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# **Palliative treatment of metastatic bone pain with radiopharmaceuticals: a perspective beyond Strontium-89 and Samarium-153**

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# **Palliative treatment of metastatic bone pain with radiopharmaceuticals: a perspective beyond Strontium-89 and Samarium-153**

## **ABSTRACT**

**Purpose:** The present review article aims to provide an overview of the available radionuclides for palliative treatment of bone metastases beyond  $^{89}\text{Sr}$  and  $^{153}\text{Sm}$ . In addition, it aims to review and summarize the clinical outcomes associated with the palliative treatment of bone metastases using different radiopharmaceuticals. **Materials and Methods:** A literature search was conducted on Science Direct and PubMed databases (1990 - 2015). The following search terms were combined in order to obtain relevant results: “bone”, “metastases”, “palliative”, “care”, “therapy”, “treatment”, “radiotherapy”, “review”, “radiopharmaceutical”, “phosphorus-32”, “strontium-89”, “yttrium-90”, “tin-117m”, “samarium-153”, “holmium-166”, “thulium-170”, “lutetium-177”, “rhenium-186”, “rhenium-188” and “radium-223”. Studies were included if they provided information regarding the clinical outcomes. **Results and Conclusions:** A comparative analysis of the measured therapeutic response of different radiopharmaceuticals, based on previously published data, suggests that there is a lack of substantial differences in palliative efficacy among radiopharmaceuticals. However, when the comparative analysis adds factors such as patient’s life expectancy, radionuclides’ physical characteristics (e.g. tissue penetration range and half-life) and health economics to guide the rational selection of a radiopharmaceutical for palliative treatment of bone metastases,  $^{177}\text{Lu}$  and  $^{188}\text{Re}$ -labeled radiopharmaceuticals appear to be the most suitable radiopharmaceuticals for treatment of small and medium/large size bone lesions, respectively.

**Key words:** Radiopharmaceutical; Bone metastases; Systematic review; Alpha particles; Beta particles; Auger electrons.

## I. INTRODUCTION

Bone metastases are a common and severe complication in patients diagnosed with primary tumours. It develops in up to 70% of patients diagnosed with prostate cancer and breast cancer and in up to 30% of those with cancers of the lung, bladder and thyroid. The major complications associated with bone involvement are severe pain, spinal cord compression, hypercalcemia and pathological fracture, all of which compromise the patient's quality of life. Several therapeutic approaches targeting bone metastases and its associated effects are available, including the use of analgesics, chemotherapy, external beam radiotherapy and radionuclide systemic therapy. The latter, systemic palliative targeted therapy with suitable radiopharmaceuticals, has emerged as a particularly appealing and efficient treatment modality for patients with multiple skeletal metastases (Maini et al., 2003; Pandit-Taskar et al., 2014; Pillai et al., 2003; Silberstein and Drive, 1996).

Radionuclide therapy is characterized by the reasonably selective delivery of therapeutic doses of radiation to systemically dispersed target tissues, with generally limited toxicity and few long-term side-effects (Unak, 2002). The basis of successful radionuclide therapy relies on a high concentration and adequate retention of the radiopharmaceutical at the tumour site. The concept of targeted therapy introduced in 1898 by Paul Ehrlich, i.e. the "magic bullet" concept, has paved the way for the development of successful approaches for treatment of different diseases based on radiopharmaceutical systemic administration (Ehrlich and Herter, 1904; Vial and Callahan, 1957). A notable example is the treatment of hyperthyroidism and thyroid cancer using  $\text{Na}^{131}\text{I}$ . Since then, a wide variety of radiolabeled agents has been used clinically for treatment of different types of diseases, but only a limited number of these preparations have obtained regulatory approval for routine clinical use in patients and are commercially available (Das and Pillai, 2013). Examples of diseases that have been treated by nuclear medicine therapy are: thyroid carcinoma, hyperthyroidism, metastatic bone pain, polycythemia rubra vera, neuroendocrine tumors (NETs), liver metastases, lymphoma and neuroblastoma. Among these, treatment of thyroid cancer with  $^{131}\text{I}$  is the most widely used radionuclide-targeted therapy. The second most widely used application is for bone pain palliation in the context of metastatic cancer (Das and Pillai, 2013).

There are essentially three main types of particulate radiations that are of interest for

palliative treatment of bone metastasis using radiopharmaceuticals: beta minus ( $\beta^-$ ) particles, alpha ( $\alpha$ ) particles and Auger electrons. Traditionally, tumor-targeted radiotherapy has used  $\beta^-$  emitting radionuclides. However, high-energy  $\beta^-$  particles, with a range of several millimeters in tissues, can irradiate cells nearby the targeted tumor. Conversely,  $\alpha$  particles (typical penetration range of less than 100  $\mu\text{m}$ ) ([Harrison et al., 2013](#)) and Auger electrons (penetration range of several nanometers to micrometers) have shorter penetration ranges and higher linear energy transfer (LET) ([Unak, 2002](#)). Radiopharmaceuticals deposition sites in the cell is another important factor to consider during palliative treatment of bone metastases using radiopharmaceuticals. For instance, if deposition occurs in the cell nucleus, an Auger electron emitter radionuclide may be adequate for cell killing, while in the case of cell surface deposition,  $\beta^-$  or  $\alpha$  particle-emitting radionuclides may be preferable. Therefore, the design of the carrier molecule to be labelled with the radionuclide should consider the physical properties of the radionuclide to be used. For short-range particles, such as Auger electrons, this means the carrier molecule should be able to cross the cellular membrane either by passive diffusion or via specific carrier mediated process, in order to reach the cell nucleus and to associate with the deoxyribonucleic acid (DNA) complex for a time corresponding to the radionuclide half-life ([Unak, 2002](#)). Cell and tissue studies have shown that once Auger electron emitters are introduced into the cell's cytoplasm, they will present similar effects to those induced by low LET radiations, but when they are introduced close to DNA, the survival curves will be similar to those obtained with high LET  $\alpha$  particles ([Sastry, 1992](#)). Dosimetric calculations have also supported these observations. For example, the decay of  $^{125}\text{I}$  has been shown to lead to the deposition of a very high dose ( $\approx 10^9$  cGy/decaying atom) in the immediate vicinity ( $\approx 2 \text{ nm}^3$ ) of the decay site and a sharp and significant drop in the energy deposited (from  $\approx 10^9$  to  $\approx 10^6$  cGy) as a function of increasing distance (few nanometres) from the decaying  $^{125}\text{I}$  atom ([Kassis, 2011](#)). For example, when  $^{125}\text{I}$  is localized within the cytoplasm, the survival curve is of the low LET type and the number of decays needed to reduce survival is  $\approx 80$  times that of DNA-incorporated  $^{125}\text{I}$  ([Kassis, 2011](#)).

In recent years, several reports have been published describing the use of multiple radionuclides in the context of palliative treatment of bone metastases. Radionuclides investigated for this application included: phosphorus-32 ( $^{32}\text{P}$ ), strontium-89 ( $^{89}\text{Sr}$ ), yttrium-90 ( $^{90}\text{Y}$ ), tin-117m

( $^{117m}\text{Sn}$ ), samarium-153 ( $^{153}\text{Sm}$ ), holmium-166 ( $^{166}\text{Ho}$ ), thulium-170 ( $^{170}\text{Tm}$ ), lutetium-177 ( $^{177}\text{Lu}$ ), rhenium-186 ( $^{186}\text{Re}$ ), rhenium-188 ( $^{188}\text{Re}$ ) and radium-223 ( $^{223}\text{Ra}$ ) ([Abbasi, 2012, 2011](#); [Argyrou et al., 2013a](#); [Bączyk, 2011](#); [Bryan et al., 2009](#); [Chakraborty et al., 2008](#); [Daha et al., 2010](#); [Das et al., 2009](#); [Harrison et al., 2013](#); [Lewington, 2005](#); [Máthé et al., 2010](#); [Neves et al., 2005](#); [Nilsson et al., 2013b, 2007, 2005a, 2005b](#); [Pandit-Taskar et al., 2014](#); [Ramdahl et al., 2013](#); [Sartor, 2004](#); [Simón et al., 2012](#); [Sivaprasad and Rajagopal, 2012](#); [Tomblyn, 2012](#); [Vigna et al., 2011](#); [Volkert and Hoffman, 1999](#); [Wang et al., 2011](#)). Despite the growing number of radionuclides investigated for treatment of bone metastases, the use of  $^{89}\text{Sr}$  and  $^{153}\text{Sm}$  still accounts for the bulk of radiopharmaceutical bone-targeted therapeutics in the clinical context and the majority of the review articles available in the literature focus on those two radionuclides. The present review article has a two-fold aim: 1) to provide an overview of all available radionuclides for palliative treatment of bone metastases, including a description of the key characteristics of such radionuclides; and 2) to describe the clinical outcomes associated with the palliative treatment of bone metastases with different radiopharmaceuticals. The ultimate objective of this review is to provide a state-of-science report on radionuclides and radiopharmaceuticals currently in clinical use or under research for the palliative treatment of bone metastases, and to propose an approach for the rational evaluation and selection of radiopharmaceuticals for palliative treatment of bone metastases.

## **II. PHYSICAL PROPERTIES AND PRODUCTION METHODS OF RADIONUCLIDES FOR BONE PAIN PALLIATION**

Table I presents the summary of the key physical properties of these radionuclides and the next sections provide details on the properties of each radionuclide.

