Bone-Localizing Electron-Emitting Therapeutic Radiopharmaceuticals

Suresh C. Srivastava
Medical Department
Brookhaven National Laboratory
Upton, New York

BROOKHAVEN NATIONAL LABORATORY

Therapy of Cancer In Bone

Conventional Treatments

- Chemotherapy, external radiation, analgesics, and hormones.
- Usually effective in controlling cancer (pain) early but may fail later on, leading to disease progression and intractable pain.

Radionuclide Therapy

- Systemic treatment with certain electron emitting radionuclides can provide pain relief which may last months to a year.
- Effective therapy dose is limited primarily due to hemopoietic toxicity from excessive radiation to bone marrow.

Radionuclides for Bone Pain Palliation Therapy

	$T_{½}$ (days)	ß⁻ Energy (MeV) Maximum	ß⁻ Energy (MeV) Average	Average Range(mm)	γ photon (MeV)
Strontium-89	50.5	1.46	0.58	2.4	None
Phosphorus-32	14.3	1.71	0.70	3.0	None
Tin-117m	14.0	0.13* 0.15*	--- ---	0.22 0.29	0.159 (86%)
Rhenium-186	3.7	1.08	0.33	1.05	0.137 (9%)
Samarium-153	1.9	0.81	0.22	0.55	0.103 (29%)

*Conversion electrons with discrete energies (and range).

Radionuclide Therapy with Conversion Electron Emitting Tin-117m DTPA

- Bone Pain Palliation
- Radiation Synovectomy
- Metastatic Bone Disease

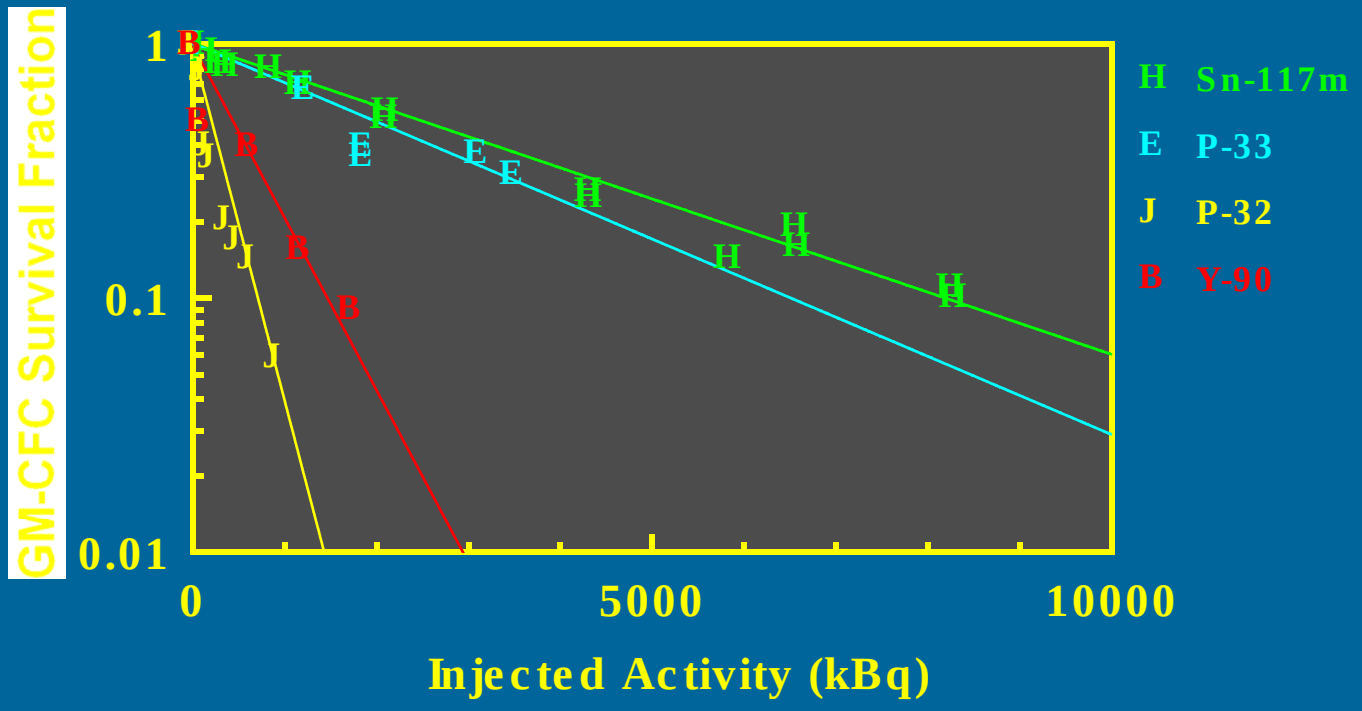
Treatment of Metastatic Bone Pain

^{117m}Sn Decay Data (T ½=14.0 d)

