(0.3%) receiving placebo. Median neutrophil values decreased from baseline at week 24 in the Ra-223 group, but recovered in follow-up (Ra-223: 4.5×10^9/L; 3.3×10^9/L; 3.9×10^9/L vs placebo: 4.6×10^9/L; 4.5×10^9/L; 4.3×10^9/L). A similar decline in median platelet values was observed in the Ra-223 group, but recovered during follow-up (Ra-223: 244×10^9/L; 202×10^9/L; 216×10^9/L vs placebo: 240×10^9/L; 232×10^9/L; 218×10^9/L). Median hemoglobin values decreased over time in both groups (Ra-223: 12.2 g/dL; 11.4 g/dL; 10.8 g/dL vs placebo: 12.1 g/dL; 11.6 g/dL; 11.2 g/dL). **Conclusions:** Overall, the incidence of hematologic AEs was relatively low with Ra-223 treatment. Laboratory assessment of hematology parameters was consistent with the hematologic AE findings. Ra-223 is an effective therapy with a highly favorable safety profile in CRPC patients with bone metastases.

OP419

Updated Analysis of Radium-223 Dichloride (Ra-223) Impact on Survival, Safety, and Skeletal-Related Events in Castration-Resistant Prostate Cancer (CRPC) Patients With Bone Metastases From the Phase 3 ALSYMPCA Trial

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Aim: Ra-223, a first-in-class alpha-emitting pharmaceutical, targets bone metastases with high-energy, short-range (<100 µm) alpha-particles. ALSYMPCA, a phase 3 double-blind, randomized, multinational study, compared Ra-223 plus best standard of care (BSoC) versus placebo plus BSoC in CRPC patients with bone metastases. Updated survival, safety, and skeletal-related event (SRE) data are presented. **Methods:** Eligible patients had progressive, symptomatic CRPC with ≥2 bone metastases on scintigraphy and no known visceral metastases; were receiving BSoC; and had received docetaxel, or were unfit for or declined docetaxel. Patients were randomized 2:1 to 6 injections of Ra-223 (50 kBq/kg IV) q4wk or matching placebo and stratified by prior docetaxel use, baseline alkaline phosphatase level, and current bisphosphonate use. The primary endpoint was overall survival (OS); secondary endpoints included SREs and safety. Updated analysis, based on 528 deaths, was performed on data from all randomized patients. Pathologic bone fractures, reported as an SRE component, were required to be clinically relevant, not asymptomatic fractures. **Results:** 921 patients were randomized (Ra-223, n = 614; placebo, n = 307); 40% had >20 metastases. Compared to placebo, Ra-223 significantly improved OS (median OS: 14.9 vs 11.3 mo; HR = 0.695; 95% CI, 0.581-0.832; *P* = 0.00007) and delayed time to first SRE (median time to first SRE: 15.6 vs 9.8 mo; HR = 0.658; 95% CI, 0.522-0.830; *P* = 0.00037). In addition, Ra-223 reduced risk for all 4 SRE components versus placebo (external beam radiotherapy [EBRT]: HR = 0.67; 95% CI, 0.53-0.85; *P* = 0.001; spinal cord compression [SCC]: HR = 0.52; 95% CI, 0.29-0.93; *P* = 0.025; pathologic bone fracture: HR = 0.62; 95% CI, 0.35-1.09; *P* = 0.095; and surgical intervention: HR = 0.72; 95% CI, 0.28-1.82; *P* = 0.479). Ra-223 was associated with a low incidence of myelosuppression (eg, grade 3/4 neutropenia in 2% and 1%, and grade 3/4 thrombocytopenia in 6% and 2% with Ra-223 and placebo groups, respectively) and fewer adverse events versus placebo. **Conclusions:** Ra-223 significantly prolonged OS, significantly delayed time to first SRE, and reduced risk for all 4 SRE components when compared to placebo in CRPC patients with bone metastases. Ra-223 patients had an approximately 50% reduction in risk for SCC. Ra-223 is an effective therapy with a highly favorable safety profile in CRPC patients with bone metastases.

1009 - Monday, Oct. 21, 16:30 - 18:00, Rhône 3A/3B

Radiopharmaceuticals & Radiochemistry & Dosimetry: Radiometals

OP420

A tripodal tris(hyroxypyrdinone) ligand for immunoconjugate PET imaging with zirconium-89