< Insert Table I around here >

### **II.A. PHOSPHORUS-32**

Phosphorus-32 ( $^{32}\text{P}$ ) was the first radioisotope to be evaluated for palliative treatment of bone metastases, and its first clinical use dates back to 1941 ([Bouchet et al., 2000](#); [Lawrence et al., 1947](#);

Nair, 1999; Silberstein et al., 1992).  $^{32}\text{P}$  ( $t_{1/2}=14.26$  d,  $E_{(\text{max})}=1.71$  MeV,  $E_{(\text{mean})}=0.696$  MeV) can be prepared by neutron activation of natural phosphorus ( $^{31}\text{P}(n,\gamma)^{32}\text{P}$ , 100% abundance,  $\sigma = 0.172$  barns) or sulfur ( $^{32}\text{S}(n,p)^{32}\text{P}$ , 95.02% and  $\sigma = 0.54$  barns). The specific activity of  $^{32}\text{P}$  formed in the former reaction is extremely low; and the cross-section of  $^{32}\text{S}(n,p)^{32}\text{P}$  is only 0.54 barns, which means that several hundred grams of sulfur need to be irradiated, in order to have few hundred milliCuries of  $^{32}\text{P}$ . The specific activity of  $^{32}\text{P}$  can also be further reduced due to the introduction of  $^{31}\text{P}$  impurities during the radiochemical processing. Moreover, as a result of the low production cross-section, large irradiation volumes are often required (Bé et al., 2008; Vimalnath et al., 2013). This radionuclide can also be produced by direct neutron capture using elemental phosphorus as the target, which is a simpler and more cost-effective method. However,  $^{32}\text{P}$  produced via this route is of very low specific activity (Das and Pillai, 2013).

## II.B. STRONTIUM-89

Strontium-89 ( $^{89}\text{Sr}$ ) ( $t_{1/2}=50.5$  d,  $E_{(\text{max})}=1.49$  MeV,  $E_{(\text{mean})}=0.585$  MeV,  $E_{\gamma}=909$  keV (0.1%)) is a pure  $\beta^-$  emitter (Ota et al., 2011). This radionuclide is usually produced via  $^{88}\text{Sr}(n,\gamma)^{89}\text{Sr}$  reaction in very high flux reactors. Despite the natural isotopic abundance of  $^{88}\text{Sr}$  being very high (82.3%), an extremely enriched target is needed to avoid the contamination of  $^{89}\text{Sr}$  with  $^{85}\text{Sr}$ . The significantly low thermal neutron capture cross-section (0.058 barns) of  $^{88}\text{Sr}(n,\gamma)^{89}\text{Sr}$  reaction results in low yield of production even when the irradiation is done in very high flux reactor. Alternatively,  $^{89}\text{Sr}$  can be produced using  $^{89}\text{Y}(n,p)^{89}\text{Sr}$  nuclear reaction, but the cross-section of this reaction with thermal neutrons is even lower than the  $^{88}\text{Sr}(n,\gamma)^{89}\text{Sr}$  reaction (0.0002044 versus 0.058 barns). Consequently, the costs of  $^{89}\text{Sr}$ -based bone pain palliation therapies are expected to remain high (Das and Pillai, 2013). In addition to the high production costs and low reactions yields, the specific activity of the formed  $^{89}\text{Sr}$  is very low when obtained by direct production.

## II.C. YTTRIUM-90

$^{90}\text{Y}$  ( $t_{1/2}=2.67$  d,  $E_{(\text{max})}=2.27$  MeV,  $E_{(\text{mean})}=0.267$  MeV, no  $\gamma$  emission) (Bé et al., 2008) is a pure  $\beta^-$  emitter which has well-established applications in targeted radiotherapy. A favorable route

for obtaining large quantities of  $^{90}\text{Y}$  is to employ a  $^{90}\text{Sr}/^{90}\text{Y}$  radionuclide generator. Alternatively,  $^{90}\text{Y}$  may be obtained by direct neutron irradiation of a natural yttrium target,  $^{89}\text{Y}(n,\gamma)^{90}\text{Y}$ . (Das and Pillai, 2013)

#### **II.D. TIN-117m**

Tin-117m ( $^{117\text{m}}\text{Sn}$ ) emits low energy conversion electrons with a very high LET ( $t_{1/2}=13.6$  d, conversion electron's energies of 127 (62%), 129 (12%) and 152 (26%) keV,  $E_{\gamma}=159$  keV (86%)) (Bé et al., 2008).  $^{117\text{m}}\text{Sn}$  is produced either by neutron activation using enriched  $^{116}\text{Sn}$  target, via the  $^{116}\text{Sn}(n,\gamma)^{117\text{m}}\text{Sn}$  nuclear reaction or by inelastic neutron scattering on enriched  $^{117}\text{Sn}$ ,  $^{117}\text{Sn}(n,n',\gamma)^{117\text{m}}\text{Sn}$  (Das and Pillai, 2013; Maslov et al., 2011). However, owing to the poor cross-section of both these reactions and the need for a very high flux reactor and highly enriched targets that are essential to produce sufficient quantities of  $^{117\text{m}}\text{Sn}$ , large-scale production of this radionuclide is not practical. Moreover, the low specific activity of the produced  $^{117\text{m}}\text{Sn}$  can be a limiting factor for radiolabelling of target compounds (Srivastava, 2013). Additional accelerator based production routes have been investigated to produce no carrier added (nca)  $^{117\text{m}}\text{Sn}$ , using  $^3\text{He}$  particle-induced reactions on  $^{116}\text{Cd}$  and  $^{115}\text{In}$  (Maslov et al., 2011; Srivastava, 2013). However, these reactions could provide only low yield.

The  $^{117\text{m}}\text{Sn}$  electrons have short penetration range and, hence, low bone marrow radiation dose. Therefore, radiotherapy agents labelled with  $^{117\text{m}}\text{Sn}$  would have low myelotoxicity (Das and Pillai, 2013). Moreover, the gamma emission of  $^{117\text{m}}\text{Sn}$  is in the ideal range for scintigraphic interrogation, thus allowing for acquisition of images for dosimetry estimates, as well as, for treatment response monitoring.

#### **II.E. SAMARIUM-153**

Presently, one of the most commonly used radionuclides for palliative treatment of bone metastases in routine clinical practice is Samarium-153 ( $^{153}\text{Sm}$ ) ( $t_{1/2}=1.93$  d,  $E_{(\text{max})}=0.81$  MeV,  $E_{(\text{mean})}=0.225$  MeV,  $E_{\gamma}=103$  keV (28%)) (Bé et al., 2008).  $^{153}\text{Sm}$  can be produced from neutron capture of natural or isotopically enriched  $^{153}\text{Sm}$  as  $\text{Sm}_2\text{O}_3$  in a nuclear reactor. Owing to the large



thermal neutron capture cross-section of  $^{152}\text{Sm}(n,\gamma)^{153}\text{Sm}$  reaction (206 barns),  $^{153}\text{Sm}$  can be produced in large quantities and with high specific activity (Neves et al., 2002). A disadvantage of  $^{153}\text{Sm}$  is its relatively short half-life, which restricts the transport of the radiopharmaceutical to distant sites far from the production site of the radioisotope (Das and Pillai, 2013).

## II.F. HOLMIUM-166

Holmium-166 ( $^{166}\text{Ho}$ ) is primarily a  $\beta^-$  emitter ( $t_{1/2}=1.12$  d,  $E_{(\text{max})}=1.85$  MeV,  $E_{(\text{mean})}=0.651$  MeV) with a maximum path length of 8.6 mm in soft tissue and 3.8 mm in bone. It has a complex energy spectrum for quantitative imaging, but the low abundance (7%) of 81 keV photons can be used for gamma-camera imaging (Breitz et al., 2006).  $^{166}\text{Ho}$  can be produced directly from neutron irradiation of  $^{165}\text{Ho}$ , but long-lived  $^{166\text{m}}\text{Ho}$  is also produced, which might result in suboptimal dosimetry. The activation cross-section is 66 barns and hence relatively large quantities of  $^{166}\text{Ho}$  can be prepared with relatively high specific activity (135mCi/mg at a thermal neutron flux of  $4 \times 10^{13}$  n.cm<sup>-2</sup>.s<sup>-1</sup>) for therapeutic applications (Zolghadri et al., 2013). No carrier added (nca)  $^{166}\text{Ho}$  can be produced from the generator system  $^{166}\text{Dy}-^{166}\text{Ho}$ .  $^{166}\text{Dy}$  ( $T_{1/2}=81$  h) is prepared by double neutron capture of  $^{164}\text{Dy}$ ; however, the production yields will only be moderate due to double neutron capture reaction. The specific activity of the  $^{166}\text{Ho}$  produced by direct neutron activation is adequate for several applications. Notwithstanding, due to its short half-life, the site to produce the radiopharmaceutical needs to have knowledge in radiochemistry, which would set limits.

