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The five "W"s and "How" of Targeted Alpha Therapy: Why? Who? What? Where? When? and How?

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Abstract

Cancer is the second cause of death and morbidity in Europe. Unfortunately, currently available treatments cannot permanently cure most cancers, especially when metastatic. New therapy approaches are, therefore, urgently needed. Radionuclide therapy deposits cytotoxic radiation by means of energetic particles (alfa, beta, and auger) labeled to a carrier that specifically targets cancer cells. Targeted Alpha Therapy is very promising, because alpha particles deliver high energy (i.e., cytotoxic effect) in a small range, binding a target cell population without significant harm to healthy tissues. The high linear energy transfer typical of alpha particles determines irreversible double-strand DNA breaks with per-unit absorbed doses of acute biologic effects three-to-seven times greater than the damage produced by external beam with photons or beta radiation. As consequence, cells—not equipped to efficiently repair this type of damage—typically undergo death. Therefore, Targeted Alpha Therapy is such a new approach to treat tumors. This article aimed to provide an overview (five "W"s and "How") on Targeted Alpha Therapy.

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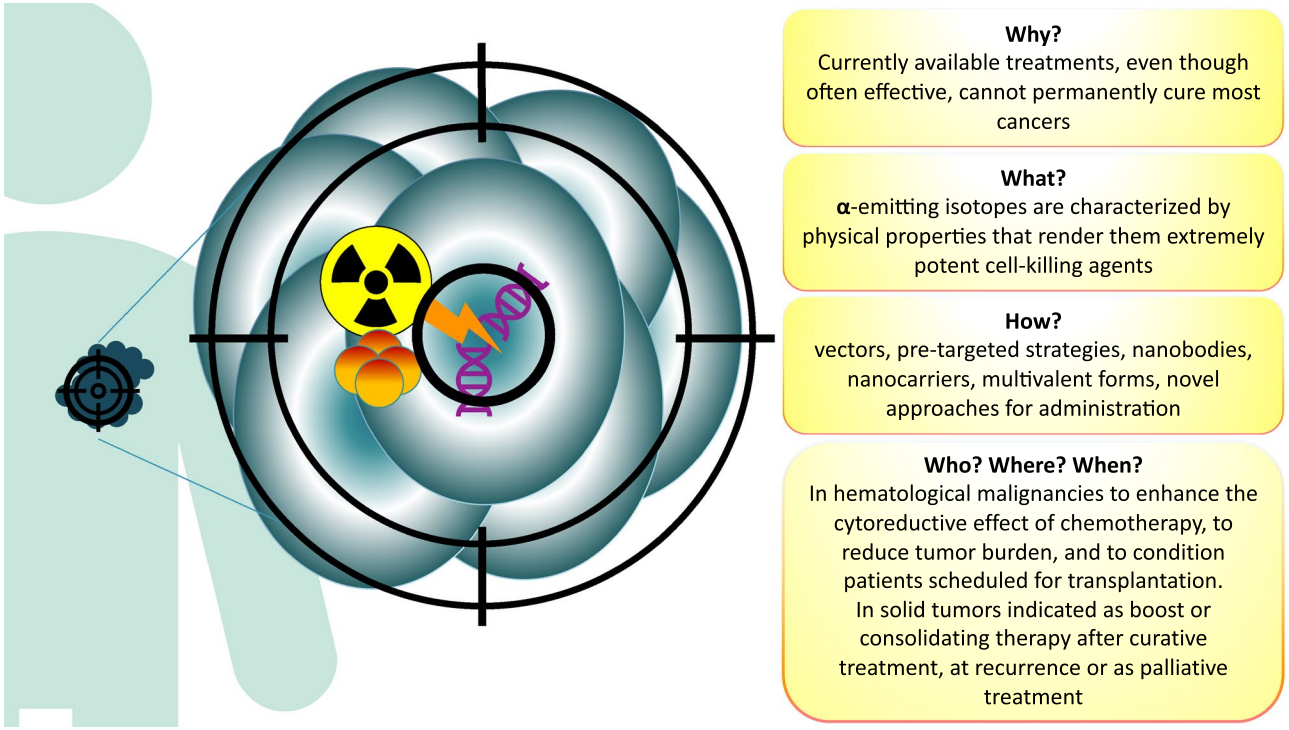
Graphical Abstract



Keywords Alpha-emitting particles · Antibodies · Radiopharmaceuticals · Prostatic neoplasms · Leukemia · Radionuclide therapy

1 Why? Background and rationale

More than 3.0 million people are newly diagnosed with cancer each year. Cancer is the second most important cause of death and morbidity in Europe. The most common causes of death for cancers are Lung (21%), Colorectal (12%), Breast (7%), Pancreas (7%), and Prostate (6%) [(Source: ECIS—European Cancer Information System. From https://ecis.jrc.ec.europa.eu, accessed on 6/12/2019 © European Union, 2019)].

The currently available treatments, even though often effective, cannot permanently cure most cancers mainly when disease have already formed distant metastases. New therapy approaches are, therefore, urgently needed.

Radionuclide therapy delivers cytotoxic radiation through energetic particles (alfa, beta, and auger) labeled to a carrier that specifically targets cancer cells.

Targeted Alpha Therapy (TAT) employing alpha particle emitters is such a new approach to cancer treatment.

Targeted Alpha Therapy is very promising, because alpha particles deposit high energy at a small distance. The short range allows delivering the cytotoxic effect to a specific cell population limiting the effect on non-targeted cells. The high linear energy transfer (LET) typical of alpha particles determines irreversible double-strand DNA breaks with per-unit absorbed doses of acute biologic effects three-to-seven times greater than the damage produced by an external beam with photons or beta radiation (Sgouros 2008; Allan 2013). As a consequence, cells—not equipped to efficiently repair this type of damage—typically undergo death (Kassis 2008).

The present paper aimed to provide an overview of TAT as *a* new approach to cancer treatment.

2 Who? Clinical need

One of the most appealing characteristics of radionuclide treatment is its adaptability. In principle, each radionuclide can combine with each targeting vehicle addressing specific requirements related to the way of administration, the stage of the disease, the accessibility of the target, and the site of action.

