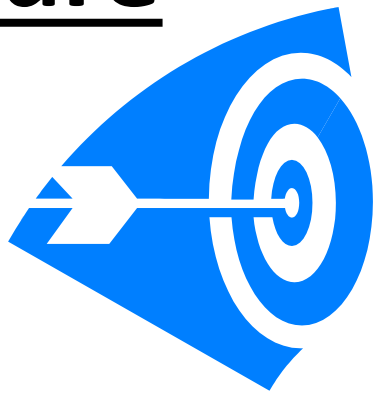
# From Bench to Bedside: Progress towards a Cure



**Neil H Bander, MD**
Bernard & Josephine Chaus Professor
of Urologic Oncology
Weill College Medicine

Us Too-Jan 19, 2023

# Disclosure

Dr. Bander is an inventor on patents that are assigned to Cornell University for anti-PSMA antibody technology. He is a Founder, Director and Advisor to Convergent Therapeutics, Inc to which the PSMA antibody technology has been licensed. He is also a Founder, Director and Advisor to XenImmune Therapeutics, Inc.

# Radiation Therapy

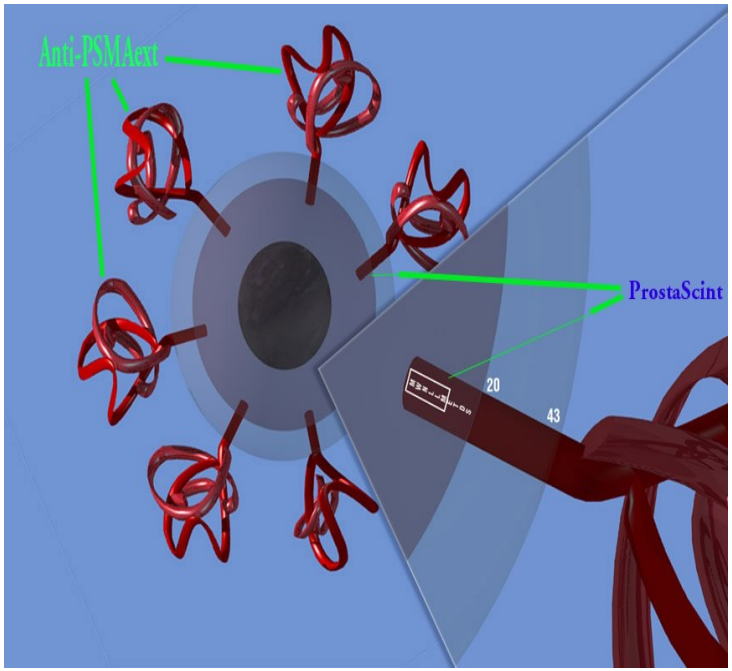
- Pca is radiosensitive
- Radiation has been sued to treat Pca for well over 100 years
  - Local
  - Metastatic

