr	4-8hr	8-12hr	12-24hr	24-48hr	48-72hr
Urine	0	0.00400338	0.020179	0.0160721	0.01503357	0.01279638	0.0115	0.00901733

Biodistribution of Re-188 liposome in tumor in patient no.1-1-002(stage1)

Re188-liposome (mCi/kg)	1 h	4h	8 h	24 h	48 h	72 h	org wt.(kg)	org wt.(g)
Lungs	1.9092	1.8519	1.8229	1.8087	0.6656	0.8404	0.4976	497.626
Heart contents	1.2267	1.1927	1.1760	0.9623	0.4886	0.4858	0.2541	254.0647
Liver	1.2252	1.2462	1.2844	1.4694	1.0996	1.2391	0.9378	937.7611
Spleen	2.5137	2.6718	2.8055	3.1869	2.7363	3.0945	0.1325	132.4725
Kidneys	0.7091	0.6756	0.7022	0.8378	0.5455	0.7345	0.1052	105.1503
Upper large intestine	0.2385	0.2282	0.2799	0.5476	0.2415	0.3834	0.1284	128.4457

Biodistribution of Re-188 liposome in tumor in patient no.1-1-002(stage1)

Re188-liposome (mCi/kg)	1 h	4h	8 h	24 h	48 h	72 h	org wt.(kg)	org wt.(g)
Tumor-abdomen-1	0.6117	0.5429	0.8746	0.4492	0.1587	0.3681	0.0007	0.709152
Tumor-abdomen-2	0.5048	0.5351	0.5938	0.7246	0.1359	0.9718	0.0006	0.600052
Tumor-abdomen-3	0.4888	0.4530	0.7011	0.6624	0.3978	0.0982	0.0004	0.411606
Tumor-abdomen-4	0.7764	0.7636	0.6577	0.9284	0.4185	0.3756	0.0006	0.570297
Tumor-abdomen-5	0.4393	0.6968	0.6757	0.7858	1.0947	0.1731	0.0005	0.490951
Tumor-abdomen-6	0.5150	0.4860	0.4489	0.4525	0.2697	0.1992	0.0005	0.500869
Tumor-abdomen-7	0.6991	0.6042	0.7796	0.6716	0.6002	0.4538	0.0014	1.358794
Tumor-abdomen-8	0.3775	0.0468	0.5649	0.4351	0.2836	0.0507	0.0008	0.848007
Tumor-abdomen-9	0.5718	0.4932	0.6124	0.6698	0.2949	0.7221	0.0014	1.378631
Tumor-abdomen-10	0.5198	0.3688	0.4504	0.8380	0.0415	0.1557	0.0005	0.490951
Tumor-abdomen-11	0.4793	0.4147	0.5097	0.5242	0.2879	0.9469	0.0002	0.238037
Tumor-abdomen-12	0.4115	0.3175	0.3290	0.8490	0.0639	0.2133	0.0004	0.436401

Dosimetry of Re-188 liposome in tumor in patient no.1-1-002(stage1)

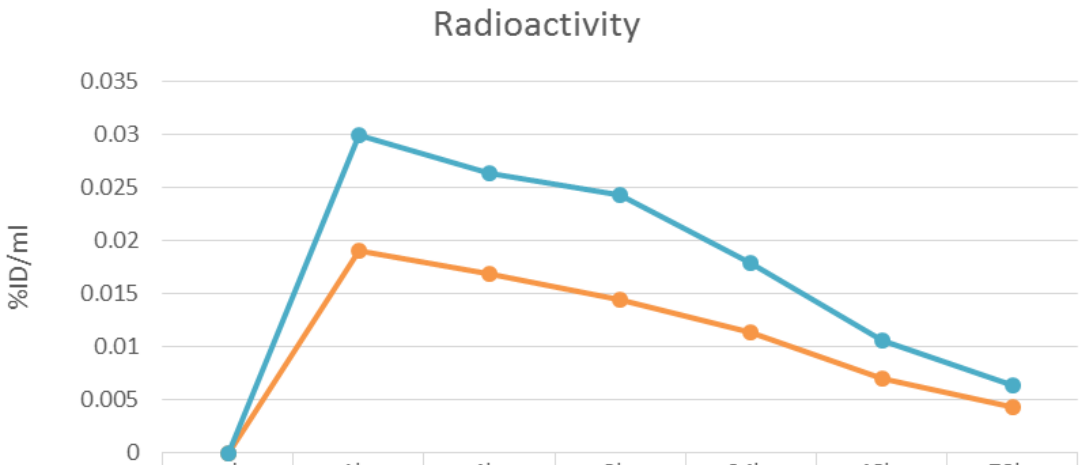
Target Organ	Total (mGy/MBq)
Adrenals	0.129
Brain	0.125
Breasts	0.125
Gallbladder Wall	0.13
LLI Wall	0.126
Small Intestine	0.126
Stomach Wall	0.128
ULI Wall	0.225
Heart Wall	0.4
Kidneys	0.327
Liver	0.822
Lungs	0.902
Muscle	0.126
Ovaries	0.126