Accordingly, the development of a new efficient probe for radionuclide treatment depends upon the optimal match between the tumor-associated antigen and the targeting vehicle. Ideally, the "perfect" antigen is overexpressed by tumor

Table 1 Radionuclides applied in targeted radionuclide therapy. [Adapted from (Gudkov et al. 2016)]

Radionuclide	$T_{1/2}$, h	E_{max}, MeV (*)	Method of Producing
^{124}I	100.1	β − 1.6 (~90%); 2.2 (~10%)	cyclotron
^{131}I	192.0	β − 0.7 (89%); γ − 0.4 (82%); β/γ ** = 1	nuclear reactor
^{86}Y	14.7	β − 1.2 (~90%); 1.6 (~10%)	cyclotron
^{90}Y	64.8	β − 2.2 (100%)	generator ^{90}Sr→^{90}Y
^{177}Lu	160.8	β − 0.5 (100%)	nuclear reactor
^{188}Re	17.0	β − 2.0 (100%)	generator ^{188}W→^{188}Re
^{64}Cu	12.7	β − 0.65 (61.5%), β − 0.58 (38.5%)	Cyclotron
^{67}Cu	61.9	β − 0.4 (100%)	cyclotron
^{89}Zr	78.0	B + 0.9 (100%)	cyclotron
^{212}Pb	10.6	β − 0.6 (~80%); γ − 0.2 (44%); 0.08 (18%)	generator ^{228}Th→^{220}Rn→^{216}Po→^{212}Pb
^{212}Bi	1.0	α − 6.0 (100%); β − 2.0 (100%); α/β ** = 0.67	generator ^{228}Th→^{224}Ra→^{212}Bi
^{213}Bi	0.7	α − 5.8 (97%); β − 1.4 (100%); α/β ** = 0.02	generator ^{229}Th→^{225}Ac→^{213}Bi
^{211}At	7.21	α − 5.9 (42)	cyclotron
^{225}Ac	240.2	α − 5.7 (100%)	generator ^{229}Th→^{225}Ac
^{223}Ra	273.6	α − 5.7 (100%)	cyclotron
^{149}Tb	4.1	α − 4.0 (~80%)	cyclotron
^{226}Th	0.5	α − 6.3 (~50%)	generator ^{230}U→^{226}Th
^{227}Th	448.8	α − 6.0 (48%)	generator ^{227}Ac→^{227}Th
^{89}Sr	1212	β − 1.5 (100%)	nuclear reactor
^{153}Sm	46.3	β − 0.81 (100%)	cyclotron

* Percentage of quanta with the indicated energy value in the total amount of quanta of this type emitted by a given radionuclide; ** Ratio of the amount of quanta of different emission types.

cells and absent or scarce in healthy tissues (Dekempeneer et al. 2016).

Because of the high binding affinity to tumor-associated antigens, four crucial aspects—high specificity, high tumor-to-background ratio, high metabolic stability, and low immunogenicity—make antibodies suitable vehicles for the delivery of therapeutic radioisotopes.

Since the early 1950s, radioimmunotherapy (RIT) has been a significant research area for cancer treatment, despite the marketing authorization of an RIT agent in non-Hodgkin lymphoma, clinical trials in solid tumors are rarely successful and progress beyond the phase I/II. Accordingly, research in solid tumors aims to find alternative approaches to improve the clinical success of radionuclide therapy (Sollini et al. 2015). Different strategies have been proposed including the use of different antibody formats (e.g., diabodies), the identification of alternative targeting agents (e.g., folate and peptides), and the selection of radionuclides with more favorable characteristics in terms of physical properties (energy and half-life), labeling chemistry properties, cytotoxic effect, and toxicity profile (Sollini et al. 2015; Dekempeneer et al. 2016; Targeted Alpha Therapy Working Group et al. 2018).

3 What? Physics and radiochemistry

Alpha particles are helium nuclei with a positive charge. They are about 8000 times larger than beta particles and have some advantages compared to beta ones. Like alpha particles, with a +2 charge, deliver energy with a short range (50–100 µm versus several mm for beta particles) and high LET (from 25 to 230 keV/µm versus about 0.2 keV/µm for beta particles) (Gudkov et al. 2016). The energy per unit path length deposited by an α-particle is ≥ 500 times higher than an electron or β-particle (Baidoo et al. 2013).

The LET is ~ 80 to 100 keV/µm along most of their up-to-100-µm path before increasing to ~ 300 keV/µm toward the end of the track (Bragg peak) (Kassis 2008).

Overall, the cytocidal effect of α-emitters is not related to dose fractionation, dose rate, or hypoxia, and it overcomes the resistance to chemotherapeutics encountered in the conventional chemo- and radiation treatment (Baidoo et al. 2013).

The therapeutic effect of alpha emitters depends on:

- the distance between the decaying atom and the nucleus of the targeted cell;
- the heavy-ion recoil of the daughter atom, mainly if the alpha-particle emitter is covalently bound to nuclear DNA; and
- the bystander effects and the magnitude of cross-dose (Sgouros 2008).

The alpha-emitting radionuclides of main interest for cancer treatment purposes are astatine-211 (^{211}At), bismuth-212 (^{212}Bi), bismuth-213 (^{213}Bi), radium-223 (^{223}Ra), actinium-225 (^{225}Ac), lead-212 (^{212}Pb), and thorium-227 (^{227}Th). Table 1 summarizes the main characteristics (Sgouros 2008; Gudkov et al. 2016).

Emitters of interest are generally radiometals, in which the highest binding constants are obtained through chelation by polydentate ligands. The halogen ^{211}At is the exception. Each radioisotope has exclusive aqueous coordination chemistry properties, and specific chemical demands, including ligand donor atom preferences (e.g., N, O, S, and hard/soft), coordination number, and coordination geometry. These characteristics must be considered for labeling strategy. The

radiometal is bind to the antibody vectors (immunoconjugates) or peptides through a ligand system (i.e., chelator) which represent an essential component of a radiometal-based radiopharmaceutical. Robust chelate chemistry is crucial for the implementation of therapeutic agents based on alpha-emitting isotopes, because it can influence biodistribution and have an impact on the potentially fatal toxicity (Price and Orvig 2014). Indeed, non-bound radionuclides might non-specifically localize in non-target tissues. For example, bismuth localizes in kidney, terbium, and radium in bone, radium, actinium in the liver, and astatine in lung, spleen, thyroid, and stomach (Dadwal et al. 2011; Wilbur 2011; Price and Orvig 2014; Ramdahl et al. 2016; Pozzi and Zalutsky 2017).