# PSMA is an Unparalleled Target in PC

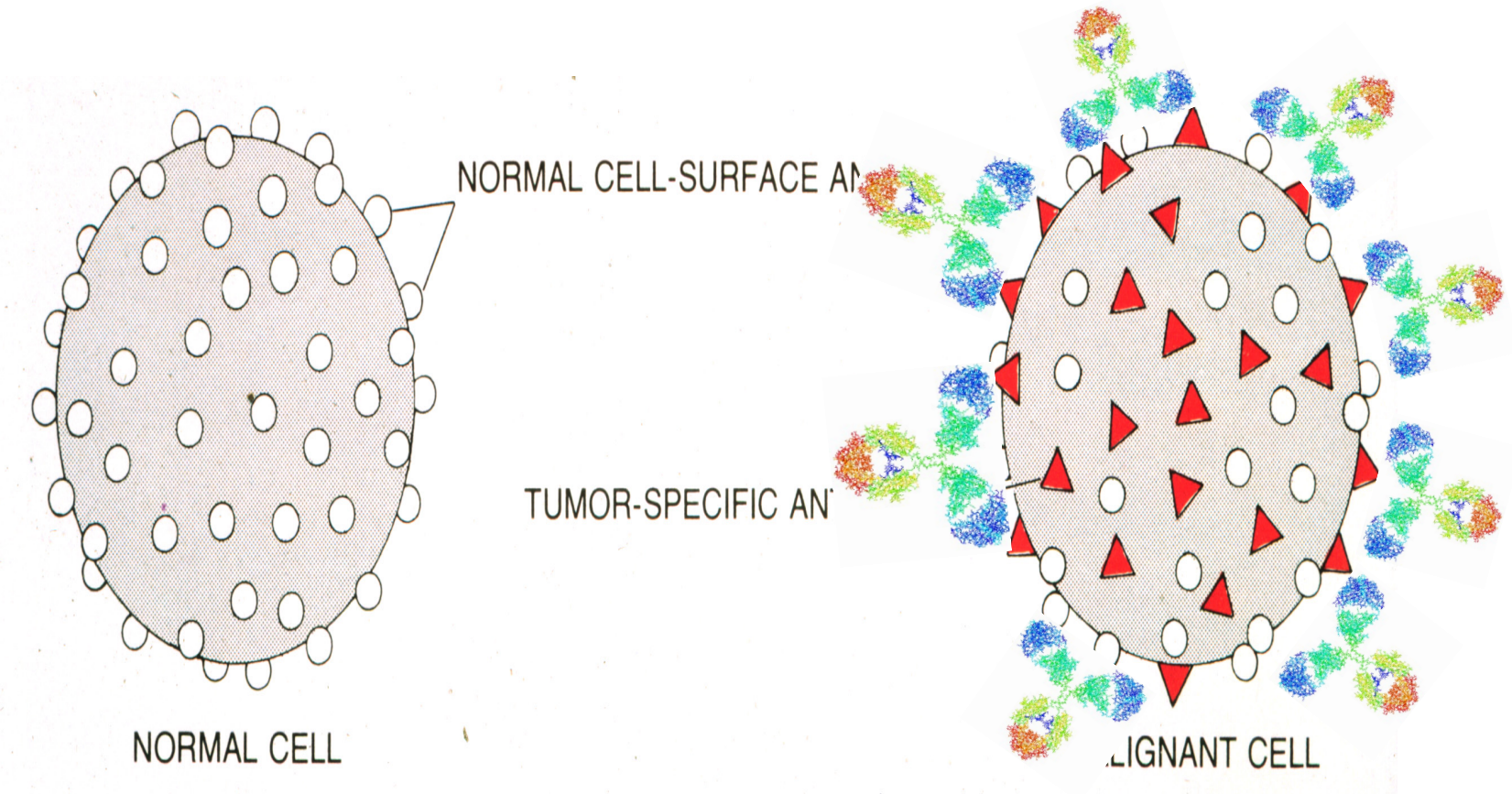
- **PSMA is the single most well-established, prostate-restricted, cell membrane antigen known**
- **90-95% of PC are PSMA-positive**
- **Highly PC-specific**
- **↑ PSMA ≅ ↑ lethality**
- **Expression levels are increased by hormonal Rx**
- **Rapidly internalized**