## II.G. THULIUM-170

Thulium-170 ( $^{170}\text{Tm}$ ) ( $t_{1/2}=128.4$  d,  $E_{(\text{max})}=0.968$  MeV,  $E_{(\text{mean})}=0.323$  MeV,  $E_{\gamma}=84$  keV (3.3%)) decays to stable  $^{170}\text{Yb}$  by emission of  $\beta^-$  particles. This radionuclide can be produced by a relatively easy route involving thermal neutron bombardment on natural  $\text{Tm}_2\text{O}_3$  ( $^{169}\text{Tm}$ ) in medium flux research reactors with a relatively low specific activity (Das et al., 2009; Neves et al., 2005). Das *et al.* in 2009 proposed the use of  $^{170}\text{Tm}$ -labelled radiopharmaceuticals as a potential alternative to  $^{89}\text{Sr}$ -chloride for bone pain palliation, as it is readily available (Das et al., 2009). The long physical half-life of  $^{170}\text{Tm}$  (128.6 days) can also be an advantage for this radiopharmaceutical

distribution and storage compared with other radionuclides (Goyal and Antonarakis, 2012). On the other hand, the long half-life of  $^{170}\text{Tm}$  has an important disadvantage in terms of radioactive contamination and disposal of contaminated waste and possibly lower biological effectiveness due to the relative low dose rate per unit of time.

## II.H. LUTETIUM-177

Another promising radionuclide recently proposed for palliative treatment of bone metastases is Lutetium-177 ( $^{177}\text{Lu}$ ) ( $E_{(\text{max})}=0.49\text{ MeV}$ ,  $E_{(\text{mean})}=0.149\text{ MeV}$ ) due to its appealing physical characteristics, in particular, its half-life of 6.73 days, gamma ray emissions of 113keV (6.4%) and 208 keV (10.4%) and tissue penetration of 1.8 mm (Das et al., 2009; Dash et al., 2015). A series of  $^{177}\text{Lu}$ -labeled compounds have been brought to clinical trials stage. The most important advantage of  $^{177}\text{Lu}$  is that it can be produced in large quantities, by employing either the neutron activation of  $\text{Lu}_2\text{O}_3$  (carrier added (ca) form by direct high cross section,  $\approx 2100\text{ b}$ ) or through an enriched  $\text{Yb}_2\text{O}_3$  as the target material (Das and Pillai, 2013). Both reactor production routes can yield  $^{177}\text{Lu}$  for nuclear medicine applications. The direct production route is based on neutron irradiation of  $^{176}\text{Lu}$ , via  $^{176}\text{Lu}(n,\gamma)^{177}\text{Lu}$  reaction, the specific activity values vary significantly depending upon the irradiation conditions (neutron flux, irradiation time, etc.). For direct irradiation of enriched  $^{176}\text{Lu}$ , a specific activity value  $>35\text{ Ci/mg}$  can be obtained at neutron flux  $>3\times 10^{13}\text{ n.cm}^{-2}.\text{s}^{-1}$  (Pillai et al., 2015, 2003). The indirect  $^{176}\text{Yb}(n,\gamma)^{177}\text{Yb}\rightarrow^{177}\text{Lu}$  production route requires chemical separation of  $^{177}\text{Lu}$  from the  $^{176}\text{Yb}$  target atoms and the specific activity should be close to the theoretical value (110 Ci/mg) (Dash et al., 2015; Pillai et al., 2015).

$\text{Lu-177}$  relatively long half-life can provide a logistical advantages when supplying to distant sites from the reactor production facility compared with other shorter lived radionuclides. This radionuclide has several advantages to be explored as a therapeutic radionuclide for bone pain palliation, including its lower  $\beta^-$  particle energy. Among the  $\beta^-$  particle emitters investigated thus far for bone pain palliation,  $^{177}\text{Lu}$  has the lowest tissue penetration range (1.8 mm). A common concern associated with the use of  $\beta^-$  particle emitters is related to their large tissue penetration range of several millimeters, which can result in energy deposition in neighboring, non-targeted cells

(Jackson et al., 2013). The short tissue penetration range of  $^{177}\text{Lu}$   $\beta^-$  particles is placed in the lowest end of the  $\beta^-$  particle emitter's tissue penetration range, minimizing the negative "crossfire" effects often associated with  $\beta^-$  particle emitters. In addition,  $^{177}\text{Lu}$  low  $\beta^-$  particle energy and intermediate physical half-life of 6.73 days allow the deposition of an adequate tumor irradiation dose with a homogeneous distribution during the treatment follow-up (14 days) (Máthé et al., 2010). Additionally, lutetium exclusively exists in the +3 oxidation state, which provides the potential for radiolabeling a variety of molecular carriers, which include small molecules, peptides, proteins and antibodies for therapy.

### III. RHENIUM-186 AND RHENIUM-188

In the late 1980s,  $^{186}\text{Re}$  ( $t_{1/2}=3.8$  d) was identified as a potential agent for palliative treatment of bone metastases and it is currently being used in phase III clinical trials (Goyal and Antonarakis, 2012).  $^{186}\text{Re}$  is a combined  $\beta^-$  and  $\gamma$ -emitter with a maximum  $\beta^-$  emission of 1.07 keV and a 9% abundant  $\gamma$ -ray emission of 137 keV, which is suitable for gamma-camera imaging (Han et al., 2002). This radionuclide can be produced either in a nuclear reactor or in a particle accelerator (cyclotron). The first method utilizes neutron capture of enriched  $^{185}\text{Re}$ ,  $^{185}\text{Re}(n,\gamma)^{186}\text{Re}$ . In the second method, the  $^{186}\text{Re}$  is obtained mainly via proton bombardment of natural tungsten  $^{186}\text{W}$  as a target (Argyrou et al., 2013b).

The therapeutic potential of  $^{188}\text{Re}$  ( $t_{1/2}=0.7$  d,  $E_{(\text{max})}=2.12$  MeV,  $E_{\gamma}=155$  keV (15%)) has recently been considered and investigated (Bé et al., 2008). The availability of no carrier added  $^{188}\text{Re}$  from the  $^{188}\text{W}/^{188}\text{Re}$  generators makes the use of  $^{188}\text{Re}$  convenient. However, currently, there are only a few reactors in the world capable of production of sufficiently high specific activity  $^{188}\text{W}$  needed for the preparation of alumina-based commercial  $^{188}\text{W}/^{188}\text{Re}$  generator (Argyrou et al., 2013a; Das and Pillai, 2013). The short physical half-life and high dose rate are predicted to lead to rapid symptom response post therapy administration (Lewington, 2005; Knut Liepe et al., 2003).

$^{186}\text{Re}$  and  $^{188}\text{Re}$  are two of the radionuclides that can be prepared in nuclear reactors with reasonably high specific activities by using enriched targets (Neves et al., 2002). Interestingly, the chemical properties of rhenium are similar to technetium as both these elements exist in group VIIb of

the periodic table (Kothari et al., 1999), which may provide for the opportunity to label the carrier molecule with either  $^{186/188}\text{Re}$  for target-radiotherapy or the vastly used imaging radionuclide, technetium-99m. However, though technetium and rhenium possess chemical analogy with each other, it is known that rhenium complexes are more difficult to prepare than technetium analogues. Rhenium complexes have a higher tendency to get reoxidized back to perrhenate than do the analogous technetium complexes (Kothari et al., 1999). This reoxidation and consequently, the presence of high radiochemical impurities in the final product, is one of the major hindrances in the development of rhenium radiopharmaceuticals.

## II.J. RADIUM-223

Recently, a significant amount of work has been carried out using Radium-223 ( $^{223}\text{Ra}$ ), a promising therapeutic agent for palliative treatment of bone metastases, in order to take advantage of the low tissue penetration range associated with its emitted  $\alpha$  particles.  $^{223}\text{Ra}$   $\alpha$  particle emission is an appealing strategy for the treatment of bone micrometastases, owing to the short tissue range penetration associated with these radioactive particles that can allow for a more circumscribed irradiation surface. Consequently,  $\alpha$  emitters induce typically less hematologic toxicity for a given bone surface dose than  $\beta^-$  emitters (Harrison et al., 2013; Nilsson et al., 2013b; Pandit-Taskar et al., 2014). Furthermore, the high LET of  $\alpha$  particles has been associated with greater biological effectiveness than  $\beta^-$  particles (Harrison et al., 2013; Nilsson et al., 2013b; Pandit-Taskar et al., 2014).

Although  $^{223}\text{Ra}$  ( $t_{1/2}=11.4$  days) is formed naturally in trace amounts by the decay of uranium-235, it is generally made artificially, via a generator from the parent  $^{227}\text{Ac}$  ( $t_{1/2}=21.8$  y) (Eriksen et al., 2012).  $^{223}\text{Ra}$  emits 4  $\alpha$  particles through its decay scheme with mean  $\alpha$  energy of 5.7 MeV. Because of inherent bone-seeking properties, cationic  $^{223}\text{Ra}$  is a suitable radionuclide for the delivery of high-LET radiation to cancer cells and bone surfaces (Bé et al., 2011; Brechbiel, 2007; Eriksen et al., 2012). The  $\alpha$  particles deposit 1500 times more energy per unit path length compared with  $\beta^-$  particles. This high mean energy deposition in tissues confers  $\alpha$  radiation exquisite cytotoxicity

properties, which commonly manifests itself within the range of cell's dimensions. Such high LET may allow for an accurately controlled therapeutic modality that can be targeted to selected malignant cells with negligible burden to normal tissues.

### **III. BIODISTRIBUTION AND CLINICAL OUTCOMES OF DIFFERENT RADIOPHARMACEUTICALS FOR BONE PAIN PALLIATION**

Table II presents the summary of the biodistribution key features and clinical outcomes of different radiopharmaceuticals currently in use in the clinical setting or under investigation for the palliative treatment of bone metastases. Detail on the characteristics summarized for each radiopharmaceutical in Table II is provided in the next sections.