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Aim: Due to its long half-life (78.4h) and decay properties (23% β$^+$, 897keV), ^{89}Zr is an appealing radionuclide for immunoPET imaging with antibodies. Desferrioxamine-B (DFO) is the most widely used bifunctional chelator to coordinate $^{89}Zr^{4+}$ because the radiolabelling of the resulting immunoconjugates is rapid under mild conditions. ^{89}Zr-DFO complexes are stable *in vitro* but recent data demonstrated the release and subsequent bone uptake of the radiometal *in vivo*. We Aim to evaluate a tripodal tris(hydroxypyridinone) ligand CP256 (Berry DJ, *et al.* (2011) ChemComm, 47, 7068-70) developed in our laboratory, as a $^{89}Zr^{4+}$ chelator and compare it with DFO. **Methods:** To compare the ability of CP256 to complex Zr^{4+} with that of DFO, decreasing concentrations of each chelator were labelled with $[^{89}Zr(oxalate)_4]$. Competition experiments were also undertaken. The radiolabelled products and radiochemical yields were evaluated by ITLC and reverse phase HPLC-MS coupled to a scintillation detector. To assess the stability of DFO/CP256-immunoconjugates radiolabeled with ^{89}Zr, maleimide derivatives of the chelators were conjugated to the monoclonal antibody trastuzumab *via* reduced cysteine side chains. Serum stability studies and *in vivo* biodistribution and microPET/CT studies with normal C57Bl/6j mice were undertaken on the ^{89}Zr-radiolabelled immunoconjugates. **Results:** CP256 coordinates Zr^{4+} (natural abundance) and comparison of HPLC-MS/scintillator chromatograms confirms that addition of $[^{89}Zr(oxalate)_4]$ to CP256 results in formation of $[^{89}Zr(CP256)]^+$. DFO and CP256 can be radiolabelled with $[^{89}Zr(oxalate)_4]$ at ambient temperature in quantitative yield at pH 6-7 at millimolar concentrations. Competition experiments demonstrate that $^{89}Zr^{4+}$ does not substantially dissociate (<10%) from $[^{89}Zr(CP256)]^+$ in the presence of a ten-fold greater concentration of DFO relative to CP256. However, $^{89}Zr^{4+}$ dissociates from $[^{89}Zr(DFO)]^{2+}$ in the presence of one equivalent of CP256 (relative to DFO), resulting largely in $[^{89}Zr(CP256)]^+$. The immunoconjugates, CP256-trastuzumab and DFO-trastuzumab, can be labelled with ^{89}Zr in >98% yield at specific activities of 55MBq mg^{-1} and 91MBq mg^{-1} respectively. Both ^{89}Zr-labelled immunoconjugates are stable in serum with respect to dissociation of the radiometal. MicroPET/CT and biodistribution studies indicate that after one day, $^{89}Zr^{4+}$ dissociates from CP256-trastuzumab with significant amounts of activity associated with bones and joints (25.88±0.58% ID g^{-1} after one week). In contrast, <8% ID g^{-1} of ^{89}Zr activity is associated with bone for animals administered ^{89}Zr-DFO-trastuzumab over the course of one week. **Conclusion:** The tris(hydroxypyridinone) ligand, CP256 coordinates $^{89}Zr^{4+}$ rapidly under mild conditions, but the ^{89}Zr-labelled immunoconjugate, ^{89}Zr-CP256-trastuzumab, was observed to release significant amounts of $^{89}Zr^{4+}$ *in vivo*, demonstrating inferior stability when compared with ^{89}Zr-DFO-trastuzumab.

OP421

Using Low Energy Medical Cyclotrons to Produce 99mTc - Technetium

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This paper refers to work in progress, addressing the global trouble in delivering 99mTc to Nuclear Medicine Departments, Aiming to develop an efficient, safe and economical way to directly produce Technetium 99metastable (99mTc) using low-energy - so-called "medical" - cyclotrons. The present delivery strategy has intrinsic limitations because it is not only based on old nuclear reactors, but also limits the weekly agenda workflow. Our approach is distinct, and is based on the broad distribution network of the low energy cyclotrons and the accessibility of Molybdenum 100 (100Mo) as the target material, so the system here presented, is not based on the use of Nuclear Reactors and highly enriched (or even low enriched) Uranium 235 (235U), but entirely complying with the current international trends and directives, concerning the need to reduce the use of this potential highly critical target material. The direct production technique is based on the nuclear reaction 100Mo(p,2n)99mTc whose production yields have already been widely documented. The 99mTc is produced in a routine, reliable and efficient manner that, remaining always flexible, entirely blends with established protocols. An additional advantage is that there are no more agenda constraints (daily workflow could be the maintained). A solid target station, that can be installed in most of the existing low energy cyclotrons has been developed; it will tolerate up to 400 µA of beam by allowing it to strike the solid target material at an oblique angle, under controlled circumstances, while allowing the remote and automatic loading and discharge of the targets. Concerning the solid target itself, several Methods of target material deposition and substrates are being studied and compared. The rationale was to create a cost effective means of depositing and intermediate the target material thickness (75 - 300µm) with a minimum of loss on a substrate that is able to easily transport the heat inherently associated with high beam currents. Finally, the separation techniques are yet under development, using a combination of both physical and column chemistry. The ultimate goal is to extract and deliver 99mTc in the identical form now in use in radiopharmacies worldwide. In addition, the solid target material needs - due to its price and relevance - to be recovered and should be recycled, adding an extra degree of complexity. This simpler, cleaner and more efficient way of producing 99mTc will bring a new solution to the present 99mTc shortage problem.