Major Emissions	Energy, KeV	Intensity, %
Auger-L	3	91.0
Auger-K	21	10.8
CE*-K1	126.8	64.8
CE-K2	129.4	11.7
CE-I1	151.6	26.1
CE-L2	154.1	1.5
CE-M1	155.1	5.6
Gamma	158.6	86.4

*C.E. = Conversion Electron

GM-CFC Survival Vs. Injected Activity



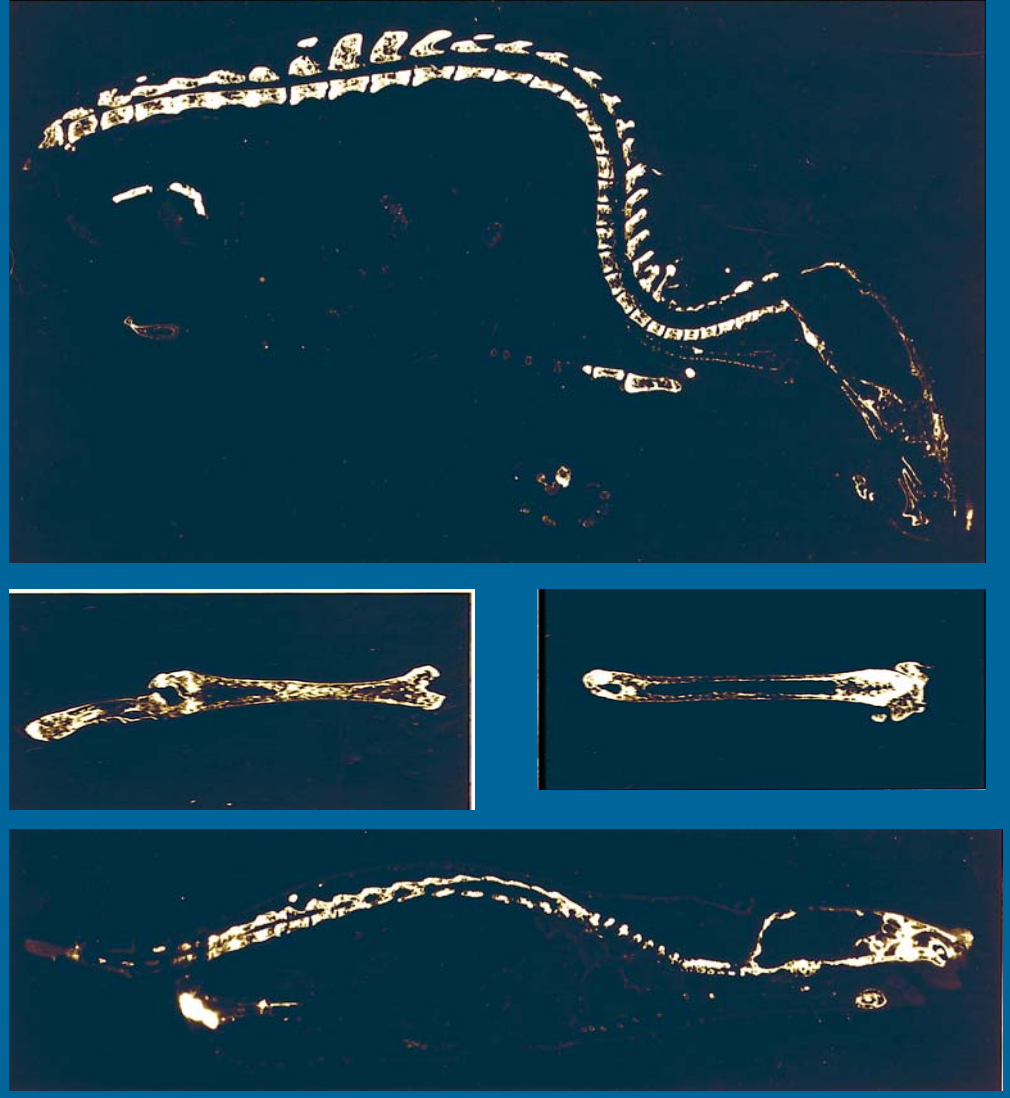
Conclusion: ***Tin-117m causes the least myelotoxicity***

Conclusion from GMCFC Survival Studies

Low-energy electron emitter Sn-117m offers a substantial therapeutic advantage in that, compared to other $ß^-$ emitters, it has the potential to deliver high doses to bone while minimizing the absorbed dose to the bone marrow.