< Insert Table II around here >

#### **III.A. <sup>32</sup>P-ORTHOPHOSPHATE**

<sup>32</sup>P-orthophosphate is used for the management of bone pain palliation in skeletal metastasis, and it is reported to have similar efficacy as that of <sup>89</sup>Sr-chloride (Das and Pillai, 2013). <sup>32</sup>P-orthophosphate has been administered orally or as a single intravenous injection of 185 to 444 MBq (5 to 12 mCi) (Silberstein, 2005). Following administration, 85% of the activity is incorporated into the bone hydroxyapatite, an uptake mechanism that was demonstrated by Lawrence *et al.* (Lawrence *et al.*, 1939).

The long path of <sup>32</sup>P β<sup>-</sup> particles means that the bone marrow will receive a considerable amount of radiation. As a result, common adverse effects from administration of <sup>32</sup>P-orthophosphate include bone marrow suppression, and there is evidence supporting for a higher degree of myelosuppression for this radionuclide compared with other radionuclides presented in Table I. Thus, poor hematological function is a contraindication to radiotherapy with <sup>32</sup>P-orthophosphate (IAEA, 2007).

The <sup>32</sup>P-orthophosphate overall response rate ranges between 50% and 87% and the mean

reported duration of response is 5 months, with the longest responses reported of 17 months (Lewington, 2005; Silberstein, 2005). The tumor to non-tumor ratio is not very favorable, and the relief of pain is primarily because of its uptake into mineral bone rather than tumor uptake. In fact, in addition to the skeletal bone uptake, this radiopharmaceutical uptake is also high in rapidly dividing tissues, such as the intestinal wall and the red marrow (Srivastava, 2007).

### III.B. <sup>89</sup>Sr-CHLORIDE

Soluble strontium compounds behave like their calcium analogs, clearing rapidly from the blood and selectively localizing in the mineral bone. Uptake of strontium by bone occurs preferentially in sites of active osteogenesis and, thus primary bone tumors and areas of metastatic involvement (blastic lesions) can accumulate significantly greater concentrations of strontium than surrounding normal bone.

Strontium chloride (<sup>89</sup>SrCl<sub>2</sub>, commercial name Metastron, GE Healthcare) is used for providing palliative care to the patients suffering from bone pain due to skeletal metastasis (Das and Pillai, 2013). When injected intravenously, <sup>89</sup>SrCl<sub>2</sub> substitutes calcium in the bone hydroxyapatite. This radiopharmaceutical is excreted by both renal (80%) and fecal (20%) routes. Approximately 30% to 35% of the radiopharmaceutical remains in the bone, with a 10-fold higher uptake for metastatic tumor compared to healthy bone (Goyal and Antonarakis, 2012; Silberstein, 2005). The usual dosage administered is either 148 MBq (4 mCi) or 1.48 MBq/kg (40 μCi/kg), where administration of larger doses of this radiopharmaceutical result in proportionally higher myelosuppression (Silberstein, 2005).

Bone marrow toxicity is to be expected following the administration of the radiopharmaceutical, with reduction in white blood cells and platelets counts. Typically, platelets will be depressed by about 30% compared to pre-administration levels. The nadir of platelet depression in most patients is found between 12 and 16 weeks following administration of the radiopharmaceutical. White blood cells are usually depressed to a varying extent compared to pre-administration levels (Silberstein, 2005). The treatment response time has been reported as early as 3 days, but it is most commonly noted in the second or third week after administration, the mean

duration of pain reduction is 3 to 6 months (Silberstein, 2005).

A variety of studies have shown effective palliation of pain following treatment with  $^{89}\text{SrCl}_2$  (palliative response in 65% to 90% of treated patients), with as many as 25% of the patients able to discontinue analgesics and 5-20% reporting complete pain relief (Bedi et al., 2014; Sartor et al., 2013; Silberstein, 2005).  $^{89}\text{SrCl}_2$  also reduces the incidence of new bone metastases, but given alone, it does not prolong life (Reddy et al., 1986; Silberstein, 2005). Published data suggest that  $^{89}\text{Sr}$  has been shown to delay the time of appearance of recurrent or new sites of pain requiring therapy. The success of  $^{89}\text{Sr}$  in providing this benefit probably relates to the long effective half-life of this radiopharmaceutical in bone (Eary and Brenner, 2007).

### III.C. $^{90}\text{Y}$ -Ethylenediaminetetramethylene phosphonic acid (EDTMP)

A disadvantage of natural  $^{90}\text{Y}$  is its tendency to accumulate in the reticuloendothelial system as well as hydroxyapatite surfaces, due to the formation of colloidal hydroxide or yttrium-transferrin complexes, followed by transport to the liver (Keeling et al., 1989). Specific deposition of yttrium into the skeleton demands its delivery to the target tissue in a chemical form with affinity for mineral bone. Compounds with these properties are the phosphonate analogues of aminopolycarboxylic acids, in particular, ethylenediaminetetramethylene-phosphonate (EDTMP).

Biodistribution studies in rats showed a significant skeleton uptake (~50% of injected dose) of  $^{90}\text{Y}$ -EDTMP, which remained almost unchanged for long periods of time (72 h), and a rapid clearance from all soft tissues (Khalid et al., 2014; Rosch et al., 1996). Furthermore, the majority of the administered radioactivity was rapidly removed via the urinary system (Keeling et al., 1989). Rosch *et al.* in 1996 reported that the average dose to  $1\text{ cm}^3$  of bone metastases per MBq of injected  $^{90}\text{Y}$ -EDTMP was 18 mGy/MBq compared to 1.8 mGy/MBq dose to the red marrow. A rapid clearance of  $^{90}\text{Y}$ -EDTMP from blood (clearance of 50% injected dose at 2.5 min post administration), high concentration of  $^{90}\text{Y}$ -EDTMP in bone metastases (maximum at 1.5 hours after administration) and negligible retention in the liver were reported in humans (Rosch et al., 1996).

### III.D. $^{117\text{m}}\text{Sn}$ -Diethylenetriaminepentaacetic (DTPA)

Optimal blood and soft tissue clearance was measured following intravenous administration of  $^{117m}\text{Sn}$ -DTPA (Gerbail et al., 1997; Lewington, 2005).  $^{117m}\text{Sn}$ -DTPA mechanism of uptake by bone metastases is postulated to rely on the precipitation of stannous oxide on bone surfaces or on hydrolysis reactions with hydroxyapatite. Post intravenous administration in humans, the radioactivity measured in the bone component accounted for 77.6% of injected activity and showed no biological clearance. The remaining 22.4% of administered activity was found to be cleared via the urinary system (Gerbail et al., 1997; Lewington, 2005). The clearance rate from blood appeared to be considerably slower than other bone agents. However, because of its rather long physical half-life relative to these biologic parameters, this is not a concern for radiation absorbed dose in target sites (Srivastava, 2007). The lesion-to-normal bone ratios ranged from as low as 2 to as high as 9 and varied from patient to patient and within the same patient (Gerbail et al., 1997).

A phase I clinical study conducted using  $^{117m}\text{Sn}$ -DTPA (activity range of 66-573 MBq, 1.78-15.48 mCi) reported symptom benefit in 9 out of the 10 evaluated patients with no significant myelotoxicity (Lewington, 2005). Subsequently, a phase II clinical trial reported a 75% overall pain response (range, 60-83%), with complete pain relief in 30% of the patients. The typical response time was  $19\pm 15$  days using activity values of  $\leq 5.29$  MBq/kg (0.143 mCi/kg) and  $5\pm 3$  days in patients receiving activities of  $\geq 6.61$  MBq/kg (0.178 mCi/kg) (Lewington, 2005). The high ratio of bone surface dose to red marrow dose from  $^{117m}\text{Sn}$ -DTPA, due to the limited range of its moderately low-energy conversion electrons emitted during radioactive decay, is one of the most appealing features of this radiopharmaceutical for treatment of bone metastases.

### **III.E. $^{153}\text{Sm}$ -Ethylenediaminetetramethylene phosphonic acid (EDTMP)**

$^{153}\text{Sm}$ -EDTMP (Quadramet®, Lantheus Medical Imaging) has a high affinity for bone and concentrates in areas of bone turnover. Quadramet® was introduced commercially in 1997 by Cytogen Corporation for the relief of pain arising from metastatic bone disease. In patients with metastatic lesions, 50% to 65% of the injected radiopharmaceutical will be chemisorbed into the bone. Metastatic lesions can accumulate about 5 times more  $^{153}\text{Sm}$ -EDTMP than healthy bone tissue (Paes and Serafini, 2010). Renal excretion is complete within 8 hours post radiopharmaceutical



administration and less than 1% remains in the blood at 5 h post injection.  $^{153}\text{Sm}$ -EDTMP given at 37 MBq/kg (1.0 mCi/kg) leads to pain reduction in 55% to 70% of evaluated patients (Eary et al., 1993; Silberstein, 2005). An initial clinical study demonstrated dose-limiting myelotoxicity following administration of  $^{153}\text{Sm}$ -EDTMP, with a maximum tolerated activity of 37 MBq/kg (1 mCi/kg) (Farhanghi et al., 1992). The distribution of  $^{153}\text{Sm}$ -EDTMP is identical to that of other bone-seeking radiopharmaceuticals, such as  $^{99\text{m}}\text{Tc}$ -methylene diphosphonate (MDP) (Singh et al., 1989). As with the other radiopharmaceuticals, pain reduction or relief begins in 1 to 4 weeks post-treatment and can last for as long as 2 to 17 weeks (Silberstein, 2005, 2000). Mild myelotoxicity predictably occurs, with a reduction in leukocyte and platelet counts of approximately 10% to 40%, and full recovery in 6 to 8 weeks (Silberstein, 2005).