3.1 Carriers

Vectors are suitable when specifically target the tumors to be treated. Many vectors are being used or are close to being introduced in clinical use. For instance, the recombinant humanized IgG1 monoclonal antibody HuM195reactive with CD33 targeting acute myelogenous leukemia; the murine 9.2.27 mAb highly specific for the melanoma-associated chondroitin sulfate proteoglycan NG2; the anti-CD20 for lymphoma; MX35 F(ab′)2 (targeting a cell surface glycoprotein), and trastuzumab (targeting Her2) for ovarian cancer; the murine 81C6 IgG2b mAb targeting an extracellular matrix glycoprotein expressed in many tumors but not in healthy tissues; the human-mouse chimeric anti-tenascin 81C6 for brain tumors, the PAI2 against urokinase-type plasminogen activator, the C595 a murine mAb against MUC-1, and the folate receptor alpha for many solid tumors. Prostate-specific membrane antigen (PSMA), investigated for various diagnostic applications, especially in prostate cancer (Vallabhajosula et al. 2004; Behe et al. 20111; Gao et al. 2014; Kiess et al. 2015; Evans et al. 2016; Hadaschik and Boegemann 2017), is one of the most promising theragnostic agents for TAT. Radium-223-dichloride, due to its natural affinity for bone, is applied in bone cancers and skeletal metastases (Allen 2012; Dekempeneer et al. 2016).

Generally, in RIT trials, whole immunoglobulins G (IgG) are used, since they are highly available, can be easily manufactured and handled. Data on preclinical studies demonstrated that whole IgG presented slow blood clearance that resulted in the highest tumor uptake as compared to F(ab′)2 or Fab′ fragments or engineered forms. However, whole IgG-based radiopharmaceuticals administration has been reported to be associate with increased risk of myelosuppression due to the exposure of red marrow to radiation even at low activities. Another disadvantage when using the whole IgG is related to low penetrance into the tumor mass due to high internal pressure within the tumor. Migration of targeted molecules is also significantly influenced by the "binding-site barrier", which affected more higher affinity molecules. A way to partially overcome this limited localization is increasing the vehicle dose. However, an excess of unbounded product competing with the labeled one might result in a significant reduction of the amount of radioactive molecule in the tumor. Structural modification of antibodies has been attempted to obtain molecules with more favorable pharmacokinetic properties including F(ab′)2, Fab or its multivalent conjugate, minibody, diabody, and single-chain variable fragments (scFv). All these molecules have the same antigen-binding properties of the whole IgG, but are characterized by faster clearance. Notably, the scFv fragments having a mass significantly lower than a whole IgG extravasate easier and diffuse more in-depth into the tumor. As a consequence, the scFv fragments result in a faster tumor uptake, in higher tumor/non-tumor ratios and potentially in a more homogeneous distribution. Multivalent antibodies including IgG, small immunoprotein (SIP), or mini-antibodies, $F(ab)_2$, $(scFv)_2$ can bind at the same time to two antigens. Furthermore, if the antibody dissociates from the antigen, at one or both binding sites, a rebinding is more likely before the complete dissociation occurs. On the other hand, small molecules have the main disadvantage of low tumor uptake as compared to the whole IgG as a consequence of their fast clearance as well as high susceptibility to the binding-site barrier effect. A rapid tumor uptake typical of the whole IgG is more cytocidal, delivering the radiation at a higher dose rate. Nonetheless, the administered activity could be theoretically increased, since the exposure of bone marrow is reduced by their fast clearance. Practically, side effects limit this increase (i.e., high dose to the tumor). Molecules smaller than 50,000 Da cleared by kidneys may cause renal toxicity, mainly when radiometals are used (Sollini et al. 2015). So far, vehicles for TAT benefited from some improvements aimed to develop and to optimize target molecules. Nonetheless, there is still considerable room for amelioration, primarily related to the development of new coupling chemistries, and the improvement of pharmacokinetic properties (Dekempeneer et al. 2016).

3.2 Dosimetry and radiation protection

Radiation treatments, even if different, may be standardized and compared using dosimetry. Fundamentally, dosimetry provides data to understand and to quantify the effects of radiation on biological tissue(s). In the case of alpha emitters, dosimetric estimates require mathematical modeling to determine the activity distribution as a function of time at the cellular and subcellular levels. Determining the activity distribution, however, remains challenging. For high-LET irradiation, the effect of even a single event in the nucleus of the cell(s) is so substantial that the mean absorbed dose can result in an inaccurate index of biological effect. This fact

may be related to different reasons, including the small number of alpha particles that generally crosses a cell nucleus making stochastic variations significant, and the path of the alpha particles through the cell nucleus. Accordingly, an alpha particle that solely grazes the surface of a cell nucleus will result in a small or even no energy deposit. Conversely, the right cross of the cell nucleus will determine a high deposit of energy. Microdosimetry, taking into account the stochastic nature of energy deposited in small targets, is another method for alpha particle dosimetry. Microdosimetry traditionally requires the calculation of specific energy (energy per unit mass) and lineal energy (energy per unit path length through the target) that could be computed using either analytical or Monte Carlo methods. Kellerer and Chmelevsky (Kellerer and Chmelevsky 1975) outlined the rationale for microdosimetry, suggesting that the stochastic variations of energy deposited within the target must be considered when the relative deviation of the local dose exceeds 20% (Sgouros et al. 2010). The therapeutic dose of an alpha-emitter clinically used may affect radiolabeling chemistry, since the activity (mCi or MBq) can differ within alpha-emitting radionuclides. TAT should be considered different from target beta-radiation therapy. In the latter case, the beta emissions benefit from cross-fire effect to kill cells. Therefore, the therapeutic effect of beta-emitters relies on the total amount of radiation administered to the patient, and localized in the target tissue, while the therapeutic effect of primarily comes from alpha-emissions on the targeted cells. Notably, alpha therapy is not affected by the dose rate or oxygen tension. While the biological half-life and nature of the targeting molecule play central roles, the number of radioactive atoms and not the activity is the primary factor when using alpha-emitters (Wilbur 2011). Radiation protection directives are implemented according to national and European regulations, in particular, the EU Directive 2103/59/EURATOM (European Commission 2014). Alpha emitting nuclei can also emit beta and gamma radiations. On one hand, alpha particles can be easily stopped and represent a significant risk only when placed in contact with biological tissues. On the other hand, beta and gamma radiations have a higher capacity to penetrate tissues and to pass physical barriers. This capacity should be considered when dealing with radiopharmaceuticals labeled with alpha-emitting isotopes.

4 Where? and When? Clinical applications of Targeted Alpha Therapy

Currently, oncological patients are treated using a multimodal approach that, guided by stage and prognostic factors, may include systemic neoadjuvant treatment alone or in association with surgery or external beam radiotherapy, and eventually, adjuvant chemotherapy with or followed by regional adjuvant radiotherapy. In hematological malignancies, TAT may be used to enhance the cytoreductive effect of the chemotherapy, to reduce the tumor burden, and to condition patients scheduled for transplantation. In the adjuvant setting of some epithelial cancers such as melanoma, ovarian cancer, mesothelioma, and neuroendocrine tumors (NETs), TAT may be proposed as boost or consolidating therapy after curative treatment (e.g., surgery and adjuvant chemotherapy). Intra-cavity administration of TAT has been evaluated in recurrent malignant gliomas and ovarian cancer. The main advantages of this route of administration are the minimizing risk of side effects (e.g., myelotoxicity) and unexpected toxicity due to unforeseen microscopic off-target localization of the radiolabeled complex in the body. The radioactive decay of emitters characterized by a short half-life, such as ^{213}Bi and ^{211}At, mainly occurs within the cavity, before the distribution of the molecule in the body. Palliative treatment can be administrated using the intravenous route as for symptom relief of bone metastases, or the intra-cavity route as in case of peritoneal carcinomatosis. As mentioned, the inherent biological features of solid tumors are less favorable for radio-conjugate binding access than hematological malignancies.

