

# THE IN-VIVO GENERATOR <sup>128</sup>BA/<sup>128</sup>CS : A NEW CALCIUM SURROGATE FOR TREATMENT OF OSTEOSARCOMA

#### CHUV, IRA, NPL & CERN CONSORTIUM MEETING 4: Public Event

INFN Legnaro (Padova, Italy) & online

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#### The in vivo generator Ba/Cs-128

- Now available at PRISMAP ("Day 3" radionuclide)
- "In vivo generator" → The aim of such approach is to inject a long half-life parent radionuclide, which after accumulation in the target tissue will act as a generator and generate shorter half-life daughter radionuclide
- Theranostics : Auger therapy & PET imaging



Generator system	Half- life	Decay Mode	Emission	Application	Daughter	Half life	Decay mode	Emission	Application
<sup>128</sup> Ba/ <sup>128</sup> Cs	2.4 d	EC	γ, <u>Auger e<sup>-</sup></u> (2.5-5.7 keV 79.3%)	Auger therapy	<sup>128</sup> Cs	3.66 m	EC, β+	γ, Auger e⁻, <u>β+ (</u> 1315.9 keV 53.2%)	PET



#### Rational

- <sup>128</sup>Ba/<sup>128</sup>Cs enters the bone matrix as a surrogate of Ca<sup>2+</sup> like <sup>223</sup>Ra and <sup>89</sup>Sr
- It is metabolized, concentrated secreted through the matrix vesicles by the osteoblast



Kyungsup Shin, Timothy Acri, Sean Geary, and Aliasger K. Salem. Tissue Engineering Part A.Oct 2017.1169-1180



#### The in-vivo generator Ba-128/Cs-128: a new calcium surrogate for treatment of osteosarcoma

#### Alpha Particle Radium 223 Dichloride in High-risk Osteosarcoma: A Phase I Dose Escalation Trial



Clinical Cancer Research

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#### Abstract

Purpose: The prognosis of metastatic osteosarcoma continues to be poor. We hypothesized that alpha-emitting, bone- (n = 7, 39%), and skull (n = 2, 11%). Patients received 1-6 targeting radium 223 dichloride (223RaCl<sub>2</sub>) can be safely administered to patients with osteosarcoma and that early signals of response or resistance can be assessed by quantitative and qualitative correlative imaging studies and biomarkers. Patients and Methods: A 3+3 phase I, dose-escalation trial of 223 RaCl2 (50, 75, and 100 kBq/kg) was designed in patients with recurrent/metastatic osteosarcoma aged ≥15 years. Objective measurements included changes in standardized uptake values of positron emission tomography (PET: 18FDG and/or NaF-18) and single-photon emission CT/CT (99mTc-MDP) as well as alkaline phosphatase and bone turnover markers at baseline, midstudy, and the end of the study. Results: Among 18 patients enrolled (including 15 males) aged 15–71 years, tumor locations included spine (n = 12, for combination therapies.

67%), pelvis (n = 10, 56%), ribs (n = 9, 50%), extre cycles of <sup>223</sup>RaCl<sub>2</sub>; cumulative doses were 6.84-57.81 MBq. NaF PET revealed more sites of metastases than did FDG PET. One patient showed a metabolic response on FDG PET and NaF PET. Four patients had mixed responses, and one patient had a response in a brain metastasis. Bronchopulmonary hemorrhage from Grade 3 thrombocytopenia (N = 1) was a DLT. The median overall survival time was 25 weeks

Conclusions: The first evaluation of the safety and efficacy of an alpha particle in high-risk osteosarcoma shows that the recommended phase II dose for 223 RaCl2 in osteosarcoma is 100 kBq/kg monthly (twice the dose approved for prostate cancer), with minimal hematologic toxicity, setting the stage



Figure 3.NaF PET–CT in a patient with pelvic osteosarcoma showing decrease in NaF with subsequent doses of <sup>223</sup>RaCl<sub>2</sub>.