### **III.F. $^{166}\text{Ho}$ -1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonic acid (DOTMP) and $^{166}\text{Ho}$ -1-2-propylene di-amino tetra(methylenephosphonic acid) (PDTMP)**

$^{166}\text{Ho}$  complexed with DOTMP localizes in the skeleton and clears rapidly and exclusively via the kidneys into the urine by virtue of its high overall negative charge. The long range of  $^{166}\text{Ho}$   $\beta^-$  particles produces higher marrow suppression compared with  $^{153}\text{Sm}$ -EDTMP, although the  $^{166}\text{Ho}$ -DOTMP toxicity profile has been reported to be acceptable (Champlin et al., 2004; Volkert and Hoffman, 1999). The efficacy and late toxicities observed indicated that even at high administered activities, the marrow was not the dose-limiting organ, but rather the kidneys and urinary bladder (Breitz et al., 2006). Skeletal uptake of  $^{166}\text{Ho}$ -DOTMP varied from 19% to 39% of the injected activity (mean skeletal uptake of 28%, n=12 patients, 2 administrations of 1.1 GBq (30mCi) of  $^{166}\text{Ho}$ -DOTMP 1 week apart) (Breitz et al., 2006). An alternative to  $^{166}\text{Ho}$ -DOTMP is  $^{166}\text{Ho}$ -PDTMP (Zolghadri et al., 2013). Following intravenous injection into rats (26 MBq),  $^{166}\text{Ho}$ -PDTMP is completely washed out from the circulation within 48h post-administration. It is rapidly taken up by the bones over 2h after administration, and it is retained in bone tissue up to 24h post-administration. This compound has almost no liver, kidney or spleen accumulation, which is a major advantage from the dosimetric perspective of a therapeutic radiopharmaceutical (Zolghadri et al., 2013).

### **III.F. $^{170}\text{Tm}$ -Ethylenediaminetetramethylene phosphonic acid (EDTMP)**

Following intravenous injection in healthy rats,  $^{170}\text{Tm}$ -EDTMP displays a good skeletal accumulation (50-55% of injected activity), with no significant uptake in others vital organs and rapid urinary excretion of 37% at 3 hours after injection (Das et al., 2009). No clinical data has been reported to date for this radiopharmaceutical. Administration of  $^{170}\text{Tm}$ -EDTMP along with short-lived radiopharmaceuticals like  $^{153}\text{Sm}$  or  $^{177}\text{Lu}$  (also labelled with EDTMP complexes) could give immediate as well as long-term pain relief, thereby combining the merits of both short- and long-lived radionuclides for bone pain palliation (Das et al., 2009).

### **III.G. $^{177}\text{Lu}$ -Ethylenediaminetetramethylene phosphonic acid (EDTMP) and $^{177}\text{Lu}$ -1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonate (DOTMP)**

Pre-clinical trials in dogs showed that  $^{177}\text{Lu}$ -EDTMP is taken up almost exclusively by the skeletal system (>70%), with minimal activity accumulation in other organs (Bahrami-samani et al., 2012; Máthé et al., 2010; Saeed et al., 2012). Clinical trials with  $^{177}\text{Lu}$ -EDTMP showed an obvious reduction in the pain scores at 2 to 6 weeks after the radiopharmaceutical administration. The rate of complete response in the bone pain palliation was between 55% and 80%. This study demonstrated that an administered activity of 1295 MBq (35 mCi) was sufficient for bone pain palliation therapy and administered activities as high as 2590 MBq (70 mCi) were well tolerated (Shinto et al., 2014; Yuan et al., 2013). Taken together the data indicated that the  $^{177}\text{Lu}$ -EDTMP had an adequate bone uptake, rapid urinary excretion and prolonged retention in the bone tissue. Hematologic toxicity was mild and transient (Agarwal et al., 2014). All these characteristics along with its optimum physical and chemical properties render  $^{177}\text{Lu}$ -EDTMP a promising therapeutic agent for pain palliation (Saeed et al., 2012). Moreover, Agarwal *et al.* in 2014 reported in a phase II clinical study (n=44) an overall response rate of 86% after intravenous administration of  $^{177}\text{Lu}$ -EDTMP, with a median time of response of 8 days and median duration of 3 months (Agarwal et al., 2014).

$^{177}\text{Lu}$ -DOTMP pre-clinical trials showed a skeletal uptake of 16% of injected dose in healthy mice, with the remaining activity being excreted almost entirely via the urinary system. This

radiopharmaceutical causes less myelosuppression than an equivalent dose of  $^{153}\text{Sm}$ -EDTMP (Bryan et al., 2009).

A comparative study between  $^{177}\text{Lu}$ -EDTMP and  $^{177}\text{Lu}$ -DOTMP showed that  $^{177}\text{Lu}$ -EDTMP has marginally higher skeletal accumulation in comparison to that of  $^{177}\text{Lu}$ -DOTMP, while the latter has slightly faster blood clearance along with lower retention in liver and kidneys in animal models (Chakraborty et al., 2008). Furthermore, another comparative study investigating EDTMP complexes labelled with different radionuclides ( $^{177}\text{Lu}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$  and  $^{153}\text{Sm}$ ) showed a skeletal uptake of 70% for  $^{177}\text{Lu}$ -EDTMP, followed by  $^{153}\text{Sm}$ -EDTMP (58%),  $^{90}\text{Y}$ -EDTMP (45%) and  $^{166}\text{Ho}$ -EDTMP (36%). All these radiopharmaceuticals showed good renal and rapid blood clearance (Sohaib et al., 2007). These data suggest that replacing the radionuclides  $^{153}\text{Sm}$  and  $^{90}\text{Y}$  with  $^{177}\text{Lu}$  in the EDTMP complex would improve the potential for cell death in the target tissue, while reducing the bone marrow toxicity due to the shorter tissue penetration range of  $^{177}\text{Lu}$   $\beta^-$  particles in comparison with those of  $^{153}\text{Sm}$  and  $^{89}\text{Sr}$   $\beta^-$  particles.

### III.H. $^{186/188}\text{Re}$ -Hydroxyethylidene-diphosphonate (HEDP)

Following administration of  $^{186}\text{Re}$ -HEDP, around 70% of the radioactivity is excreted in the urine over 72 hours (Rijk et al., 1992; Silberstein, 2005). Similar to  $^{89}\text{Sr}$ -EDTMP, this radiopharmaceutical is retained longer in the reactive bone around the lesion than in normal bone. In initial clinical trials, approximately 1221 MBq (33 mCi) of  $^{186}\text{Re}$ -HEDP was administered as a single intravenous injection to 20 patients diagnosed with prostate cancer with osseous metastases. Pain relief was reported in 80% of patients with only mild and transient marrow toxicity. Later, with administered activities of  $^{186}\text{Re}$ -HEDP ranging between 1110 to 2590 MBq (30 to 70 mCi), a therapeutic response has been reported in about 55% to 80% of the cases, and pain relief occurred within 1 to 3 weeks (Sartor, 2004; Silberstein, 2005). On another clinical trial, administration of  $^{186}\text{Re}$ -HEDP resulted in pain relief in 77% of the treated patients and around 20% of the patients receiving  $^{186}\text{Re}$ -HEDP reported to be pain free (K. Liepe et al., 2003; Liepe et al., 2005). Overall, most clinical studies using  $^{186}\text{Re}$ -HEDP to relieve pain from bone metastases have reported rates of pain relief up to 87% (Han et al., 2002). The mean duration of pain relief after the first dosage of

$^{186}\text{Re}$ -HEDP was 6 weeks (Goyal and Antonarakis, 2012).

The maximum tolerated administered activity of  $^{186}\text{Re}$ -HEDP in patients with metastatic cancer was found to be 2405 MBq (65 mCi) with thrombocytopenia as the dose-limiting toxicity (De Klerk et al., 1980).  $^{188}\text{Re}$ -HEDP has similar biodistribution and radiation dosimetry characteristics as  $^{186}\text{Re}$ -HEDP and appears to result in similar benefits and toxicities in patients with skeletal metastases (Maxon et al., 1998).

The pain relief data reported following administration of  $^{186}\text{Re}$ -HEDP compare favorably with the reported pain relief of 67% for  $^{188}\text{Re}$ -HEDP. Moreover, 16% of patients treated with  $^{188}\text{Re}$ -HEDP and 13% treated with  $^{186}\text{Re}$ -HEDP were able to discontinue their analgesics and were pain-free (Liepe, 2005). Treatments with  $^{186}\text{Re}$ -HEDP have a mean duration of response of seven weeks. The only toxicity reported was mild and reversible thrombocytopenia (Liepe, 2005).