Target Organ	Total (mGy/MBq)
Pancreas	0.13
Red Marrow	0.0844
Osteogenic Cells	0.22
Skin	0.124
Spleen	2.35
Testes	
Thymus	0.127
Thyroid	0.125
Urinary Bladder Wall	0.125
Uterus	0.126
Total Body	0.168
Effective Dose	0.3

Target Organ	Total (mGy/MBq)
Tumor	
abdomen1	0.506
abdomen2	0.407
abdomen3	0.533
abdomen4	0.543
abdomen5	0.540
abdomen6	0.290
abdomen7	0.593
abdomen8	0.363
abdomen9	0.517
abdomen10	0.384
abdomen11	0.497
abdomen12	0.441
Tumor sum	5.612

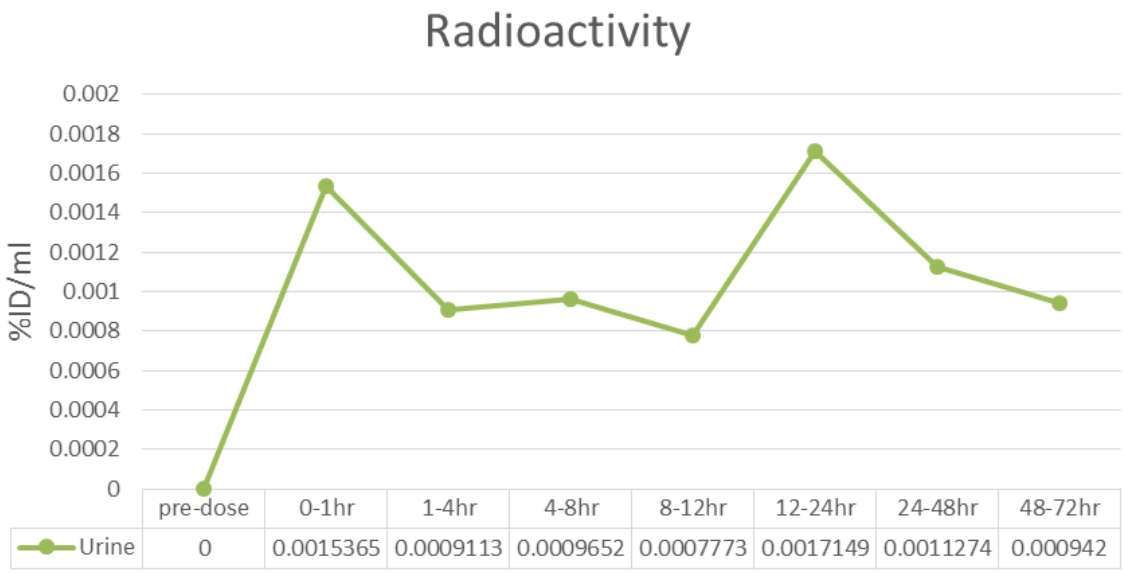
Ratio	
Tumor / Non-tumor	**24.94**
Tumor / Liver	**6.83**
Tumor / Lung	**6.22**
Tumor / Red marrow	**66.49**

Radioactivity of Re-188 liposome in blood in patient no.1-1-002(stage1)



	pre-dose	1hr	4hr	8hr	24hr	48hr	72hr
Blood	0	0.01901404	0.01691529	0.0144498	0.01129997	0.00703137	0.00431776
Plasma	0	0.02989468	0.0262614	0.02429946	0.01784622	0.01062776	0.00634599

Radioactivity of Re-188 liposome in urine in patient no.1-1-002(stage 1)



Biodistribution of Re-188 liposome in tumor in patient no.1-1-002 (stage 2)