#### The PRISMAP Network

27 EU

Prisman



The in-vivo generator Ba-128/Cs-128: a new calcium surrogate for treatment of osteosarcoma

### **Production & Purification**

- Produced and purified at the CERN-MEDICIS Facility
- Tantalum carbide targets were irradiated by the CERN PS Booster proton beam at 1.4 GeV
- After irradiation, the targets is placed on the MEDICIS isotope separator and the Ba ions were implanted on "salt foils" or zinc coated gold foils
- The zinc foils were dissolved in concentrated HCl and loaded in TK-100 resin
- <sup>128</sup>Ba/<sup>128</sup>Cs was then eluted with HCl
- At least 75% activity yield was obtained

# Metrology & Calibration

- At NPL and IRA
- Radiochemical purity assay by HPGe
  - No long lived gamma-emitting contaminants detected
- Half-life
  - ENSDF half-life = 2.43(5) d
  - Primary TCIR (transportable reference ionization chamber):
     2.3566(5) d
  - HPGe gamma-ray spectrometry (273 keV & 443 keV) = 2.3665(15) d
- Calibration factors using activity from TCIR for dose calibrator, gamma counter and microPET were created



Rate (s<sup>-1</sup>)

### First phantom study of <sup>128</sup>Ba/<sup>128</sup>Cs PET imaging





Micro-PET IQ Phantom (according to NEMA NU 4-2008)

4 MBq in 21 ml $\rightarrow$  190 kBq/mlIn VOI $\rightarrow$  134 kBq/mlMLEM 12 iteration

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#### Whole body PET imaging of <sup>128</sup>Ba/<sup>128</sup>Cs in naïve mice



### Whole body PET imaging of <sup>128</sup>Ba/<sup>128</sup>Cs of an euthanized naïve mouse



- PET acquisition immediately after sacrifice of a naïve mouse injected with Ba-128 (24h)
- No uptake was observed in kidney, in accordance with what observed in biodistributions
- May support an impact of isoflurane on accumulation of Ba by the kidneys



#### Biodistribution of <sup>128</sup>Ba/<sup>128</sup>Cs in naïve mice & Dosimetry



Source organ	TIAC (h)
Tumour	2.46E-03
Liver	4.42E-02
Kidney	5.20E-02
Lung	2.70E-02
Spleen	3.46E-02
Heart content	1.14E-01
Muscle	1.69E-02
Bone	2.00E+01
Skin	3.21E-02
Stomach	4.24E-02
Small Int.	1.90E-01
Large Int.	5.01E-01
Tail	9.04E+00
Head	1.69E+01
Blood	1.82E-02
ROB	5.00E+00