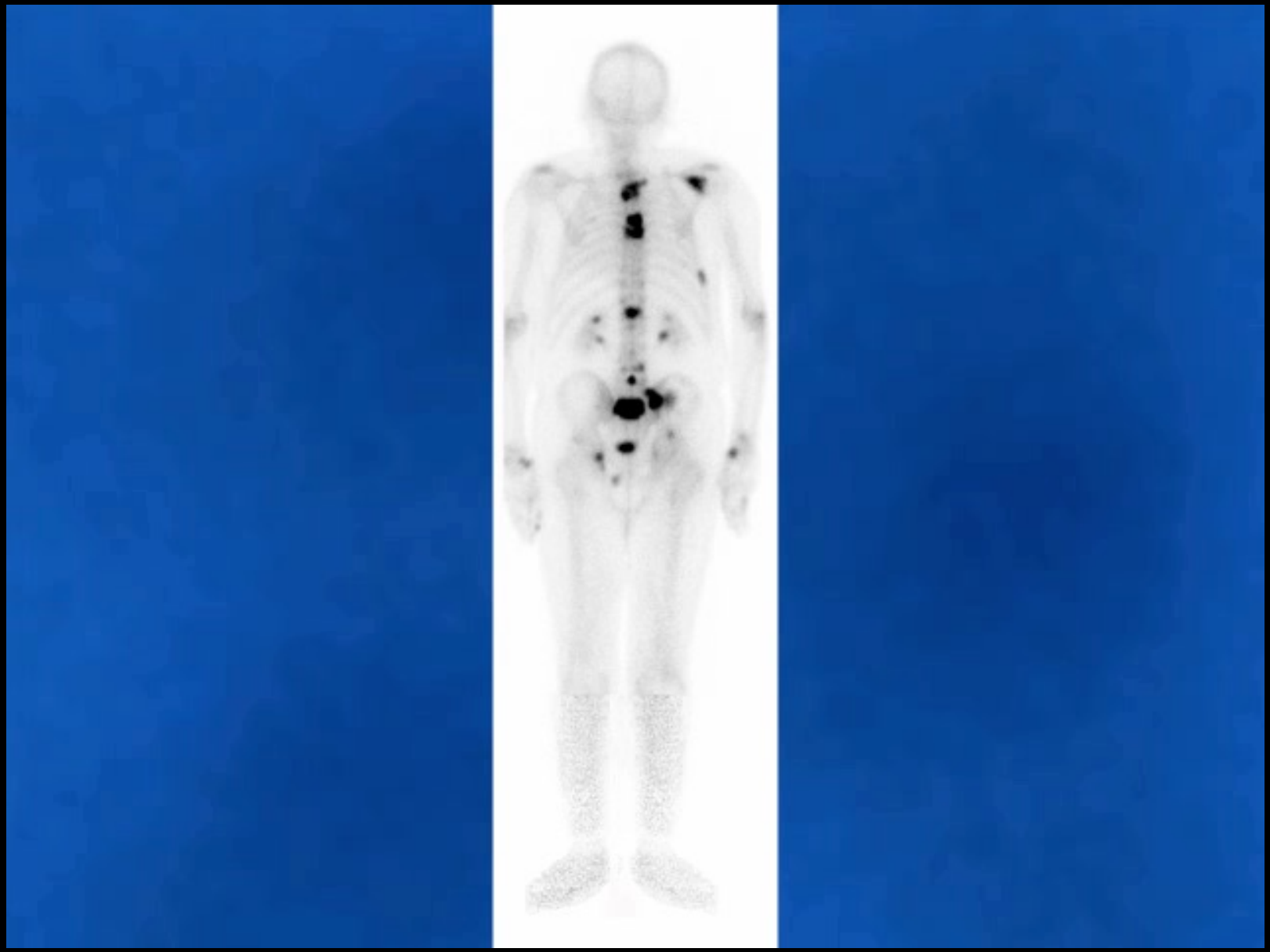
# 1st mAbs to PSMA$_{ext}$

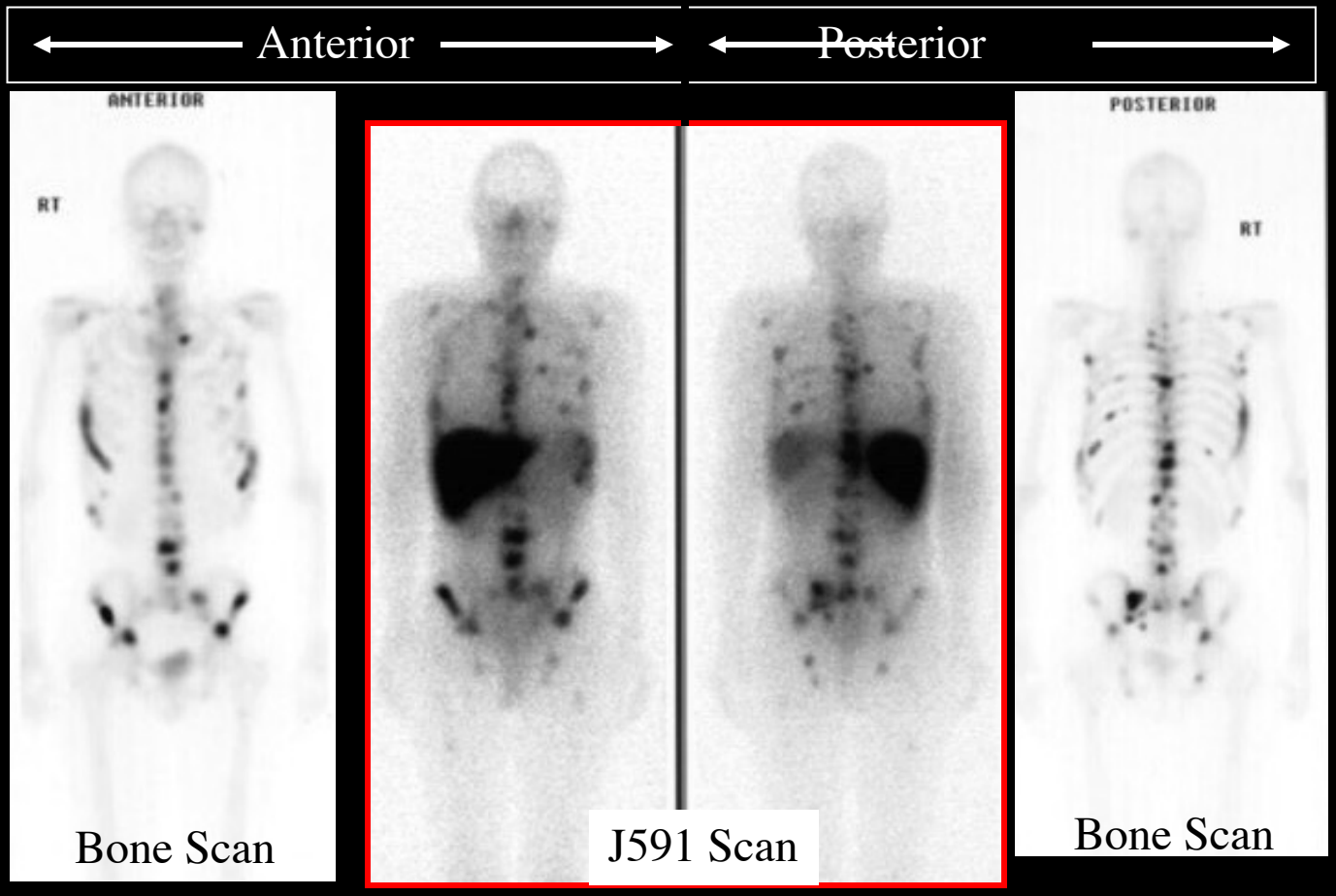
Weill/Cornell group
1st to make mAbs to
PSMA able to bind
***living*** PC cells (1997)