### III.I. $^{223}\text{Ra}$ -Chloride

$^{223}\text{Ra}$ -Chloride ( $^{223}\text{RaCl}_2$ ) concentrates in bone as a consequence of being calcium-mimetic and its peak skeletal uptake occurs within 1 hour of injection, with no subsequent redistribution. Its blood clearance is rapid after intravenous administration and the total skeletal uptake is estimated to range between 40% and 60% of the administered activity (Goyal and Antonarakis, 2012). Unlike most bone-seeking radionuclides, excretion is predominantly via gastrointestinal tract, with less than 10% renal clearance (Lewington, 2005).

In clinical reports, this radiopharmaceutical had a pain response up to 71% and the pain-relieving effect was present after 2 weeks, presenting a mean duration in responders of approximately 50 days. Data from these studies showed that there was no evidence of long-term toxicity during the 2-year follow-up and administered activities of at least 50 kBq/kg had a significant positive effect in bone alkaline phosphatase (ALP), prostate-specific antigen (PSA) levels, pain reduction and overall survival (El-Amm et al., 2013; Harrison et al., 2013; Nilsson et al., 2012). In general,  $^{223}\text{RaCl}_2$  was well tolerated, and no dose-limiting hemotoxicity was observed (Harrison et al., 2013). Some reversible mild myelosuppression events were reported, with nadirs 2 to 4 weeks after injection and complete recovery during 8 weeks post radiopharmaceutical

administration. The neutrophils were more frequently affected than the platelets, whereas for  $\beta^-$  emitters thrombocytopenia is often the clinically important toxicity. The most common forms of adverse event were transient diarrhea, fatigue, nausea and vomiting (Nilsson et al., 2005a). In clinical studies,  $^{223}\text{RaCl}_2$  has demonstrated a highly significant improvement on patient overall survival, with mild side effects owing to its localized tissue penetration (2-10 cells). Overall,  $^{223}\text{RaCl}_2$  has demonstrated highly favorable toxicity profile, though long-term toxicity data are not available (Sullivan et al., 2013).

$^{223}\text{RaCl}_2$  (Xofigo™, Bayer Pharmaceuticals) is the first alpha particle-emitting radiopharmaceutical approved for routine clinical use by the FDA (Harrison et al., 2013). To date,  $^{223}\text{Ra}$ -dichloride is the only radiopharmaceutical identified for treatment of palliative bone metastasis with shown ability to increase patients' life-expectancy (Harrison et al., 2013; Nilsson et al., 2013a).

#### **IV. THE IDEAL RADIOPHARMACEUTICAL FOR BONE PAIN PALLIATION**

Over the years, efforts have been undertaken to identify radionuclides with improved physical properties for use in palliative care of metastatic bone pain, as well as, to develop better bone-seeking agents to be used for radiolabelling with promising radionuclides. Based on the literature review conducted here, it is proposed a flowchart to support selection of the most suitable radionuclide and radiopharmaceutical based on the characteristics of an ideal radiopharmaceutical for bone pain palliation (Figure 1).

< Insert Figure 1 around here >

Treatment success depends on matching the physiologic characteristics of the target tissue to a specific pharmaceutical carrier and optimal radionuclide. Interestingly, when comparing the clinical response across the available data, there appears to be no substantial difference in palliative efficacy among radiopharmaceuticals. Although the clinical outcomes of the palliative

treatment of bone metastases using radiopharmaceuticals can vary with the radionuclide used, in general, it can be stated that the overall benefit from all these treatments is around 75% and that about 25% of the patients have complete response. Despite the similar overall benefit reported across different radiopharmaceuticals, the measured uptake by the bone tissue varies as much as between 16% and 85%. Because most bone seeking radiopharmaceuticals act as calcium-mimetic agents, and thus localize in bone crystal rather in or on cancer cells, it may be reasonable to hypothesize that the disjointed observation of similar pain relief across radiopharmaceuticals versus varying uptake values in bone could be due to DNA damage of cancer cells from decay, with subsequent cell death, as well as damage to cells producing pain modulators or analgesic effect by targeting nerve terminals in and around the metastasis. Given the overall benefit from metastatic bone palliation treatments of around 75% across different radiopharmaceuticals, the choice of the radiopharmaceutical most suitable to a given patient may rely on the combination of the physical properties of the radionuclide, patient's life expectancy and patient's overall clinical state at the time of the therapeutic, including myelosuppression response.

The radionuclide properties play one of the most important roles to achieve effective accumulated dose per unit time. In this regard, a shorter half-life is an advantage to achieve large doses per unit time (Unak, 2002). Different half-lives imply different dose rates, if the surviving cells in the irradiated volume are continuously proliferating (Guerra Liberal et al., 2014; Neves et al., 2005). For example, delivery of 90% of the total dose of radiation requires approximately 3.5 half-lives of decay (Sartor, 2004), which will correspond to a time interval of approximately 64 weeks for  $^{170}\text{Tm}$ , 25 weeks for  $^{89}\text{Sr}$  and 1 week for  $^{153}\text{Sm}$  (Sartor, 2004). Data from clinical studies has shown that the duration of treatment response is variable and is usually reported to range between 2 and 6 months. Moreover, typically, there is a delay in treatment response that can vary between 1 and 3 weeks after injection. This delay is shorter using shorter-lived radionuclides. Taken together, this information can be particularly valuable when defining which radiopharmaceutical to use for treatment of patients with short life expectancies (<3 months), given that longer time periods required to deliver 90% of the radiation dose (i.e. radionuclides with longer half-lives) may be

disadvantageous for patients with short life expectancy (Krishnan et al., 2014). Consequently, it is possible to rank the radionuclides available in two major groups: 1) useful for treatment of short-life expectancy patients, namely,  $^{32}\text{P}$ ,  $^{90}\text{Y}$ ,  $^{117\text{m}}\text{Sn}$ ,  $^{153}\text{Sm}$ ,  $^{166}\text{Ho}$ ,  $^{177}\text{Lu}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$  and  $^{223}\text{Ra}$ ; and 2) useful for treatment of long-life expectancy patients, namely,  $^{32}\text{P}$ ,  $^{89}\text{Sr}$ ,  $^{90}\text{Y}$ ,  $^{117\text{m}}\text{Sn}$ ,  $^{153}\text{Sm}$ ,  $^{166}\text{Ho}$ ,  $^{177}\text{Lu}$ ,  $^{170}\text{Tm}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$  and  $^{223}\text{Ra}$ .

A major challenge associated with the palliative treatment of bone pain using selective radiopharmaceuticals is to deliver the adequate dose of ionizing radiation to the bone lesion while minimizing the dose to healthy bone sites and adjacent tissues. Consequently, the emitted particles should have an energy and tissue penetration range compatible with the volume of the lesion to be irradiated (Chakraborty et al., 2008; Daha et al., 2010; Wang et al., 2011). Zalutsky *et al.* in 2000 compared the penetration ranges of different radioactive particles and reported that  $^{90}\text{Y}$   $\beta^-$  particles ( $E_{(\text{max})}=2.3$  MeV) had the range of 215 cells size,  $^{131}\text{I}$   $\beta^-$  particles ( $E_{(\text{max})}=0.8$  MeV) had a range of 40 cells size and  $^{211}\text{At}$   $\alpha$  particles ( $E_{(\text{max})}=6.8$  MeV) had a range of only 3 cells size (Zalutsky and Vaidyanathan, 2000). Therefore, owing to their short penetration range, systemic tumor-targeted radiotherapy with Auger electrons or alpha particles often yields lower toxicity to the bone marrow in comparison to  $\beta^-$  particles (Tavares and Tavares, 2010). Hence, radionuclides emitting Auger electrons or alpha particles are appropriate for single cell killing or micro-metastasis, while radionuclides emitting  $\beta^-$  particles seem better placed to destroy large size tumors. Bernhardt *et al.* in 2001 reported that as the energy of electrons increased, absorbed dose rate decreased in small tumors (Bernhardt et al., 2001; Uusija et al., 2006). This study highlights the importance of particle energy in target-tumor radiotherapy. This together with the penetration range of different particles helps ranking the radionuclides available in two major groups: 1) useful for treatment of small tumors and micro-metastases, namely,  $^{117\text{m}}\text{Sn}$ ,  $^{177}\text{Lu}$  and  $^{223}\text{Ra}$ ; and 2) useful for treatment of medium to large tumors, namely,  $^{32}\text{P}$ ,  $^{89}\text{Sr}$ ,  $^{90}\text{Y}$ ,  $^{153}\text{Sm}$ ,  $^{166}\text{Ho}$ ,  $^{170}\text{Tm}$ ,  $^{186}\text{Re}$  and  $^{188}\text{Re}$ . In agreement with this ranking perspective are previous studies demonstrating that  $^{177}\text{Lu}$  is found to be effective in localizing cytotoxic radiation in relatively small areas and proficient in destroying small tumors, as well as, metastatic lesions (typically less than 3 mm diameter) with less damage to surrounding normal tissue (Dash et al., 2015).