Mouse Biodistribution (24h) of Tin-117m Chelates

Compound	% ID/g in bone	Ratio, Bone to Blood	Muscle	Kidney	Spleen	Liver
Sn(4+)DTPA	21.5	1903	863	49	274	72
Sn(2+)DTPA	12.3	3.3	91	4.1	6.8	4.1
Sn(4+)MDP	17.7	1135	881	36	15	13
$Sn(4+)Cl_4$	3.4	70	121	6.9	0.23	0.06
^{99m}TcMDP	11.0	149	321	21	7.0	18



Autoradiography in rats (top) and in mice (middle and bottom) demonstrates high uptake of tin-117m DTPA in bone and not in bone marrow or other organs.

Tin-117m Stannic DTPA (STANAMET®) Clinical Studies

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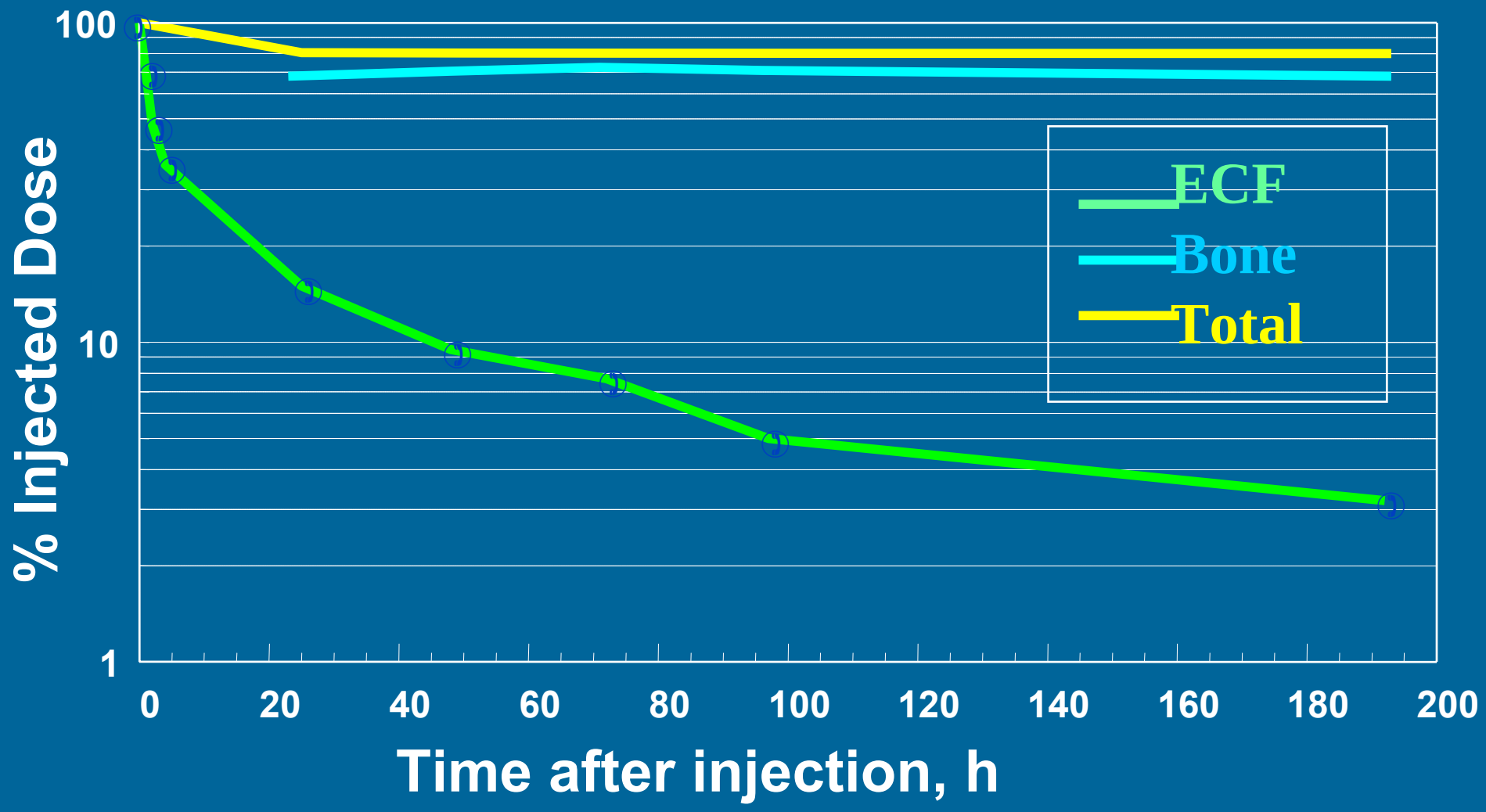
Clinical Trials for Bone Pain Palliation with ®Stanamet