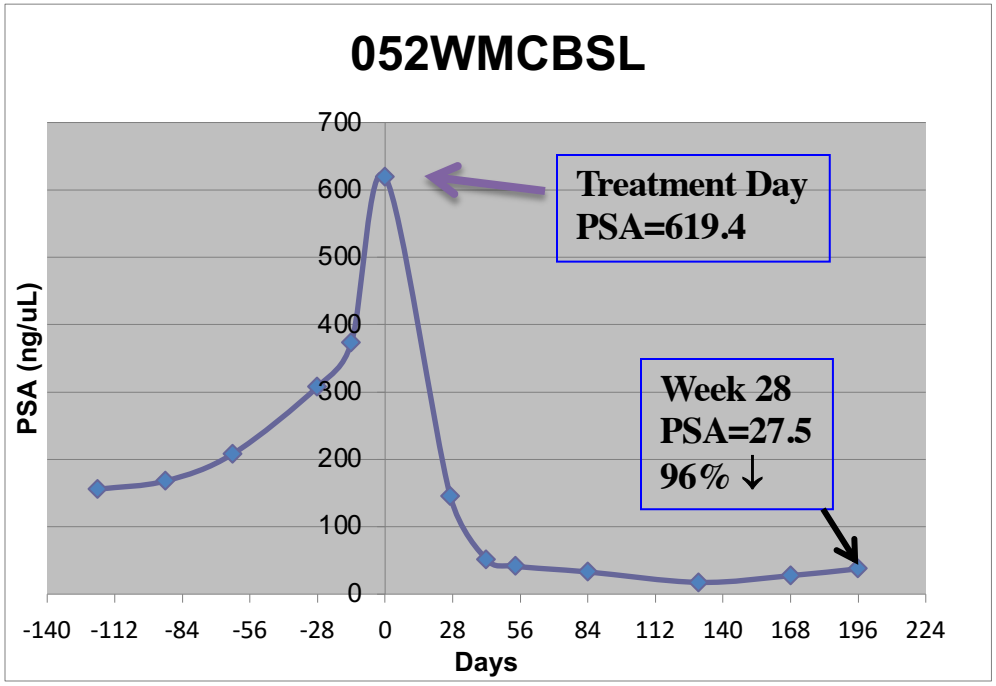


# Pca Target: PSMA

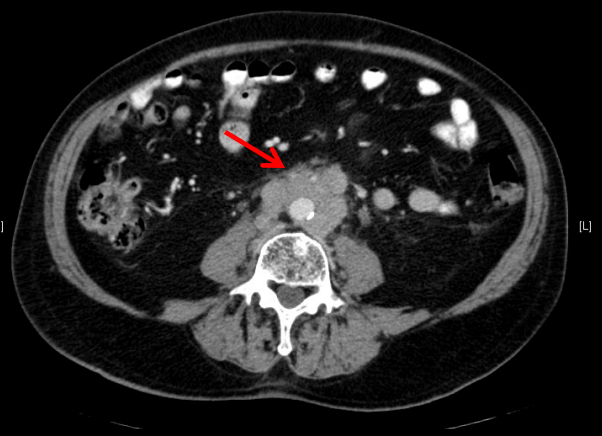


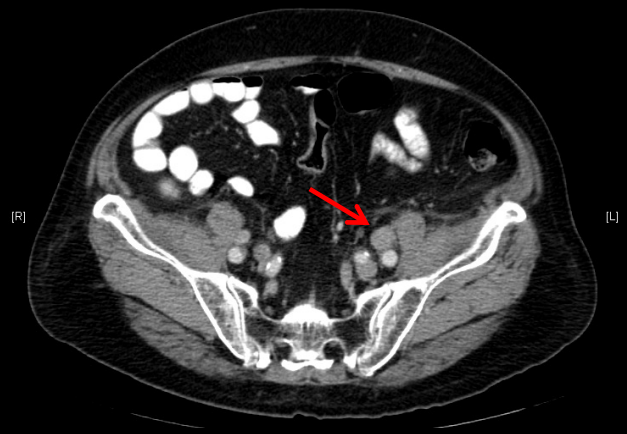



Anterior
Posterior
ANTERIOR
RT
POSTERIOR
RT
Bone Scan
J591 Scan
Bone Scan

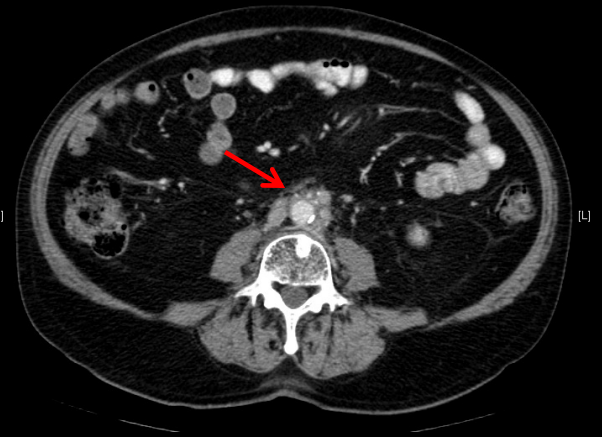

052WMCBSL
PSA (ng/uL)
700
600
500
400
300
200
100
0
-140
-112
-84
-56
-28
0
28
56
84
112
140
168
196
224
Days
Treatment Day
PSA=619.4
Week 28
PSA=27.5
96% ↓

