Table 2 | **Selected RPT agents that are on the market or under development**

RPT agent	Company	Indication	Properties	Development phase	NCT number	Refs
Radium-223 chloride[a]	Bayer	Bone metastasis	Calcium analogue	Commercially available	–	56,127–131
^{90}Y-loaded glass microspheres	BTG	Hepatic malignancies	Radioembolization of liver microvasculature	Commercially available	–	274–279
^{90}Y-loaded resin microspheres	CDH Genetech/ Sirtex	Hepatic malignancies	Radioembolization of liver microvasculature	Commercially available	–	274–279
^{131}I radioiodine	Jubilant Draximage/ Malklincrodt	Thyroid cancer	Active uptake through Na–I symporter and storage in follicular cells	Commercially available	–	93,117–121,124
^{153}[Sm]lexidronam	Lantheus	Cancer bone pain	Binding to hydroxyapatite matrix	Commercially available	–	132–134
^{177}Lu-labelled DOTATATE	Novartis/AAA	Neuroendocrine tumours	SSR-mediated binding	Commercially available	–	192,194–196,200
[^{131}I]mIBG	Progenics	Adrenergic receptor$^+$ tumours	Active uptake mechanism via the adrenaline transporter and storage in presynaptic neurosecretory granules	Commercially available	–	140–152
^{131}I-labelled aCD45	Actinium Pharmaceuticals	Bone marrow transplant preparation	^{131}I-based antibody targeting CD45$^+$ cells for bone marrow ablation before transplantation	Phase III; recruiting	NCT02665065	229–231
^{177}Lu-labelled PSMA-617	Novartis/ Endocyte	Prostate cancer, tumour neovasculature	PSMA-mediated binding	Phase III; active, not recruiting	NCT03511664	166–169
^{177}Lu-labelled NeoBOMB1	Novartis/AAA	GRPR$^+$ tumours	GRPR binding	Phase II; completed Phase I/II; completed	NCT03724253 NCT02931929	202–210
^{166}Ho microspheres	Terumo	Hepatic malignancies	Radioembolization of liver microvasculature	Phase II; unknown recruitment status	NCT02067988	280–282
^{177}Lu-labelled DOTA-JR11	Ipsen	Neuroendocrine tumours	SSR-mediated binding and internalization	Phase I/II	NCT02592707	193
^{177}Lu-labelled PSMA-R2	Novartis/AAA	Prostate cancer, tumour neovasculature	PSMA-mediated binding and internalization	Phase I/II; recruiting	NCT03490838	155–162
^{225}Ac-labelled aCD38[a]	Actinium Pharmaceuticals	Multiple myeloma	CD38 antibody α-targeting	Phase I; recruiting	NCT02998047	244,245
^{225}Ac-labelled aCD33[a]	Actinium Pharmaceuticals	Leukaemia, MDS	CD33 antibody α-targeting	Phase I; withdrawn	NCT03705858	239,241–243
^{227}Th-labelled MSLN-TTC[a]	Bayer	Mesothelin$^+$ tumours	Anti-mesothelin–α-emitter immunoconjugate	Phase I; recruiting	NCT03507452	248,249
^{227}Th-labelled PSMA-TTC[a]	Bayer	Prostate, tumour neovasculature	PSMA-targeting α-emitter immunoconjugate; PSMA$^+$ prostate cancer targeting	Phase I; recruiting	NCT03724747	250,251
^{227}Th-labelled aCD22-TTC[a]	Bayer	Lymphoma	Anti-CD22–α-emitter immunoconjugate; CD22$^+$ tumours (lymphoma)	Phase I; active, not recruiting	NCT02581878	252
^{177}Lu-labelled CTT-1403	Cancer Targeted Technologies	Prostate, tumour neovasculature	PSMA-mediated binding	Phase I; active, not recruiting	NCT03822871	65,184–191
^{131}I-labelled CLR 131	Cellectar	Paediatric cancer, head and neck cancer, multiple myeloma, leukaemia, lymphoma	^{131}I-labelled phospholipid ether analogue targeting cancer cell-specific lipid raft microdomains	Phase I; recruiting Phase I; suspended (owing to COVID-19) Phase II; recruiting	NCT03478462 NCT04105543 NCT02952508	65,184–191
^{131}I-labelled CLR1404	Cellectar	Unresponsive solid tumour, multiple myeloma	^{131}I-labelled phospholipid ether analogue targeting cancer cell-specific lipid raft microdomains	Phase I; not recruiting Phase I; completed	NCT02278315 NCT01495663	65,184–191
^{225}Ac-labelled FPX-01[a]	J&J/Fusion Pharma	NSCLC, pan-cancer target	Insulin growth factor 1$^+$ tumours	Phase I; recruiting	NCT03746431	246

Table 2 (cont.) | **Selected RPT agents that are on the market or under development**