Moreover, in the case of manifest macroscopic disease (5–10 mm), TAT efficacy might be suboptimal. However, there are some clinical indications such as melanoma and refractory non-Hodgkin lymphoma. The use of pre-targeting strategies might increase the potential efficacy of TAT. Table 2 summarizes the state of development of targeted alpha-particle therapy radiopharmaceuticals classified per clinical setting.

4.1 Leukemia and multiple myeloma

As above-mentioned myeloid-lymphoproliferative malignancies are more prone to RIT than solid tumors. Broadly, the accumulation of radiolabeled antibodies in the bone marrow occurring when the targeted antigen is expressed on healthy hematopoietic cells or even when the bone-marrow minimally involved made RIT a suitable treatment for myeloid-lymphoproliferative malignancies. Accordingly, RIT may be used to enhance the cytoreductive effect of the chemotherapy, to reduce the cancer load alone or in combination with chemotherapeutics, and to condition patients scheduled for transplantation (Behr et al. 2002; Richman et al. 2005; Nademanee et al. 2005).

Particularly, myeloablative RIT may fill the gap between benefit and toxicity of conditioning therapies. RIT when used to condition patients scheduled for transplantation, induces hypoplasia/aplasia in bone marrow, determining a low rate of relapse and toxicity since organs which not express the target are spared. Moreover, it does not cause a

Table 2 State of development of targeted alpha-particle therapy radiopharmaceuticals classified per clinical setting [modified from (Dekempeneer et al. 2016)]

Isotope	TAT agent	Indication	Target	Clinical phase of development				Reference(s)
				Phase I	Phase II	Phase III	Market	
^{211}At	Anti-BC8-B10	Leukemia	CD45					([NCT03128034]; [NCT03670966])
^{211}At	Anti-BC8-B10	Nonmalignant diseases candidate to hematopoietic cell transplant	CD45					([NCT04083183])
^{211}At	Chimeric 81C6 IgG2	Brain tumor	Tenascin-C					(Zalutsky et al. 2008)
^{211}At	Anti-MX35 F(ab')$_2$	Ovarian cancer	NaPi2b					(Andersson et al. 2009; Cederkrantz et al. 2015)
^{212}Pb/^{212}Bi	Anti-HER2 IgG (TCMC-trastuzumab)	Breast/ovarian cancer	HER2					([NCT04083183]; Meredith et al. 2014a)
^{212}Pb	DOTAMTATE	Neuroendocrine tumor	Somatostatin receptors					([NCT04083183])
^{213}Bi	Anti-CD33 IgG (HuM195)	Leukemia	CD33					([Home-ClinicalTrials.gov. https://clinicaltrials.gov/. Accessed 8 Jan 2020]; Jurcic et al. 2002; Rosenblat et al. 2010)
^{213}Bi	Anti-CD20 IgG (rituximab)	Non-Hodgkin lymphoma	CD20					(Heeger et al. 2003)
^{213}Bi	Substance P	Brain tumor	Neurokinin type-1 receptor					(Cordier et al. 2010; Morgenstern et al. 2014; Królicki et al. 2019)
^{213}Bi	Anti-NG2 IgG (9.2.27 IgG)	Melanoma	NG2 proteoglycan					(Allen et al. 2005, 2011; Raja et al. 2007)
^{213}Bi	DOTATOC	Neuroendocrine tumor	Somatostatin receptors					(Kratochwil et al. 2014)
^{223}Ra	^{223}Ra-dichloride	Multiple myeloma	Hydroxyapatite					([NCT02928029])
^{223}Ra	^{223}Ra-dichloride	Prostate cancer (bone metastases)	Hydroxyapatite					([NCT02396368]; [https://clinicaltrials.gov/ct2/results?term=alpharadin&cond=%22Prostatic+Neoplasms%22. https://clinicaltrials.gov/ct2/results?term=alpharadin&cond=%22Prostatic+Neoplasms%22. Accessed 16 Jan 2020]; [NCT03344211]; [NCT02097303]; [NCT03093428]; Nilsson et al. 2005, 2013; Parker et al. 2013b, a; Sartor et al. 2014; Humm et al. 2015; Saad et al. 2019; Heidenreich et al. 2019)

Table 2 (continued)

^{223}Ra	^{223}Ra-dichloride	Renal cell carcinoma (bone metastases)	Hydroxyapatite					([NCT02406521]; McKay et al. 2017)
^{223}Ra	^{223}Ra-dichloride	Breast cancer (bone metastases)	Hydroxyapatite					([NCT02258464]; [NCT02258451]; [NCT02366130]; Coleman et al. 2014)
^{223}Ra	^{223}Ra-dichloride	Osteosarcoma	Hydroxyapatite					([NCT01833520])
^{223}Ra	^{223}Ra-dichloride	Lung cancer (bone metastases)	Hydroxyapatite					([NCT03996473])
^{225}Ac	Anti-CD33 IgG (HuM195)	Leukemia	CD33					([NCT00672165]; [NCT02575963]; Baidoo et al. 2013)
^{225}Ac	DOTATATE	Neuroendocrine tumor	Somatostatin receptors					(Ballal et al. 2019)
^{225}Ac	Anti-CD33 IgG (lintuzumab)	Leukemia/multiple myeloma	CD33					([NCT02998047]; [NCT03932318]; [NCT03867682]; [NCT03441048]; Atallah et al. 2019)
^{225}Ac	FPI-1547 mAb	Refractory solid tumors	Insulin-like growth factor-1 receptor					([NCT03746431])
^{225}Ac/^{177}Lu	PSMA-617 mAb	Prostate cancer	PSMA					(Khreish et al. 2019)
^{227}Th	BAY1862864 mAb	Non-Hodgkin lymphoma	CD22					([NCT02581878])
^{227}Th	BAY2710439 mAb	Breast/gastric or gastroesophageal cancer	HER2					([NCT04147819])
^{227}Th	BAY2287411 mAb	Mesothelioma/ovarian cancer/pancreatic ductal adenocarcinoma	Mesothelin					([NCT03507452])
^{227}Th	BAY2315497 mAb	Prostate cancer	PSMA					(Hammer et al. 2019)

significant increase in therapy-related mortality (Buchmann et al. 2009).