Biodistribution of Sn-117m DTPA in Patients



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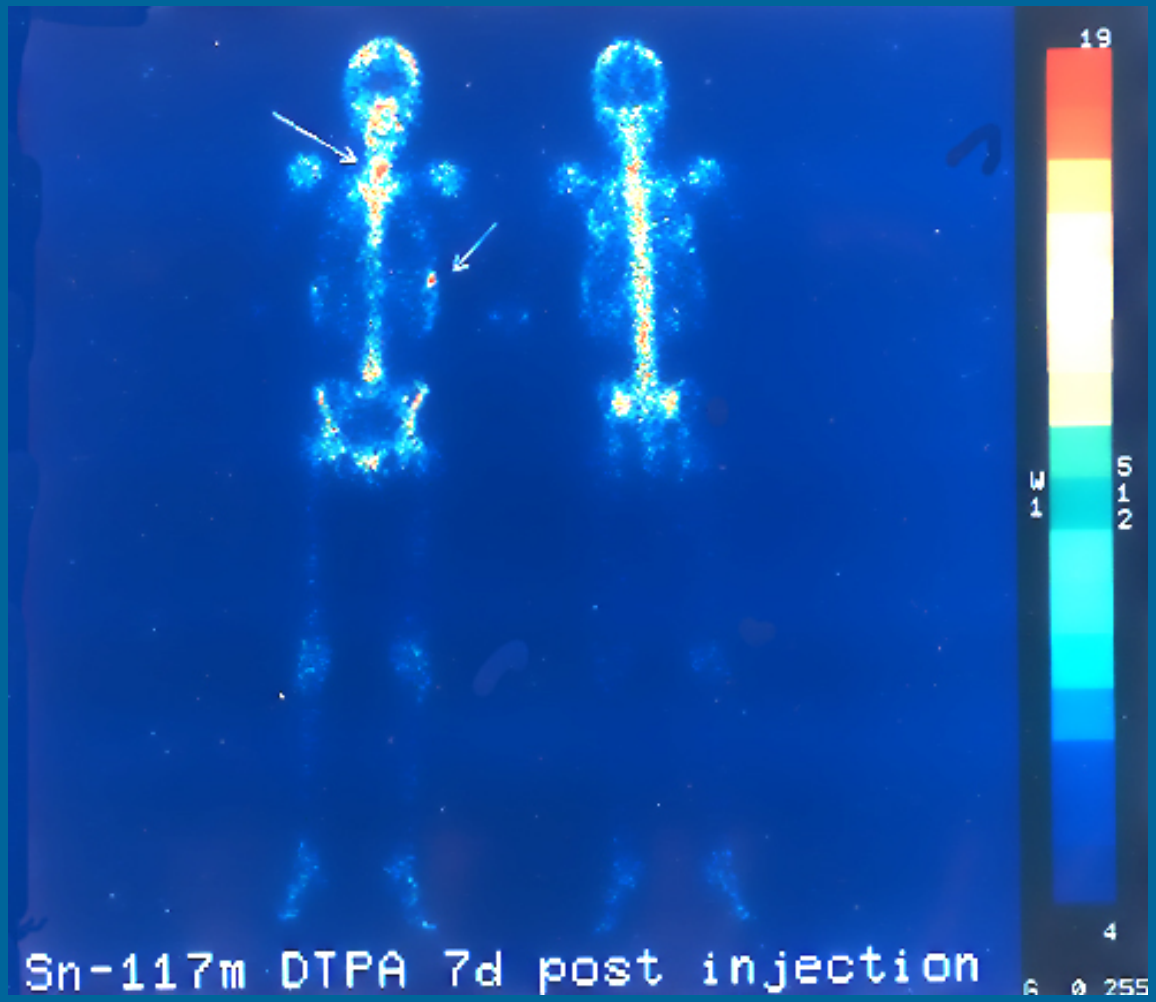
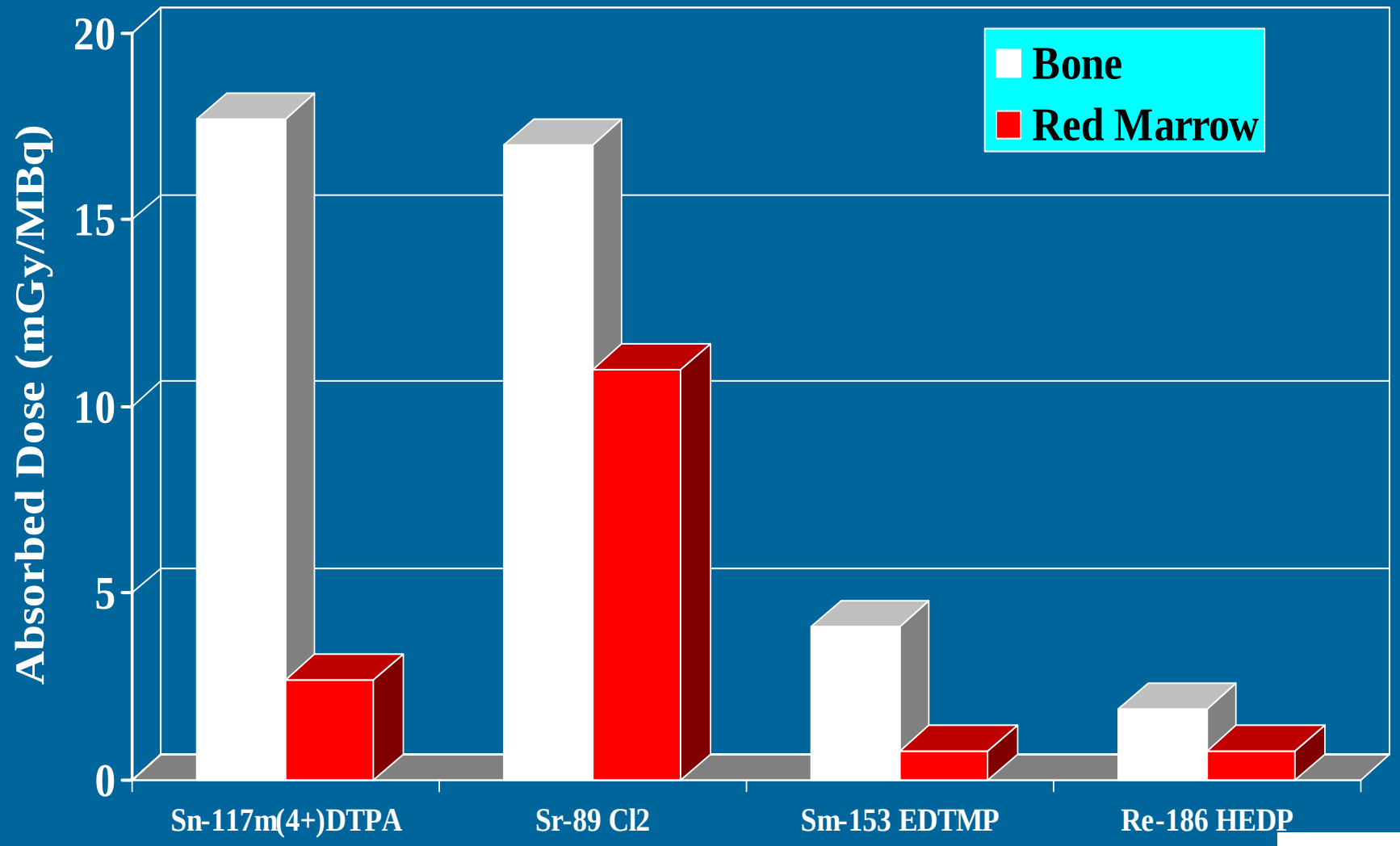


Bone image (1.0 mCi, 7d post-injection, anterior and posterior views) in a prostate cancer patient. Arrows (anterior image) point out the cancerous lesions.