RPT agent	Company	Indication	Properties	Development phase	NCT number	Refs
[^{153}Sm]CycloSam	Oncolix/ Isotherapeutics	Osteosarcoma	Binding to hydroxyapatite matrix	Phase I; not yet recruiting	NCT03612466	138,139
^{212}Pb-labelled DOTAMTATE[a]	OranoMed/ Radiomedix	SSR$^+$ tumours	SSR-mediated binding	Phase I; active, not recruiting	NCT03466216	197–199
^{177}Lu-labelled RM2	ABX GmbH	GRPR$^+$ tumours	GRPR binding	First in human	–	212
^{227}Th-labelled HER2-TTC[a]	Bayer	HER2$^+$ tumours	Anti-HER2–α-emitter immunoconjugate	Preclinical	–	253–256
^{212}Pb-labelled PLE[a]	OranoMed/ Cellectar	Solid tumours	–	Preclinical	–	–
^{212}Pb-labelled aTEM1[a]	OranoMed/ Morphotek	TEM1$^+$ tumours	–	Preclinical	–	–
^{212}Pb-labelled aCD37[a]	OranoMed/ NordicNanovector	Leukaemia/ lymphoma	CD37 antibody α-targeting	Preclinical	–	–
^{211}At-labelled aLAT-1[a]	Telix Pharma	Multiple myeloma	–	Preclinical	–	–

The list is not exhaustive and includes only agents that are being developed by a commercial sponsor. [a]α-Emitter-based radiopharmaceutical therapy (RPT) agents. MDS, myelodysplastic syndrome; mIBG, *meta*-iodobenzylguanidine; NSCLC, non-small-cell lung cancer; PSMA, prostate-specific membrane antigen; SSR, somatostatin receptor.

any one particular patient. The scheme used to calculate these values is shown in BOX 1. This scheme provides the foundation for RPT dosimetry but because the calculation is oriented towards assessing radiation-induced risks of diagnostic imaging, it is not appropriate for toxicity and antitumour efficacy evaluations relevant to RPT. The dosimetry methods summarized in BOX 2 describe a scheme appropriate to RPT. The implications of adopting such a scheme and necessary extensions, not summarized in BOX 2, are briefly described below.

Image-based, patient-specific dosimetry allows the distribution of the agent in tumours and normal organs to be quantified[65]. The amount of RPT agent that concentrates in the tumour can be increased by increasing the administered activity, which also impacts the tumour-absorbed dose. Dosimetry analysis following a low-activity administration has the potential to inform the amount of activity to administer for subsequent therapy. For example, from radiotherapy experience, an absorbed dose of 60–70 Gy is required to achieve greater than 3-year tumour control for patients with osteosarcoma[66,67]. Although such high average tumour-absorbed doses can be achieved with high administered activities, studies have indicated that intratumour variability can be large, with some portions of a tumour meeting and exceeding this dose range, but the overall average being well below therapeutic efficacy[68]. These observations led to a rational, absorbed-dose driven approach for combining radiotherapy with RPT[69].

In the context of RPT, organ toxicity is usually reflected not by a whole-organ absorbed dose but rather by absorbed dose 'hot spots'. This is particularly so if such regions of high absorbed dose correspond to organ subregions that are critical to organ function. For example, some RPT agents (primarily peptides) concentrate and are retained in the renal cortex, so the absorbed dose in the renal cortex better predicts toxicity than the absorbed dose in the whole kidney volume[70]. For certain RPT agents, the biologically relevant region can be microscopic (for example, the kidney nephron[71] or the collecting ducts of the salivary glands[72,73]). The converse is also true. Estimates of the average absorbed dose in bone marrow do not predict the very low haematological toxicity of radium-223 dichloride (lower than that of almost all other RPT agents). In a pivotal randomized clinical trial, the grade 3 or grade 4 haematological toxic effects observed in patients receiving radium-223 dichloride (Xofigo) included neutropenia (2%), thrombocytopenia (3%), leukopenia (3%) and pancytopenia (1%)[56]. This discrepancy could be resolved by a calculation that considered the microscale distribution of radium-223 in the bone marrow. Such an analysis demonstrated that because of the short range of α-particle emissions and the known localization of the RPT agent on the trabecular bone surface, only haematopoietic (bone marrow) cells within 80 μm of the bone surface were irradiated, meaning that most of the bone marrow space was not irradiated and, accordingly, the average bone marrow absorbed dose was not predictive of toxicity[74].

Current imaging techniques do not possess the resolution required to resolve activity distributions at the microscopic scale. However, by pairing whole-organ macroscale measurements that can be performed in humans with microscale information that can be obtained from preclinical studies, it is possible to extract microscale information from macroscale measurements. A contour may be drawn on an image obtained with a patient imaging modality such as PET/CT or SPECT/CT that encompasses the entire organ (for example, kidney) or macroscopic subcompartments within the organ (for example, renal cortex). These macroscale contours may be used to obtain time-versus-activity curves (TACs) for the entire organ or macroscale subcompartments within the organ. Microscale structures within these macroscale contours may be obtained in preclinical models by tissue extraction and high-resolution imaging of tissue

Time-versus-activity curves
The amount of radioactivity in a particular region of the body as a function of time. Time-versus-activity curves are used in absorbed dose calculations; they may be obtained from imaging or direct sampling (for example, urine or serial biopsy or from animal studies).