The first clinical trial with ^{213}Bi-HuM195 in patients with relapsed/refractory AML or CML demonstrated the safety, feasibility, and anti-leukemic effects of TAT (Jurcic et al. 2002). Based on the promising results of this preliminary study, safety and efficacy of ^{213}Bi-HuM195 after partially cytoreductive chemotherapy with cytarabine were tested in 31 patients with newly diagnosed or relapsed/refractory AML within a phase I/II study. Marrow blasts significantly decreased at all dose levels (Rosenblat et al. 2010). ^{213}Bi-anti-CD33, binding the CD33 antigen expressed by AML cells, exerted its cytotoxic effect inducing apoptosis. Similarly, ^{211}At-anti-CD33 exhibited a high cytotoxic effect in CD33-positive AML cell lines. This evidence suggested the reactivation of the apoptotic pathways, being TAT a promising opportunity for patients with resistant AML untreatable by the conventional therapies (Petrich et al. 2010; Friesen et al. 2013).

A phase I/II clinical trial on ^{211}At-BC8-B10 treatment before donor stem cell transplant in patients with high-risk AML, ALL, or myelodysplastic syndrome is currently ongoing ([NCT03670966]).

The ^{225}Ac-HuM195 proved to have anti-leukemic activity in advanced AML patients regardless of the activity ([NCT00672165]; Baidoo et al. 2013), which is now being investigated combined to low-dose cytarabine in elderly AML patients within a multicenter phase I/II trial ([NCT02575963]). A combined treatment to reduce tumor burden in AML consisting of chemotherapy followed by

α-RIT (^{213}Bi- or ^{225}Ac-immunoconjugates) has been recently completed [(Home—ClinicalTrials.gov. https://clinicaltrials.gov/. Accessed 8 Jan 2020)].

Some phase I/II study combining ^{225}Ac-lintuzumab with the other agents is planned in refractory or relapsed AML ([NCT03932318]; [NCT03867682]; [NCT03441048]). Of note, preliminary data of ^{225}Ac-lintuzumab in 40 older AML patients unfit for standard induction chemotherapy showed moderate efficacy. The study was closed based on the hypothesis that other AML therapies, will likely have better outcomes when used in combination or in settings where myelosuppression is expected (Atallah et al. 2019).

A phase I trial to evaluate ^{225}Ac-lintuzumab as monotherapy in multiple refractory myelomas is currently ongoing ([NCT02998047]) as well-known typically multiple myeloma has lytic bone involvement. Therefore, the application of bone-seeking agents would result inappropriate. However, the osteoclastic activity may be altered by bisphosphonates and other anti-responsive agents, which potentially turn the newly deposited bone matrix into a target for bone-seeking radiopharmaceuticals (Humm et al. 2015). A phase I/II trial evaluating ^{223}Ra-dichloride in combination with bortezomib and dexamethasone in the early relapsed multiple myeloma patients is currently ongoing ([NCT02928029]).

4.2 Lymphoma

RIT with ^{90}Y-ibritumomab tiuxetan (Zevalin®) is a commercially available agent for relapsed or refractory, low-grade or transformed B cell non-Hodgkin lymphoma. However, other molecules and approaches are under evaluation to treat lymphoma patients. As above-mentioned, RIT can be used with a dual purpose—targets tumor cells and suppresses immunocompetent recipient cells—in allogeneic hematopoietic cell transplantation. RIT with beta-emitters has been successfully used for intensification of myeloablative conditioning before allogeneic hematopoietic cell transplantation. The advantages offered by alpha-emitters to target hemopoietic cells have been wildly proved (Bethge et al. 2006). Heeger et al. (Heeger et al. 2003) conducted a phase I with ^{213}Bi-CHX-A″-anti-CD20 radioconjugate (up to 1640 MBq) in non-Hodgkin lymphoma patients with promising results (response in 20% of cases). An open-label phase I with BAY1862864, an anti-CD22 antibody linked to thorium-227, in patients with refractory/relapsed CD22-positive non-Hodgkin lymphoma is currently ongoing ([NCT02581878]).

4.3 Primary brain tumors

The majority of brain tumors, glioblastomas (GBM) in particular, appear as a single lesion that will locally recur. Accordingly, loco-regional application of bifunctional molecules consisting of a target domain (e.g., the transferrin receptor, the interleukin-4 and interleukin-13 receptors, the neurokinin type-1 receptors, or a mAb against tenascin-C) and of an effector domain (e.g., bacterial toxins or radioisotopes) has been developed as potentially effective treatment (Kneifel et al. 2006). TAT for its intrinsic properties might accurately irradiate of tumors, protecting from side effects neighboring functional or critical areas of the brain. Based on the evidence of the over-expression of the peptide, carrier substance P (SP) targets the neurokinin type-1 receptors by GBM cells (Morgenstern et al. 2014), Cordier et al. (Cordier et al. 2010) conducted an encouraging pilot study in five newly diagnosed glioma patients treated with ^{213}Bi-SP, providing the proof-of-concept for ^{213}Bi-SP application in gliomas. These preliminary results were confirmed in 20 recurrent GBM patients treated with ^{213}Bi-SPin. Intracavitary or intratumoral treatment resulted in safe, causing mild transient adverse reactions. ^{213}Bi-SP improved patient's median survival compared to reoperated patients (7.5 months versus < 6 months), resulting in a better outcome when repeated (up to 11.2 GBq) (Morgenstern et al. 2014; Królicki et al. 2019). Zalutsky et al. (Zalutsky et al. 2008) reported their experience with ^{211}At-ch81C6 in 18 patients with recurrent malignant brain tumors. Astatine-211-ch81C6 was administered into a surgically created resection cavity, and after TAT patients received salvage chemotherapy. Treatment resulted feasible, safe, and with promising antitumor activity, providing the proof-of-concept for local TAT.

4.4 Melanoma

Successful treatment of melanoma remains a challenge in oncology. Therefore, several attempts have been made in drug development research to discover active molecules to improve patients' outcome. Notably, in RIT, several efforts and strategies have been set up to find out novel targets, to develop novel ligands, bifunctional chelators, and forms of mAbs with suitable binding and pharmacokinetics properties, to test different administration strategies including pre-targeting and "cocktail" approaches (i.e., the mix of different radioisotopes with a variety of emission types and half-lives). Melanoma was thought to be relatively resistant to radiation, but the use of external beam radiotherapy as palliative treatment in metastatic cases has been proved to have particular effectiveness to control the disease locally. This evidence suggested that melanoma cells have peculiar radiobiology being more susceptible when higher radiation dose per fraction regimens has been applied, and supported the use of α-RIT (high LET in a short-range) in melanoma (Contessa and Roberson 2006).