				Total
Ba-128 Target Organ	Alpha	Beta	Gamma	[mGy/MBq]]
Brain	0.00E+00	1.44E+00	3.63E+00	5.06E+00
Large Int	0.00E+00	5.34E+00	2.64E+00	7.98E+00
Small Intestine	0.00E+00	1.59E+00	1.98E+00	3.57E+00
Stomach Wall	0.00E+00	4.97E+00	2.62E+00	7.59E+00
Heart	0.00E+00	3.72E+00	4.49E+00	8.21E+00
Kidneys	0.00E+00	1.88E+00	2.53E+00	4.41E+00
Liver	0.00E+00	1.32E+00	2.97E+00	4.29E+00
Lungs	0.00E+00	4.56E+00	5.59E+00	1.02E+01
Pancreas	0.00E+00	1.07E+00	2.26E+00	3.33E+00
Skeleton	0.00E+00	6.56E+01	5.80E+00	7.14E+01
Spleen	0.00E+00	2.54E+00	2.14E+00	4.68E+00
Testes	0.00E+00	1.03E+00	2.30E+00	3.33E+00
Thyroid	0.00E+00	1.55E+00	5.38E+00	6.93E+00
Urin Blad	0.00E+00	1.04E+00	2.36E+00	3.40E+00
Total Body	0.00E+00	2.78E+00	2.92E+00	5.69E+00
				Total
Cc 129			-	
Cs-128 Target Organ	Alpha	Beta	Gamma	[mGy/MBq]
<b>Cs-128</b> Target Organ Brain	Alpha 0.00E+00	Beta 5.83E+02	Gamma 2.24E+01	[mGy/MBq] 6.05E+02
<b>Cs-128</b> Target Organ Brain Large Int	Alpha 0.00E+00 0.00E+00	Beta 5.83E+02 1.75E+02	Gamma 2.24E+01 1.47E+01	[mGy/MBq] 6.05E+02 1.89E+02
<b>Cs-128</b> Target Organ Brain Large Int Small Intestine	Alpha 0.00E+00 0.00E+00 0.00E+00	Beta 5.83E+02 1.75E+02 1.18E+02	Gamma 2.24E+01 1.47E+01 1.33E+01	[mGy/MBq] 6.05E+02 1.89E+02 1.31E+02
<b>Cs-128</b> Target Organ Brain Large Int Small Intestine Stomach Wall	Alpha 0.00E+00 0.00E+00 0.00E+00 0.00E+00	Beta 5.83E+02 1.75E+02 1.18E+02 2.49E+02	Gamma 2.24E+01 1.47E+01 1.33E+01 1.59E+01	[mGy/MBq] 6.05E+02 1.89E+02 1.31E+02 2.65E+02
Cs-128 Target Organ Brain Large Int Small Intestine Stomach Wall Heart	Alpha 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00	Beta 5.83E+02 1.75E+02 1.18E+02 2.49E+02 8.94E+02	Gamma 2.24E+01 1.47E+01 1.33E+01 1.59E+01 2.74E+01	[mGy/MBq] 6.05E+02 1.89E+02 1.31E+02 2.65E+02 9.21E+02
<b>Cs-128</b> Target Organ Brain Large Int Small Intestine Stomach Wall Heart Kidneys	Alpha 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00	Beta 5.83E+02 1.75E+02 1.18E+02 2.49E+02 8.94E+02 2.20E+02	Gamma 2.24E+01 1.47E+01 1.33E+01 1.59E+01 2.74E+01 1.62E+01	[mGy/MBq] 6.05E+02 1.89E+02 1.31E+02 2.65E+02 9.21E+02 2.36E+02
<b>Cs-128</b> Target Organ Brain Large Int Small Intestine Stomach Wall Heart Kidneys Liver	Alpha 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00	Beta 5.83E+02 1.75E+02 1.18E+02 2.49E+02 8.94E+02 2.20E+02 3.71E+02	Gamma 2.24E+01 1.47E+01 1.33E+01 1.59E+01 2.74E+01 1.62E+01 1.92E+01	[mGy/MBq] 6.05E+02 1.89E+02 1.31E+02 2.65E+02 9.21E+02 2.36E+02 3.90E+02
Cs-128 Target Organ Brain Large Int Small Intestine Stomach Wall Heart Kidneys Liver Lungs	Alpha 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00	Beta 5.83E+02 1.75E+02 1.18E+02 2.49E+02 8.94E+02 2.20E+02 3.71E+02 1.09E+03	Gamma 2.24E+01 1.47E+01 1.33E+01 1.59E+01 2.74E+01 1.62E+01 1.92E+01 3.02E+01	[mGy/MBq] 6.05E+02 1.89E+02 1.31E+02 2.65E+02 9.21E+02 2.36E+02 3.90E+02 1.12E+03
Cs-128 Target Organ Brain Large Int Small Intestine Stomach Wall Heart Kidneys Liver Lungs Pancreas	Alpha 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00	Beta 5.83E+02 1.75E+02 1.18E+02 2.49E+02 8.94E+02 2.20E+02 3.71E+02 1.09E+03 1.23E+02	Gamma 2.24E+01 1.47E+01 1.33E+01 1.59E+01 2.74E+01 1.62E+01 1.92E+01 3.02E+01 1.40E+01	[mGy/MBq] 6.05E+02 1.89E+02 1.31E+02 2.65E+02 9.21E+02 2.36E+02 3.90E+02 1.12E+03 1.37E+02
Cs-128 Target Organ Brain Large Int Small Intestine Stomach Wall Heart Kidneys Liver Lungs Pancreas Skeleton	Alpha 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00	Beta 5.83E+02 1.75E+02 1.18E+02 2.49E+02 8.94E+02 2.20E+02 3.71E+02 1.09E+03 1.23E+02 2.74E+03	Gamma 2.24E+01 1.47E+01 1.33E+01 1.59E+01 2.74E+01 1.62E+01 1.92E+01 3.02E+01 1.40E+01 3.40E+01	[mGy/MBq] 6.05E+02 1.89E+02 1.31E+02 2.65E+02 9.21E+02 2.36E+02 3.90E+02 1.12E+03 1.37E+02 <b>2.78E+03</b>