Average Absorbed Dose to Bone Surfaces and Bone Marrow in Patients (MIRDOSE 3)



Pain Relief from Tin-117m DTPA Phase I/II Clinical Studies[1]

Dose Group (MBq/kg)	n[2]	Patients Experiencing Relief			
		Complete (100%)	Partial (>50%)	None (0-50%)	Total Response[3] (%)
2.6	5	0	3	2	3 (60)
5.3	9	3	4	2	7 (78)
6.6	5	3	1	1	4 (80)
8.5	9	2	4	3	6 (67)
10.6	12	4	6	2	10 (83)
All Doses	40	12	18	10	30 (75)

[1]Total patients 57; 54 received a single dose and 3 received 2 doses each.
[2]A total of 40 therapeutic administrations were assessable. [3]Avg. duration 98d

Myelotoxicity Levels[1]

Agent	Dose group (MBq/kg)	n	No. of Patients, Grades ≥2[1] WBC	Platelets
Sr-89 Cl_2[2]	5.7	67	25 (37%)	41 (61%)
Sm-153 EDTMP[3]	37	20	3 (15%)	5 (25%)
	111	4	(100%)	2 (50%)
Sn-117m DTPA[4]	6.6	5	0 (0%)	0 (0%)
	10.6	12	1 (8%)	0 (0%)

[1]NCI criteria used: 0, none; 1, mild; 2, moderate; 3, severe; 4, unacceptable. [2]Porter et al, *Int. J. Radiat. Oncol. Biol. Phys. 25:805, 1993;* [3]Collins et al, *J. Nucl. Med. 34:1839, 1993;* [4]Srivastava et al, *Clin. Cancer Res. 4:61, 1998.*

Sn-117m: Projected Clinical Status

Phase I - II	**Completed by BNL/SUNY-SB**	**N=57**
Extended Phase II	**Dose Ranging (Multicenter)**	**4Q98-4Q02**
	Osteoblastic (Prostate)	**N=100 (72)***
	Osteolytic (Breast; Others)	**N=75 (5)***
Phase III	**Future Protocols (Pending)**	**4Q04-4Q05**
NDA Submission, FDA Approval		**4Q05-3Q06**

Patients actually studied

CONCLUSION
Advantages of Sn-117m as a Therapeutic Isotope

- High-LET, Short-range, Monoenergetic Electrons
- Simple Production, High Chemical and In-vivo Stability
- Much Less Toxicity to Bone Marrow; Higher MTD
- Increased Treatment Options for Myelosuppressed Patients, including Metastron and Quadramet Failures for Pain Palliation
- Use in Early Stages to Delay/Prevent Disease Progression
- Possible Synergy with External Beam and Chemotherapy in Treating Early Stage Cancer
- Very Promising for Various Radionuclide Therapies: Bone Pain Palliation; Radiosynovectomy; Treatment of Bone Metastases…

STANAMET® Research Team

Brookhaven National Laboratory/ University Hospital, Stony Brook

S.C. Srivastava, Ph.D. (P.I.)
H.L. Atkins, M.D.
C.J. Cabahug, M.D.
T. D'Alessandro, M.D .
Y. Lau, M.D.
Z. Li, Ph.D.
S. Madajewicz, M.D.
L. Mausner, Ph.D.
G. Meinken, M.S.
T. Park, M.D.
P. Som, Ph.D.

Diatide, Inc.

J.L. James, Ph.D. (P.I.)
E. Aten, M.D.
V.J. Becker, M.S.
R.T. Dean, Ph.D.
R. Schlief, M.D.

VA Medical Center, Tucson

G.T.Krishnamurthy,M.D.(P.I)
F. Swailem, Ph.D.
F. Ahmann, M.D.
T. Walsh, M.D.
J. Shah, M.D.

North Shore Univ. Hospital

I. Zanzi, M.D. (P.I.)
D. Margouleff, M.D.

Univ. of Cincinnati Med Center

E.B.Silberstein, M.D. (P.I.)

Oak Ridge National Laboratory

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F.F. Knapp, Jr., Ph.D.
S. Mirzadeh, Ph.D.

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