The mAb anti-NG2 IgG (9.2.27 mAb) radiolabeled with ^{213}Bi has been proved to be safe and effective in stage IV melanoma patients. Cell deaths occurred 2 weeks after

intralesional treatment as confirmed by apoptosis, tumor debris, and both Ki67 and serum marker melanoma-inhibitory-activity (MIA) protein decrease (Allen et al. 2005). The maximum tolerance dose was not achieved, and no adverse events of any type or level were observed when TAT was intravenously administrated. Treatment determined stable disease or partial response in half of the patients (40% and 10%, respectively) at 8 weeks, resulting in an independent prognostic factor for survival (Raja et al. 2007; Allen et al. 2011).

4.5 Prostate cancer

Prostate-specific membrane antigen (PSMA) also named glutamate carboxypeptidase II (GCPII), *N*-acetyl-L-aspartyl-L-glutamate peptidase I (NAALADase I) or *N*-acetyl-aspartyl-glutamate (NAAG) peptidase, is an enzyme encoded by the folate hydrolase (FOLH1) gene (O'Keefe et al. 1998). The N-terminal cytoplasmic tail of PSMA interacts with membrane scaffold proteins that control the endocytosis of some molecules such as filamin A. The central portion of PSMA is represented by the extracellular component which included three domains—protease, apical, and C-terminal domain or dimerization domain—responsible for the substrate/ligand recognition (Bařinka et al. 2012; Evans et al. 2016). PSMA has different functions, and it is highly expressed by many tissues, including the prostatic one (Evans et al. 2016). Particularly, prostate cancer (PCa) overexpressed PSMA at higher levels than normal or hyperplastic prostates (Horoszkiewicz et al. 1987). In PCa, androgens act as PSMA repressor, while the other growth factors such as basic fibroblast growth factor, act positively (Israeli et al. 1993; Evans et al. 2016). The exact role of PSMA in tumors, including PCa, is not explored yet, but it has been reported to be associated with cancer progression and invasion (Yao et al. 2008). PSMA is rapidly internalized and recycled by positive cells. Its overexpression determines an increase in folate processing. Based on its characteristics, PSMA has been explored as a target agent to imaging and treat PCa (Behnam Azad et al. 2015; Evans et al. 2016). Preclinical data of radiolabeled PSMA showed, as mentioned above, that there was a high level of target-specific uptake in malignant PCa cells. These data were confirmed in vivo using both animal models and human tissues (Evans et al. 2016). Moreover, PSMA levels are related to Gleason score and disease progression (i.e., the more aggressive the disease and the more advanced stage, the higher the PSMA level). As for the unbound form of the molecule, also radiolabeled PSMA is internalized by positive cells (Hadaschik and Boegemann 2017). Therefore, the possibility to deliver cytotoxic radiation to a specific target makes PSMA a suitable and attractive molecule for RIT. RIT with PSMA radiolabeled with beta emitters ($^{125/131}$I, ^{177}Lu, and ^{90}Y) determined a reduction of tumor volume or a delayed tumor growth in preclinical PCa animal models (Vallabhajosula et al. 2004; Behe et al. 2011; Gao et al. 2014; Kiess et al. 2015; Evans et al. 2016; Hadaschik and Boegemann 2017). In men, RIT with PSMA radiolabeled with beta emitters showed biochemical or radiological response associated with clinical benefit (e.g., pain relief) in the majority of cases (Bander et al. 2005; Vallabhajosula et al. 2005; Tagawa et al. 2013; Zechmann et al. 2014; Ahmadzadehfar et al. 2015, 2017; Kratochwil et al. 2015; Rahbar et al. 2017), even if about one-third of treated patients did not respond despite the in vivo demonstration of PSMA overexpression by ^{68}Ga-PSMA PET/CT (Hadaschik and Boegemann 2017). In this regard, TAT might be used as a strategy to overcome the primary radio-resistance to ß-RIT and to reduce toxicity (Hadaschik and Boegemann 2017). It is worth mentioning that clinical trials with ^{225}Ac-PSMA may have an impact on other clinical development activities featuring the use of TAT also in the other clinical settings. First-in-human retrospective experience with ^{225}Ac-PSMA has been recently reported (Kratochwil et al. 2016, 2017). They treated 14 end-stage castration-resistant PCa patients with empirically dose-escalation activity of ^{225}Ac-PSMA. The treatment schedule was defined on individual decisions resulting incomparable in terms of timing, number of cycles, and administered activities. Nonetheless, this experience suggested a potential benefit for castration-resistant PCa patients treated with ^{225}Ac-PSMA. The same group reported a remarkably clinical antitumor activity (PSA response was used as surrogate endpoint) of ^{225}Ac-PSMA (3 cycles 100 kBq/kg at 2-month interval) in metastatic castration-resistant PCa (Kratochwil et al. 2018). More recently, results of pilot experience in 20 metastatic castration-resistant PCa treated with ^{225}Ac-PSMA as part of tandem therapy (combination with ^{177}Lu-PSMA) have been published, suggesting that TAT powered the efficacy of single-agent PSMA-targeted radioligand therapy (Khreish et al. 2019). A phase I trial with ^{227}Th-BAY 2315497 is currently ongoing in patients with metastatic castration-resistant PCa (Hammer et al. 2019). Overall than 90% of metastatic PCa had bone involvement, and typically, bone metastases from PCa are related to blastic new osseous formation, making them especially amenable to targeted therapies with bone-seeking agents such as ^{223}Ra-dichloride (Lange and Vessella 1999; Bourgeois et al. 2011). Starting from the hypothesis that ^{223}Ra-dichloride would localize to the bone and would spare the bone marrow, a phase I clinical trial was begun in breast and prostate cancers. Patients experienced pain relief without toxicity, and serum alkaline phosphatase levels decreased, providing the evidence of treatment effectiveness (Nilsson et al. 2005; Humm et al. 2015). These results were confirmed in symptomatic metastatic castration-resistant PCa by phase II and III trials (Nilsson et al. 2013; Parker et al. 2013a, b; Sartor et al. 2014). Notably, improved