Re188-liposome (mCi/kg)	1 h	4h	8 h	24 h	48 h	72 h	org wt.(kg)	org wt.(g)
Lungs	2.8451	2.6625	2.5182	2.2849	1.1011	0.9243	0.5681	568.1229
Heart contents	2.0110	1.7550	1.6730	1.2097	0.5892	0.4053	0.2385	238.4534
Liver	2.1106	2.1974	2.2536	2.3668	2.0457	1.9021	0.9401	940.1068
Spleen	4.8491	5.8640	6.7997	8.9713	9.1563	8.1564	0.1198	119.7921
Kidneys	0.9716	0.9885	1.0247	1.1416	0.7609	0.8325	0.0969	96.92565
Upper large intestine	0.1763	0.2045	0.2696	0.4798	0.1896	0.0608	0.1659	165.8745
Tumor-abdomen-1	1.2551	1.3625	1.4987	1.2942	0.9775	1.1809	0.0008	0.768661
Tumor-abdomen-2	1.1328	1.0513	1.1003	1.0160	0.4494	0.4574	0.0005	0.500869
Tumor-abdomen-3	0.7538	0.7536	0.8794	0.8442	0.7838	0.4644	0.0006	0.585174
Tumor-abdomen-4	1.0314	1.0128	0.9058	1.1155	0.6392	0.4816	0.0027	2.722548
Tumor-abdomen-5	0.7307	0.5496	0.8684	1.1160	0.8672	0.5309	0.0007	0.699234
Tumor-abdomen-6	0.7547	0.7575	1.0541	0.9174	0.4802	0.3389	0.0013	1.289367
Tumor-abdomen-7	0.4550	0.7134	0.5441	0.6154	0.2326	0.4253	0.0013	1.259612

Dosimetry of Re-188 liposome in tumor in patient no.1-1-002 (stage 2)

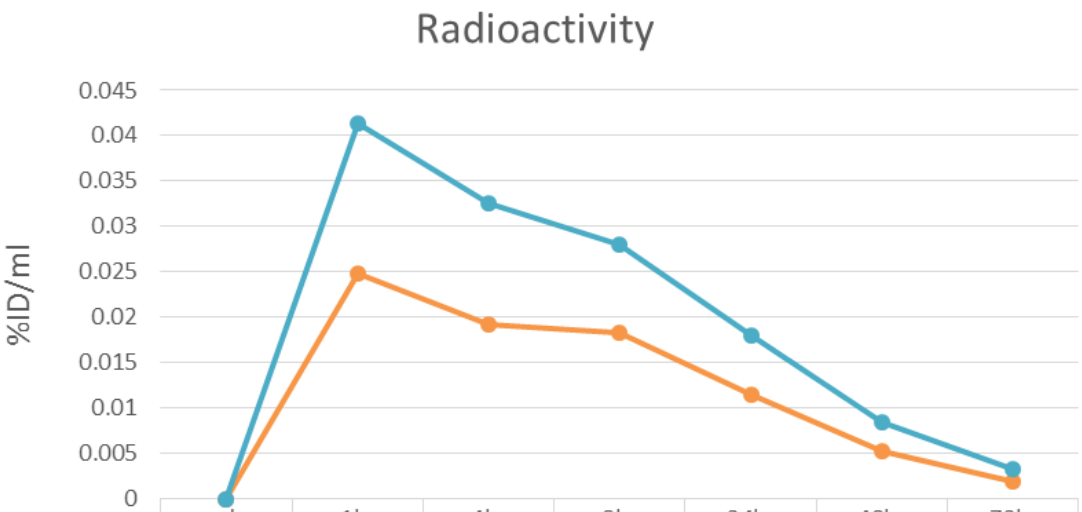
Target Organ	Total (mGy/MBq)
Adrenals	0.121
Brain	0.116
Breasts	0.116
Gallbladder Wall	0.121
LLI Wall	0.12
Small Intestine	0.117
Stomach Wall	0.118
ULI Wall	0.187
Heart Wall	0.354
Kidneys	0.222
Liver	0.942
Lungs	0.924
Muscle	0.117
Ovaries	0.117
Pancreas	0.122
Red Marrow	0.0786
Osteogenic Cells	0.205
Skin	0.115
Spleen	3.58
Testes	
Thymus	0.118
Thyroid	0.116
Urinary Bladder Wall	0.117
Uterus	0.117
Total Body/Rem body	0.165
Effective Dose	0.332