Hematologic toxicity has been the primary adverse effect associated with radiopharmaceutical administration reported in the studies that assessed this outcome. Thrombocytopenia was reported as an adverse effect in 30-50% of patients treated with radiopharmaceutical and was typically mild. Neutropenia was a less commonly reported side effect when radiopharmaceuticals were used alone, but was more common in reports of radiopharmaceuticals combined with chemotherapy and in treatments using  $^{223}\text{Ra}$  (Bauman et al., 2005). The major dose-limiting factor for radionuclide therapy is bone marrow toxicity, which results in a reduction in peripheral blood count, especially count of platelets. Consequently, treatment of bone pain palliation with  $^{32}\text{P}$  would be suboptimal owing to the substantial bone marrow toxicity of this  $\beta^-$  emitter, most likely due to the high tissue penetration range of the emitted radioactive particles. In this regard, using radiopharmaceuticals with mild side effects such as,  $^{177}\text{Lu}$ -DOTMP,  $^{177}\text{Lu}$ -EDTMP or  $^{117\text{m}}\text{Sn}$ -DTPA, would be preferable than radiopharmaceuticals reported to yield significant side effects, such as  $^{89}\text{SrCl}_2$  or  $^{32}\text{P}$ -orthophosphate, in particular, when multi-treatment regimens are foreseen for a given patient with high life-expectancy.

It is also important that the radionuclide to be used for palliative treatment of bone metastases allows for *in vivo* imaging, in order to assist with the determination of the suitable administered activity to be used and to facilitate treatment response monitoring over time, which is particularly valuable for patients with long term life-expectancy (Henriksen et al., 2003; Pandit-Taskar et al., 2014). To this regard, the Auger electron emitter  $^{117\text{m}}\text{Sn}$  has the highest percentage of gamma ray emission, followed by  $^{153}\text{Sm}$ ,  $^{188}\text{Re}$  and  $^{177}\text{Lu}$ .

Typically, radiopharmaceuticals must also meet several specifications in order to fulfill clinical requirements, including high specific activity, high radiochemical and radionuclide purity, and high radiochemical yield. No carrier added radionuclides are ideal to obtain high specific activity radiopharmaceuticals. This will ensure that a larger amount of radioactive tagged carrier molecules is delivered to the tumor, thus improving the delivery of radiation absorbed dose per unit of injected activity. Notwithstanding, while targeted radionuclide therapy is primarily based on selecting appropriate radiopharmaceuticals and targeting mechanisms, the number of target sites (receptors,



cells, etc.) available for radiopharmaceutical targeting dictates the specific activity of the radionuclide that is suitable for a particular application. Trabecular bone is considered a large capacity site and does not require a radionuclide with very high specific activity. For this reason, the need for a radionuclide with high specific activity for treatment of bone metastases is less pressing than other receptor based therapies. Under this premise, medium-low specific activity radionuclides can generally be used for palliative treatment of bone metastases (Dash et al., 2015).

In addition to the radionuclide and radiopharmaceutical properties discussed above, other factors should be taken into consideration while searching for the ideal radiopharmaceutical for palliative treatment of bone metastases. Inevitably, one would have to consider the costs of a given therapeutic and the logistics associated with a particular radionuclide production. Radionuclides produced via generator or presenting longer half-lives would represent a less cumbersome approach in terms of production and worldwide distribution than radionuclides with short half-lives and complicated production routes. Nonetheless, the benefit to the patient needs to be factored here by considering the patient life-expectancy and hematologic profile at the time of the therapy.

## V. CONCLUDING REMARKS AND FUTURE PROSPECTS

Despite the increasing availability of radionuclides for palliative treatment of bone metastases (Das et al., 2009; Goyal and Antonarakis, 2012), the choice of which therapeutic agent to use is far from unanimous and no standardization or guideline exists to assist with this choice.  $^{89}\text{SrCl}_2$  and  $^{153}\text{Sm-EDTMP}$ , two commercially available radiopharmaceuticals, still account for the bulk of bone pain palliation radiotherapy (Das and Pillai, 2013). Remarkably, the range of physical properties of the radionuclides available for bone pain palliation is wide, with half-lives ranging from less than a day ( $^{188}\text{Re}$ ) to 128.4 days ( $^{170}\text{Tm}$ ) and mean particles energy as low as 0.13 MeV ( $^{117\text{m}}\text{Sn}$ ) and as high as 5.716 MeV ( $^{223}\text{Ra}$ ). Thus, the time might be right for a careful rationalization exercise to assist with the process of selecting the best agent for a given therapeutic application within the context of bone pain palliation.

While a myriad of factors contribute to the success of palliative treatment of bone metastasis

using radiopharmaceuticals, the patients' life expectancy and overall clinical status, including hematologic profile can be defining initial criteria for subsequent selection of which radionuclide and radiopharmaceutical to use. Given that the reported therapeutic effects of various radiopharmaceuticals has been similar, we propose the use of patients' life expectancy together with the radionuclide half-life as the first line of approach for selection of the ideal radiopharmaceutical for a given patient. Then the size of tumor may be factored in together with the radionuclide tissue penetration range. Ability to image patients and follow treatment response can be another important feature, in particular, in patients with long term life expectancy. Cost-effectiveness of a given radiopharmaceutical production and distribution can then further narrow the choice. Using this strategy,  $^{177}\text{Lu}$ - and  $^{188}\text{Re}$ -labeled radiopharmaceuticals appear to be the most favorable for treatment of small and medium/large size tumors, respectively. Their cost-effective and convenient availability would be advantageous for underpinning the success of using  $^{177}\text{Lu}$ - and  $^{188}\text{Re}$ -labeled radiopharmaceuticals for *in vivo* targeted therapy of bone metastases. Unfortunately, current wide access and clinical use of these radiopharmaceuticals is not yet a reality, and a solution to this and other unresolved issues can be time consuming and hinder the use of these radiopharmaceuticals in the near future.

In conclusion, several aspects need to be considered when choosing the radiopharmaceutical to use for target-tumor radiotherapy. This should go beyond the inevitable analysis of costs and logistics, and should include an analysis of the radionuclide physical properties, as well as, size of the lesions to be treated, patient's clinical condition and life expectancy, in order to optimize the therapeutic efficacy. In this paper, we proposed an approach to assist with the rational selection of the ideal radiopharmaceutical for palliative treatment of bone metastases for a given patient, based on previously published literature for different radionuclides and radiopharmaceuticals.

#### **CONFLICT OF INTEREST**

The authors declare no conflict of interests regarding the publication of this paper.

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## FIGURE CAPTIONS

**Figure 1.** Selection of the radionuclide/radiopharmaceutical based on the physical characteristics of the radionuclide and patient's life expectancy.  $^{177}\text{Lu}$  and  $^{188}\text{Re}$ -labeled radiopharmaceuticals appear to be the most suitable choices for treatment of small and medium/large size bone lesions, respectively.

## **TABLE CAPTIONS**

**TABLE I:** Summary of main physical properties of different radionuclides in clinical use or under research for palliative treatment of bone metastases.

**TABLE II.** Summary of the key clinical outcomes of different radiopharmaceuticals currently used in the clinical setting or under research for palliative treatment of bone metastases.

**FIGURES**

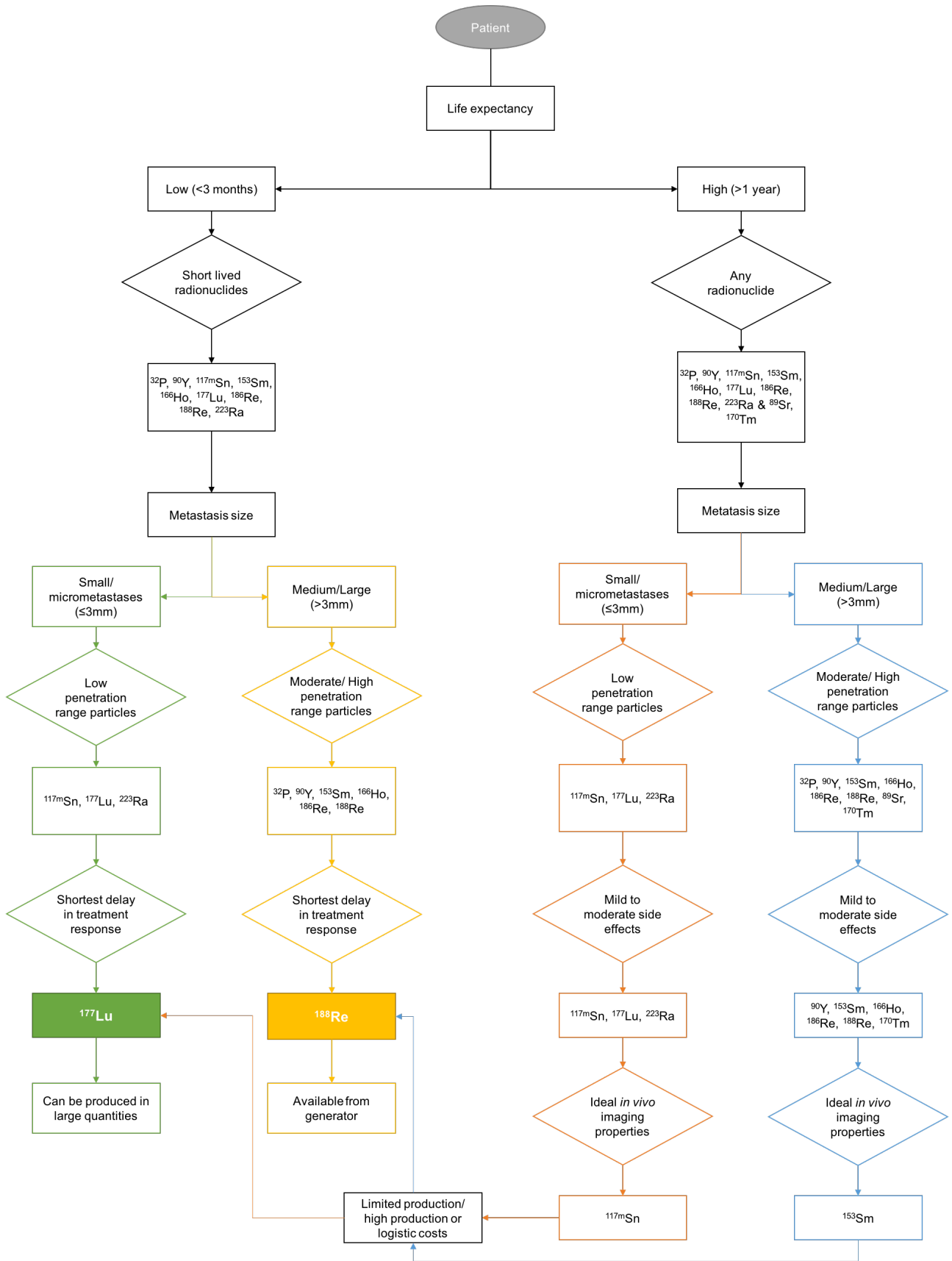


Figure 1

**TABLES**

**Table I:** Summary of main physical properties of different radionuclides in clinical use or under research for palliative treatment of bone metastases.