overall survival (14.9 months versus 11.3 months), low myelosuppression rates, and a few adverse events have been reported in patients treated with ^{223}Ra-dichloride within the randomized, double-blind, placebo-controlled "ALSYMPCA" trial (Parker et al. 2013a). Moreover, phase IIIb study showed that patients with more advanced metastatic castration-resistant PCa were more unlikely to complete ^{223}Ra-dichloride treatment (i.e., fewer cycles), and showed worst outcome compared to patients with less advance disease (Saad et al. 2019; Heidenreich et al. 2019). Treatment with ^{223}Ra-dichloride induced variable pain control. The first or the second infusion(s) of the usual six planned administrations may result in a prompt and permanent pain relief in the majority of lesions even if, sometimes it may be incomplete or shorter. In the latter case, attention should be paid to possible other or concurrent causes of pain, including neuropathic pain, suboptimal analgesic control, or even no-related to the tumor. However, when the pattern of pain changes (pain-flare after a subside phase or different location), new metastatic localizations should be ruled out (Humm et al. 2015). In 2013, ^{223}Ra-dichloride received marketing approval (Xofigo®) by both the U.S. Food and Drug Administration and the European Medicine Agency (EMA) for the treatment of adults with castration-resistant PCa, symptomatic bone metastases, and no known visceral metastases. However, in 2018, the EMA restricted its use after docetaxel, and at least one androgen receptor-targeted agent or in case of patients without the other therapeutic options (Medicines Agency 2018). This restrictive action was the effect of the significant safety risks (fractures and deaths) observed within the phase III trial, which combined ^{223}Ra-dichloride to abiraterone plus steroids. Currently, the European Association of Urology Guidelines on prostate cancer recommends the ^{223}Ra-dichloride as a life-prolonging drug for metastatic castration-resistantprostate cancer (Mottet et al. 2020). Some clinical trials evaluating the association of ^{223}Ra-dichloride with other drugs (s) or interventions (e.g., olaparib, enzalutamide, sipuleucel-T, pembrolizumab, and radiotherapy) are currently ongoing ([Search of: radium-223|Recruiting, Active, not recruiting Studies|Interventional Studies|Prostate Cancer—List Results—ClinicalTrials.gov. https://clinicaltrials.gov/ct2/results?term=radium-223&cond=Prostate+Cancer&recrs=a&recrs=d&age_v=&gndr=&type=Intr&rslt=&Search=Apply. Accessed 7 Jan 2020]).

4.6 Renal cell carcinoma

Metastatic renal cell carcinoma has limited therapeutic options. It frequently presents bone involvement and bone metastases are associated with worse survival. Data on ^{223}Ra-dichloride effectiveness in PCa supported an exploratory phase I which combined ^{223}Ra-dichloride (55 kBq/kg every 4 weeks × 6 cycles) to vascular endothelial growth factor targeted therapy (sorafenib or pazopanib) in renal cell carcinoma patients with bone metastases ([NCT02406521]). Preliminary results in 12 patients suggested that treatment with ^{223}Ra-dichloride plus sorafenib was safe and effective on bone turnover markers (McKay et al. 2017).

4.7 Breast cancer

Data on ^{223}Ra-dichloride in PCa support its use also in the other cancers with bone metastases with blastic characteristics (Coleman 2016). An open-label, phase IIa nonrandomized study investigated the effects of ^{223}Ra-dichloride (50 kBq/kg IV every 4 weeks for four cycles) in 23 patients with advanced breast cancer and progressive bone-dominant disease no longer amenable to endocrine treatment. ^{223}Ra-dichloride determined a significant reduction of disease biomarkers associated with a metabolic response in more than one-third of lesions (32% at week 9 after two injections, and 41% at week 17 upon completion of treatment). Treatment was safe and well tolerated (Coleman et al. 2014). ^{223}Ra-dichloride is under evaluation within three international phase II trials focused on bone predominant metastatic breast cancer either hormone-positive (^{223}Ra-dichloride + hormonal treatment + denosumab ([NCT02366130])) or hormone-positive HER2 negative (^{223}Ra-dichloride or placebo + hormonal treatment ([NCT02258464]), or exemestane + everolimus ([NCT02258451])).

4.8 Ovarian cancer

The majority of ovarian cancer cases are diagnosed when carcinomatosis is already present. Surgery followed by the conventional adjuvant chemotherapy results commonly in complete response. Nonetheless, the disease will recur in approximately half of cases. Intraperitoneal chemotherapy and radionuclides have shown to be effective, improving survival or decreasing abdominal failure (Armstrong et al. 2006; Verheijen et al. 2006). Previous experience with intraperitoneal radionuclide treatment suggested that some benefits (higher activity without excess in toxicity) could be obtained from an isotope with a shorter half-life and fewer γ emissions than β-emitter commonly used for RIT (Macey and Meredith 1999). Experiments in mouse ovarian cancer model showed the therapeutic potential of trastuzumab, MOv18 (mAb targeting cell membrane glycoprotein), and MX35 labeled with α-emitter (Andersson et al. 2000; Elgqvist et al. 2006; Palm et al. 2007). Data obtained in the first 3 HER-2 positive ovarian cancer patients treated with intraperitoneal ^{212}Pb-TCMC-trastuzumab within a phase I trial, were consistent with biodistribution and safety results obtained in preclinical experiments ([NCT02258451]; Meredith et al. 2014b). Overall, 16 patients (15 recurrent ovarian

cancer and one colorectal cancer) were treated with minimal toxicity drug-related, which was expected, according to dosimetry (Meredith et al. 2014a). Intraperitoneal ^{211}At-MX35 F(ab′)$_2$ as adjuvant treatment for the microscopic disease was safety administered in nine patients in complete clinical remission after second-line chemotherapy for recurrent ovarian carcinoma (Andersson et al. 2009; Cederkrantz et al. 2015).

4.9 Osteosarcoma

Osteosarcoma is a primary bone tumor in which spindle cells produce osteoid. Accordingly, osteosarcoma, as osteoblastic metastases from PCa and breast tumors, is suitable for bone-seeking agents treatment. The positive clinical therapeutic experience based on β-emitting radiopharmaceuticals opens the possibility for the use of ^{223}Ra-dichloride in selected osteosarcoma patients (Humm et al. 2015). A phase I/II dose trial is active in osteosarcoma ([NCT01833520]).