Target Organ	Total (mGy/MBq)
Tumor	
Tumor-abdomen1	0.823
Tumor-abdomen2	0.435
Tumor-abdomen3	0.407
Tumor-abdomen4	0.546
Tumor-abdomen5	0.461
Tumor-abdomen6	0.452
Tumor-abdomen7	0.309

Tumor sum	3.433

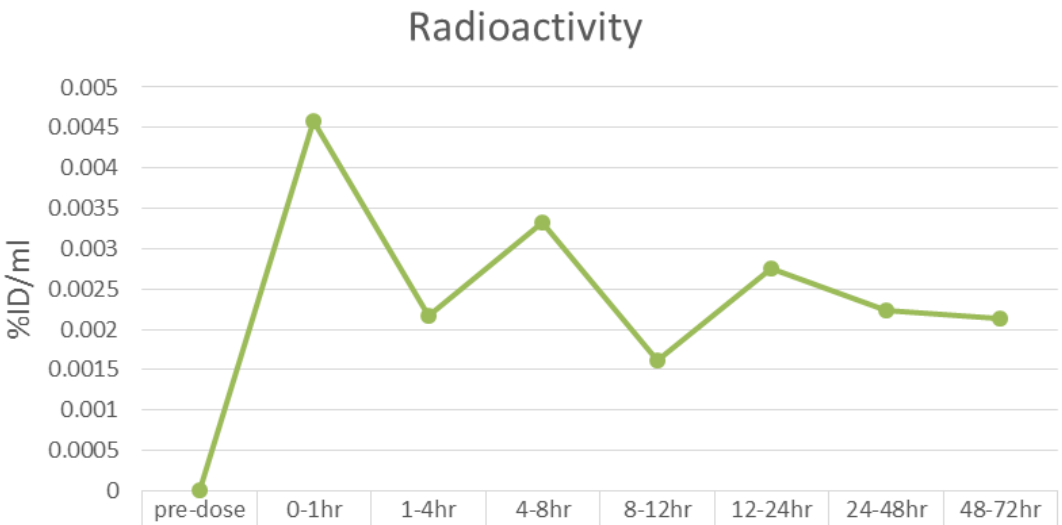
Ratio	
Tumor / Non-tumor	18.36
Tumor / Liver	3.64
Tumor / Lung	3.72
Tumor / Red marrow	43.67

Radioactivity of Re-188 liposome in blood in patient no.1-1-002(stage2)



	pre-dose	1hr	4hr	8hr	24hr	48hr	72hr
Blood	0	0.02487784	0.01914126	0.0183679	0.01146373	0.00530711	0.00197481
Plasma	0	0.04129479	0.03252575	0.02797774	0.01792498	0.00840636	0.00329455

Radioactivity of Re-188 liposome in urine in patient no.1-1-002 (stage2)



	pre-dose	0-1hr	1-4hr	4-8hr	8-12hr	12-24hr	24-48hr	48-72hr
Urine	0	0.004578	0.00217	0.003318	0.0016	0.002751	0.002242	0.002142

Biodistribution of Re-188 liposome in tumor in patient no.1-1-003 (stage 1)

Re188-liposome (mCi/kg)	1 h	4h	8 h	24 h	48 h	72 h	org wt.(kg)	org wt.(g)
Lungs	0.6316	0.5014	0.4485	0.4827	0.0422	0.1838	0.8307	830.7217
Heart contents	0.2925	0.2312	0.2050	0.2224	0.0148	0.0496	0.2709	270.8971
Liver	2.1424	2.1030	1.8867	1.6530	0.9947	0.8697	1.2604	1260.379
Spleen	2.4621	2.3344	2.2708	2.0742	1.4111	1.3410	0.2235	223.4534
Kidneys	0.8897	1.0450	1.0437	0.8897	0.4960	0.4672	0.1316	131.6195
Upper large intestine	0.2677	0.2614	0.3985	0.5515	0.2422	0.0316	0.0708	70.80853

Biodistribution of Re-188 liposome in tumor in patient no.1-1-003(stage 1)