Radionuclide	Emission type	E mean (MeV) (%)	E <sub>γ</sub> (keV) (%)	T <sub>1/2</sub> (days)	Tissue penetration max. (mm)	Main production mode (impurities)	Production and logistics cost	References
<sup>32</sup> P	β <sup>-</sup>	0.6955 (100)	-	14.3	8.0	<sup>31</sup> P(n,γ) <sup>32</sup> P (None)	High	(Bé et al., 2008; Lewington, 2005; Vimalnath et al., 2013; Volkert and Hoffman, 1999)
						<sup>32</sup> S(n,p) <sup>32</sup> P ( <sup>33</sup> P, <sup>35</sup> S)	Cost-effective	
						<sup>34</sup> S(d,α) <sup>32</sup> P (None)	High	
<sup>89</sup> Sr	β <sup>-</sup>	0.5846 (99.99)	909 (0.1)	50.5	6.7	<sup>88</sup> Sr(n,γ) <sup>89</sup> Sr ( <sup>85</sup> Sr, <sup>90</sup> Sr)	High	(Bé et al., 2008; Lewington, 2005; Volkert and Hoffman, 1999)
						Fission Product ( <sup>90</sup> Sr)	High	
						<sup>87</sup> Sr(t,p) <sup>89</sup> Sr (None)	High	
						<sup>86</sup> Kr(α,nγ) <sup>89</sup> Sr (None)	High	
<sup>90</sup> Y	β <sup>-</sup>	0.927 (99.98)	-	2.67	11	<sup>90</sup> Sr(β) <sup>90</sup> Y (None)	High	(Bé et al., 2008; Volkert and Hoffman, 1999)
						<sup>89</sup> Y(n,γ) <sup>90</sup> Y ( <sup>91</sup> Y)	Cost-effective	
<sup>117m</sup> Sn	Auger	0.1268 (64.8)	159 (86)	13.6	0.3	<sup>116</sup> Sn(n,γ) <sup>117m</sup> Sn (None)	High	(Bé et al., 2008; Lewington, 2005; Maslov et al., 2011; Volkert and Hoffman, 1999)
						<sup>117</sup> Sn(n,n') <sup>117m</sup> Sn (None)	High	
<sup>153</sup> Sm	β <sup>-</sup>	0.2253 (48.2)	103 (28)	1.93	3.4	<sup>152</sup> Sm(n,γ) <sup>152</sup> Sm (None)	High	(Bé et al., 2008; Lewington, 2005; Volkert and Hoffman, 1999)
						<sup>150</sup> Nd(n,α) <sup>153</sup> Sm (None)	High	
<sup>166</sup> Ho	β <sup>-</sup>	0.6511 (50.5)	81 (6.4)	1.12	8.6	<sup>165</sup> Ho(d,p) <sup>166</sup> Ho ( <sup>166m</sup> Ho)	High	(Bé et al., 2008; Knapp, 2001; Volkert and Hoffman, 1999)
						<sup>165</sup> Ho(n,γ)(E=thermal) <sup>166</sup> Ho (None)	Cost-effective	
						<sup>166</sup> Dy - decay chain (None)	High	
<sup>170</sup> Tm	β <sup>-</sup>	0.3231 (81.6)	84 (3.3)	128.4	5	<sup>169</sup> Tm(n,γ) <sup>170</sup> Tm (None)	Cost-effective	(Bé et al., 2008; Das et al., 2009)
						<sup>170</sup> Er(p,n) <sup>170</sup> Tm ( <sup>168</sup> Tm)	High	
<sup>177</sup> Lu	β <sup>-</sup>	0.1494 (79.3)	208 (10.4)	6.2	1.8	<sup>176</sup> Lu(n,γ) <sup>177</sup> Lu ( <sup>176m</sup> Lu)	High	(Bé et al., 2008; Knapp, 2001; Pillai et al., 2003; Volkert and Hoffman, 1999)
						<sup>176</sup> Yb(n,γ) <sup>177</sup> Yb → <sup>177</sup> Lu	Cost-effective	
<sup>186</sup> Re	β <sup>-</sup>	0.3596 (70.9)	137 (9)	3.8	4.7	<sup>185</sup> Re(n,γ) <sup>186</sup> Re ( <sup>186m</sup> Re, <sup>188</sup> Re)	Cost-effective	(Bé et al., 2008; Lewington, 2005; Volkert and Hoffman, 1999)
						<sup>186</sup> W(n,p) <sup>186</sup> Re (None)	Cost-effective	
<sup>188</sup> Re	β <sup>-</sup>	0.7304 (71.1)	155 (15)	0.7	10.4	<sup>188</sup> We(n,n) <sup>188</sup> Re (None)	Cost-effective	(Argyrou et al., 2013a, 2013c; Bé et al., 2008; Lewington, 2005)
<sup>223</sup> Ra	α	5.71581 (45.6)	154 (5.6)	11.4	0.1	<sup>235</sup> U - decay chain (None)	High	(Bé et al., 2008; Henriksen et al., 2003; Lewington, 2005)
						<sup>227</sup> Ac/ <sup>227</sup> Th Generator (None)	Cost-effective	

Legend: T<sub>1/2</sub> (days) – radioisotope half-life in days; E (MeV) (%) – particle energy and respective decay abundance shown in parentheses; E<sub>γ</sub> (keV) (%) – gamma ray energy and respective abundance in total energy emission shown in parentheses; Tissue penetration range (mm) – maximum tissue penetration in soft tissue shown in millimeters.

**TABLE II.** Summary of the key clinical outcomes of different radiopharmaceuticals currently used in the clinical setting or under research for palliative treatment of bone metastases.

Radiopharmaceuticals	%bone uptake	Main elimination route	Response to therapy (%)	Duration of therapeutic response (months)	Hematologic effects (% patients with toxicity grade >2)		Side effects rating	Regulatory status	References
					WBC	Platelets			
<sup>32</sup> P-orthophosphate	85	Urinary	50-87	2-7	14	34	Significant	Approved and commercially available in undeveloped countries	(Silberstein, 2005)
<sup>89</sup> SrCl <sub>2</sub>	55	Urinary	65-90	3-6	37	61	Significant	Approved and commercially available	(Fosså et al., 1992; Silberstein, 2005; Srivastava, 2004)
<sup>90</sup> Y-EDTMP	45-50	Urinary	--	--	--	--	--	--	(Khalid et al., 2014)
<sup>117m</sup> Sn-DTPA	77	Urinary	60-83	4-5	11	0	Mild	In clinical trails	(Srivastava, 2004)
<sup>153</sup> Sm-EDTMP	65	Urinary	55-83	2-3	15	25	Moderate	Approved and commercially available	(Serafini et al., 1998; Srivastava, 2004)
<sup>166</sup> Ho-DOTMP	16-54	Urinary	NE	NE	--	--	Moderate	In clinical trails	(Champlin et al., 2004; Ueno et al., 2009)
<sup>170</sup> Tm-EDTMP	50-55	Urinary	--	--	--	--	--	--	(Das et al., 2009)
<sup>177</sup> Lu-DOTMP	70	Urinary	NE	NE	--	--	Mild	--	(Chakraborty

$^{177}\text{Lu-EDTMP}$	54-80	Urinary	55-86	3	14	11	Mild	In clinical trails	et al., 2008) (Agarwal et al., 2014; Yuan et al., 2013)
$^{186}\text{Re-HEDP}$	55	Urinary	55-85	2-4	17	25	Moderate	Approved and commercially available in Europe	(Han et al., 2002; Srivastava, 2004)
$^{188}\text{Re-HEDP}$	30	Urinary	64-77	3-6	20	25	Moderate	In clinical trails	(K. Liepe et al., 2003)
$^{223}\text{RaCl}_2$	41	Intestinal	58-75	2-3	4	2	Mild	Approved and commercially available	(Harrison et al., 2013; Nilsson et al., 2012; Sartor et al., 2013)

Legend: NE – not established; WBC – white blood cells. Note: Data for  $^{90}\text{Y-EDTMP}$  and  $^{170}\text{Tm-EDTMP}$  is preclinical.