4.10 Neuroendocrine tumors

Peptide radioreceptor therapy (PRRT) with somatostatin analogues labeled with beta-emitters is an effective treatment for NETs (Zaknun et al. 2013; Hicks et al. 2017). However, some patients are resistant to PRRT. As abovementioned, α-emitters may overcome resistance to β-emitters (Friesen et al. 2007), and that both ^{225}Ac-DOTATOC and ^{213}Bi-DOTATOC have shown promising antitumor effects in preclinical studies (Norenberg 2006; Miederer et al. 2008). Kratochwil et al. (Kratochwil et al. 2014) reported the first-in-human experience with ^{213}Bi-DOTATOC in eight patients refractory to ^{90}Y/^{177}Lu-DOATOC with progressive advanced neuroendocrine liver metastases. Treatment was administered by intra-arterial ($n=7$) or systemic ($n=1$) infusion (up to 5 cycles with a cumulative activity of 3.3–20.8 GBq). Six patients were evaluable for treatment response which resulted in a complete response (> 28 months, ongoing), two partial responses (up to 17 months), and three stable diseases (up to > 31 months, ongoing). Acute hematological toxicity was low. Three patients developed chronic anemia. Twenty-four months after TAT (5 years after the first administration of ^{90}Y-DOTATOC), one patient developed a myelodysplastic syndrome that progressed 6 months after into acute myeloid leukemia, and the patient died. Recently, short-term results of a prospective study recruiting patients with metastatic gastroenteropancreatic neuroendocrine tumors stable or progressive on ^{177}Lu-DOTATATE therapy showed partial response or stable disease (24/32 and 9/32, respectively) in all cases after ^{225}Ac-DOTATATE treatment (100 kBq/kg body weight, 1–5 cycles at 8 weeks) (Ballal et al. 2019).

5 How? New technologies and targets

Targeted therapies delivery their cytocidal effect after the binding between the vector and its target. Improvements made in genetic engineering result in the development of several vectors suitable for RIT. Nonetheless, the suboptimal pharmacokinetic properties of these molecules often hamper treatments. As above-mentioned, an accurate trade-off between tumor uptake and clearance is crucial. In this regard, fast clearance limits the organs irradiation. However, too rapid clearance may affect the targeting time. In turn, a targeting time too short could deliver an insufficient adsorbed dose to target cells. Pre-targeted strategies may be used to solve the pharmacokinetic challenge. This approach physically and temporally separates the distribution phase from the delivery one. This approach requires first the administration of a pre-targeting molecule which should be followed by sufficient time for the antigen-site binding. Normal organs are not affected by this binding phase, since the pre-targeting molecule is free from any cytotoxic substance. Before the injection of the radiolabeled vector, an agent is used to remove from the circulation of the unbound molecule (effector molecule). The effector molecule is specifically designed to bind to the antigen-associated pre-targeting molecules and diffuse more in-depth into the tumor. The rapid removal of circulating unbound effector molecule is in favor of a higher tumor-to-normal tissue ratio. Pre-targeting does not require a compromise between efficient binding/diffusion/tumor residence time and protection of dose-limiting normal tissues (Elgqvist et al. 2014). Examples of pre-targeted strategies are based on streptavidin–biotin (Lesch et al. 2010) or bispecific antibodies (Chang et al. 2002). ^{211}At and ^{213}Bi having some favorable properties (e.g., availability, daughter nuclides) has emerged as most promising α-emitters candidates. Indeed, even if their half-life could be too short of ensuring a sufficient targeting time, a pre-targeting strategy may be successfully used to increase the therapeutic index, overcoming the issue related to these short-lived α-particle emitters (Elgqvist et al. 2014). The positive effects of pre-targeted strategies on TAT have been reported in preclinical studies, mainly focused on hematological malignancies (Zhang et al. 2003; Park et al. 2010; Pagel et al. 2011). The advances in engineering lead to a growing interest in the use of nanobodies—the smallest, antigen-binding fragments from unique heavy-chain-only antibodies naturally occurring in Camelidae (Hamers-Casterman et al. 1993)—as vectors for RIT. Nanobodies have some favorable properties, including high antigen affinity and specificity, facile production, and high stability even in harsh conditions (e.g., high temperatures and extreme pHs), which offer the possibility to use a broader range of radiochemistry methods. Nanobodies being extremely specific for the antigen regardless of the isotope used for labeling are suitable vehicles for both nuclear imaging and RIT.

Moreover, nanobodies have certain advantages over mAbs such as a lower molecular weight (15 kDa versus 150 kDa), lower immunogenicity, and a more efficient penetration in the tumor, which results in a rapid site binding (Dekempeneer et al. 2016). The limited unspecific binding to non-target tissues together with the fast clearance of nanobodies determines an early high tumor-to-background ratio (as early as 1 h after injection). Accordingly, nanobodies might be the solution to the off-target toxicity related to the long-lasting blood circulation of mAb (Dekempeneer et al. 2016). A variety of labeled nanobodies directed against membrane-bound biomarkers have been developed to image by SPECT or PET different conditions in animal models (Vaneycken et al. 2010, 2011; D'Huyvetter et al. 2014; Dekempeneer et al. 2016). Moreover, a promising experience of anti-HER2 nanobodies labeling with Astatine-211 has recently been reported in an animal model (Dekempeneer et al. 2019). Recoiling daughter nuclides may be an issue if the α-particles are not retained at the target site, since they may harm to healthy tissues. Some strategies may be applied to limit this phenomenon, including the encapsulation of α-particles in nanocarriers, or the development of multivalent forms rapidly internalized inside the target cells. Polymersomes proved to be safe carriers to encapsulate ^{225}Ac, but they resulted inadequate to retain recoiling daughters isotopes which were significantly re-distributed throughout the body (Kruijff et al. 2019). Multivalent nanobody forms—differently from the monovalent counterparts which are characterized by a low level of internalization—may be used to augment the number of α-particles trapped inside target cells (Oliveira et al. 2010; Dekempeneer et al. 2016). Innovative approaches for micro- and small-scale dosimetry are required to calculate reliable estimates of α-emitters used in TAT. The recent development of techniques to image α-particle deposits at a cellular level is emerging among novel dosimetric methods. Moreover, the recent identification of mutations in some damage-repair associated genes in patients resistant to TAT paves the way to test combined approach with DNA-damage-repair targeting agents such as Poly(ADP-ribose)–Polymerase inhibitors (Kratochwil et al. 2019). A new strategy for α-treatment is the use of implantable seeds embedded with a low activity of radium-224. This strategy, called DaRT (Diffusing Alpha-emitters Radiation Therapy), does not target a binding site, but represents a novel alpha-emitting brachytherapy. It has been investigated in some solid tumors, including skin and head and neck cancers with promising results in terms of efficacy and safety (Popovtzer et al. 2019).

6 Conclusions

In conclusion, α-emitting isotopes are characterized by physical properties that render them extremely potent cell-killing agents. Progress in gene engineering allowed the creation of novel targeting vehicles, and characterized by high specificity and favorable pharmacokinetics. The possibility to label highly specific carriers with such radionuclides offers multiple possibilities of combinations to tailor the treatment to a specific disease. Optimal biodistribution, toxicity profile, dosimetry, and vectors design are challenges, that researchers will face in the next years. Nonetheless, there is growing evidence on the effectiveness of TAT in many oncological diseases that constitute a significant cause of morbidity and mortality worldwide.

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Compliance with ethical standards

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