Re188-liposome (mCi/kg)	1 h	4h	8 h	24 h	48 h	72 h	org wt.(kg)	org wt.(g)
LLT-1	0.0800	0.0630	0.0528	0.0674	0.00002	0.0001	0.0008	0.825691
LLT-2	0.1328	0.0763	0.0110	0.0747	0.00002	0.0001	0.0006	0.572777
LLT-3	0.1061	0.0999	0.0797	0.1606	0.00002	0.0104	0.0004	0.405407
LLT-4	0.1627	0.0779	0.0904	0.1340	0.00002	0.00004	0.0003	0.316143
LLT-5	0.1308	0.0944	0.1043	0.0810	0.00003	0.1453	0.0003	0.301266
LLT-6	0.1527	0.1457	0.1586	0.1765	0.00002	0.0001	0.0004	0.383091
LLT-7	0.1895	0.1587	0.0746	0.1650	0.02616	0.0351	0.0033	3.25813
LLT-8	0.3345	0.3475	0.2022	0.2262	0.15875	0.0495	0.0006	0.595093
LLT-9	0.3205	0.2934	0.4479	0.3634	0.00002	0.3657	0.0005	0.479793
RLT-10	0.1990	0.0944	0.1371	0.2204	0.01359	0.0001	0.0034	3.380867
RLT-11	0.1684	0.1356	0.0519	0.0433	0.00002	0.00005	0.0002	0.219441
RLT-12	0.1314	0.0733	0.1150	0.1712	0.00314	0.0013	0.0015	1.532363
RLT-13	0.1990	0.1424	0.1254	0.1567	0.00223	0.0467	0.0893	89.33449
RLT-14	0.1911	0.1901	0.1431	0.0711	0.01165	0.0001	0.0030	3.016374
RLT-15	0.2326	0.1913	0.1467	0.1815	0.00013	0.0560	0.0115	11.52991
RLT-16	0.2588	0.0920	0.0631	0.2894	0.00002	0.0568	0.0003	0.312424
RLT-17	0.1938	0.1790	0.0995	0.1252	0.00002	0.0001	0.0014	1.391028
RLT-18	0.1740	0.2163	0.1772	0.1804	0.00607	0.1736	0.0014	1.357554

LLT = left lung tumor RLT=right lung tumor

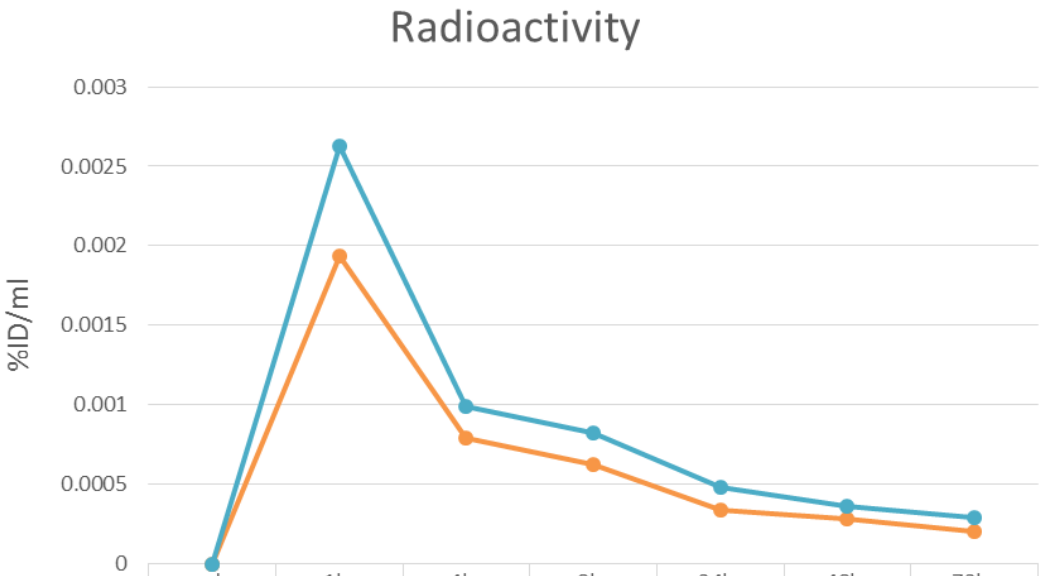
Dosimetry of Re-188 liposome in tumor in patient no.1-1-003 (stage 1)