Cs-128 Target Organ Brain Large Int Small Intestine Stomach Wall Heart Kidneys Liver Lungs Pancreas Skeleton Spleen	Alpha 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00	Beta         5.83E+02         1.75E+02         1.18E+02         2.49E+02         8.94E+02         2.20E+02         3.71E+02         1.09E+03         1.23E+02         2.74E+03         1.84E+02	Gamma 2.24E+01 1.47E+01 1.33E+01 1.59E+01 2.74E+01 1.62E+01 1.92E+01 3.02E+01 1.40E+01 3.40E+01 1.24E+01	[mGy/MBq] 6.05E+02 1.89E+02 1.31E+02 2.65E+02 9.21E+02 2.36E+02 3.90E+02 1.12E+03 1.37E+02 <b>2.78E+03</b> 1.96E+02
Cs-128 Target Organ Brain Large Int Small Intestine Stomach Wall Heart Kidneys Liver Lungs Pancreas Skeleton Spleen Testes	Alpha 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00	Beta         5.83E+02         1.75E+02         1.18E+02         2.49E+02         8.94E+02         2.20E+02         3.71E+02         1.09E+03         1.23E+02         2.74E+03         1.84E+02         1.52E+02	Gamma 2.24E+01 1.47E+01 1.33E+01 1.59E+01 2.74E+01 1.62E+01 1.92E+01 3.02E+01 1.40E+01 1.24E+01 1.40E+01	[mGy/MBq] 6.05E+02 1.89E+02 1.31E+02 2.65E+02 9.21E+02 2.36E+02 3.90E+02 1.12E+03 1.37E+02 <b>2.78E+03</b> 1.96E+02 1.66E+02
Cs-128 Target Organ Brain Large Int Small Intestine Stomach Wall Heart Kidneys Liver Lungs Pancreas Skeleton Spleen Testes Thyroid	Alpha 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00	Beta5.83E+021.75E+021.18E+022.49E+028.94E+022.20E+023.71E+021.09E+031.23E+022.74E+031.84E+021.52E+029.33E+02	Gamma 2.24E+01 1.47E+01 1.33E+01 1.59E+01 2.74E+01 1.62E+01 1.92E+01 3.02E+01 1.40E+01 1.24E+01 1.40E+01 3.54E+01	[mGy/MBq] 6.05E+02 1.89E+02 1.31E+02 2.65E+02 9.21E+02 2.36E+02 3.90E+02 1.12E+03 1.37E+02 <b>2.78E+03</b> 1.96E+02 1.66E+02 9.69E+02
Cs-128 Target Organ Brain Large Int Small Intestine Stomach Wall Heart Kidneys Liver Lungs Pancreas Skeleton Spleen Testes Thyroid Urin Blad	Alpha 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00	Beta5.83E+021.75E+021.18E+022.49E+028.94E+022.20E+023.71E+021.09E+031.23E+022.74E+031.84E+021.52E+029.33E+021.14E+02	Gamma 2.24E+01 1.47E+01 1.33E+01 1.59E+01 2.74E+01 1.62E+01 1.92E+01 3.02E+01 1.40E+01 1.24E+01 1.40E+01 3.54E+01 1.54E+01	[mGy/MBq] 6.05E+02 1.89E+02 1.31E+02 2.65E+02 9.21E+02 2.36E+02 3.90E+02 1.12E+03 1.37E+02 <b>2.78E+03</b> 1.96E+02 1.66E+02 9.69E+02 1.29E+02

# Other radionuclides are under preparation: e.g. <sup>103</sup>Ag

Ag 103 66 m ε β<sup>+</sup>1.7... γ 119, 148, 267...

- Special interest for Ag-radiopharmaceuticals in Padova !
- To be available later ("Day 4" radionuclide)
- <sup>103</sup>Ag is the theranostic partner of the therapeutic <sup>111</sup>Ag that is already available at PRISMAP
- Production: Ag-103 for demo image produced by 1.4 GeV proton induced spallation and mass separation at CERN, implanted into Ag foil. Shipment of short-lived nuclide to CHUV as WP9 demo.

Nuclide	Half-Life	Decay Mode	Emission	Application
<sup>103</sup> Ag	65.7 min	EC, β+	γ (119 keV 31.2%, 148 keV 28.3%, 267 keV 13.3%, <u>β+</u> 640 keV 27%	PET imaging

Radionuclidic purity and characterization ongoing at IRA



## Very first phantom study of <sup>103</sup>Ag PET imaging





1.9 MBq <sup>103</sup>Ag in NEMA-NUC 4 phantom
60 min acquisition MLEM 12 iteration reconstruction

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#### The in-vivo generator Ba-128/Cs-128: a new calcium surrogate for treatment of osteosarcoma

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