Target Organ	Total (mSv/MBq)
Adrenals	0.0853
Brain	0.0791
Breasts	0.0798
Gallbladder Wall	0.0878
LLI Wall	0.0803
Small Intestine	0.0812
Stomach Wall	0.0829
ULI Wall	0.146
Heart Wall	0.146
Kidneys	0.445
Liver	1.61
Lungs	0.425
Muscle	0.0803
Ovaries	0.0806
Pancreas	0.0864
Red Marrow	0.0542
Osteogenic Cells	0.14
Skin	0.079
Spleen	3.19
Testes	
Thymus	0.0806
Thyroid	0.0794
Urinary Bladder Wall	0.0799
Uterus	0.0805
Total Body/Rem body	0.137
Effective Dose	0.271

Target Organ	Total (mSv/MBq)
Tumor	
Tumor-LLT 1	0.058
Tumor-LLT 2	0.022
Tumor-LLT 3	0.108
Tumor-LLT 4	0.119
Tumor-LLT 5	0.103
Tumor-LLT 6	0.157
Tumor-LLT 7	0.119
Tumor-LLT 8	0.201
Tumor-LLT 9	0.287
Tumor-RLT10	0.165
Tumor-RLT11	0.063
Tumor-RLT12	0.112
Tumor-RLT13	0.131
Tumor-RLT14	0.103
Tumor-RLT15	0.150
Tumor-RLT16	0.185
Tumor-RLT17	0.105
Tumor-RLT18	0.186
Tumor Sum	2.373

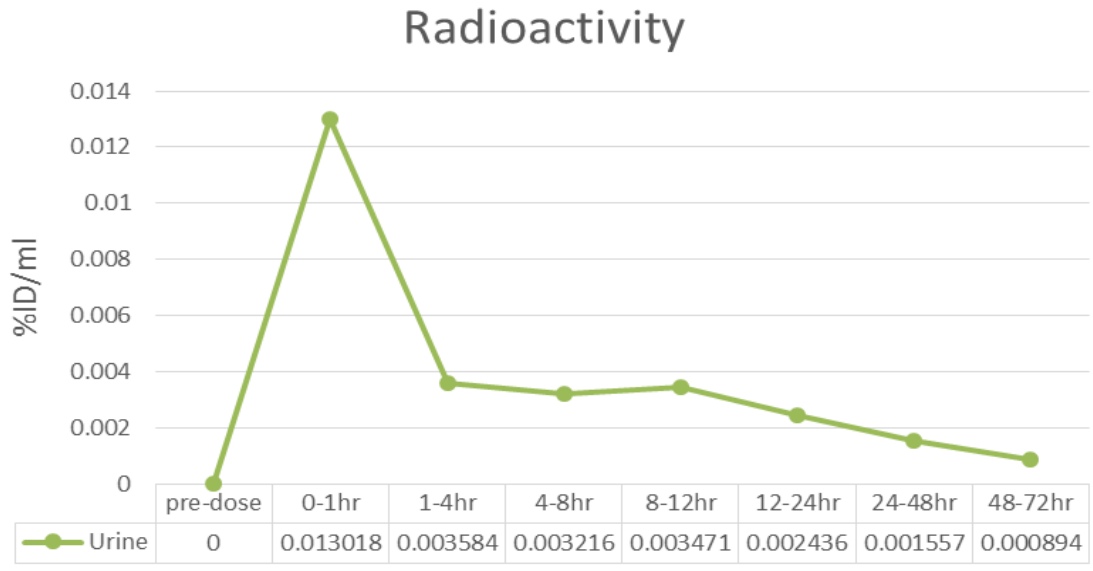
Ratio	
Tumor / Non-tumor	5.58
Tumor / Liver	1.47
Tumor / Lung	5.58
Tumor / Red marrow	43.39

Radioactivity of Re-188 liposome in blood in patient no.1-1-003(stage1)



	pre-dose	1hr	4hr	8hr	24hr	48hr	72hr
Blood	0	0.00193216	0.00079338	0.00062078	0.00033991	0.00028147	0.00020572
Plasma	0	0.00262571	0.00098858	0.0008194	0.00048253	0.0003661	0.00029359

Radioactivity of Re-188 liposome in urine in patient no.1-1-003(stage1)



	pre-dose	0-1hr	1-4hr	4-8hr	8-12hr	12-24hr	24-48hr	48-72hr
Urine	0	0.013018	0.003584	0.003216	0.003471	0.002436	0.001557	0.000894

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