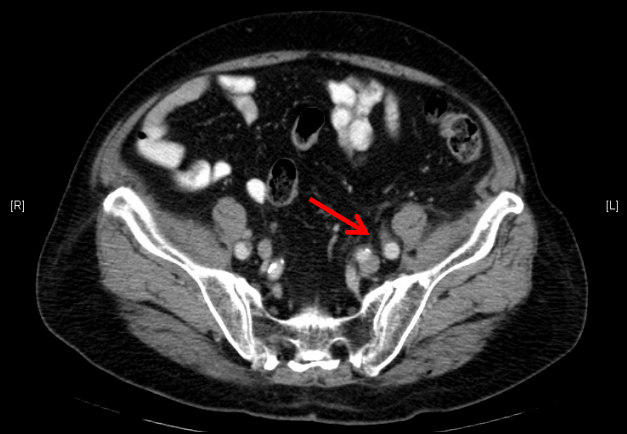
Baseline
pre-Rx




3 months



Published Ahead of Print on June 1, 2004 as 10.1200/JCO.2004.09.154

VOLUME 22 · NUMBER 13 · JULY 1 2004

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

# Phase I Trial of Yttrium-90–Labeled Anti–Prostate-Specific Membrane Antigen Monoclonal Antibody J591 for Androgen-Independent Prostate Cancer

*Matthew I. Milowsky, David M. Nanus, Lale Kostakoglu, Shankar Vallabhajosula, Stanley J. Goldsmith, and Neil H. Bander*

From the Division of Hematology and Medical Oncology, Department of Medicine, Division of Nuclear Medicine, Department of Radiology, and Department of Urology, Weill Medical College of Cornell University, New York, NY.

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Previously presented, in part, at the poster presentation of the 39th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 3, 2003.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Neil H. Bander, MD, Weill Medical College of Cornell University, 525 E 68th St, E-300, New York, NY 10021; e-mail: nhbander@med.cornell.edu.



0732-183X/04/2213-1/$20.00

DOI: 10.1200/JCO.2004.09.154

## ABSTRACT

**Purpose**
To determine the maximum-tolerated dose (MTD), toxicity, human antihuman antibody (HAHA) response, pharmacokinetics, organ dosimetry, targeting, and preliminary efficacy of yttrium-90–labeled anti–prostate-specific membrane antigen monoclonal antibody J591 ($^{90}$Y-J591) in patients with androgen-independent prostate cancer (PC).

**Patients and Methods**
Patients with androgen-independent PC and evidence of disease progression received indium-111–J591 for pharmacokinetic and biodistribution determinations followed 1 week later by $^{90}$Y-J591 at five dose levels: 5, 10, 15, 17.5, and 20 mCi/m$^2$. Patients were eligible for up to three re-treatments if platelet and neutrophil recovery was satisfactory.

**Results**
Twenty-nine patients with androgen-independent PC received $^{90}$Y-J591, four of whom were re-treated. Dose limiting toxicity (DLT) was seen at 20 mCi/m$^2$, with two patients experiencing thrombocytopenia with non–life-threatening bleeding episodes requiring platelet transfusions. The 17.5-mCi/m$^2$ dose level was determined to be the MTD. No re-treated patients experienced DLT. Nonhematologic toxicity was not dose limiting. Targeting of known sites of bone and soft tissue metastases was seen in the majority of patients. No HAHA response was seen. Antitumor activity was seen, with two patients experiencing 85% and 70% declines in prostate-specific antigen (PSA) levels lasting 8 and 8.6 months, respectively, before returning to baseline. Both patients had objective measurable disease responses. An additional six patients (21%) experienced PSA stabilization.

**Conclusion**
The recommended dose for $^{90}$Y-J591 is 17.5 mCi/m$^2$. Acceptable toxicity, excellent targeting of known sites of PC metastases, and biologic activity in patients with androgen-independent PC warrant further investigation of $^{90}$Y-J591 in the treatment of patients with PC.

*J Clin Oncol 22. © 2004 by American Society of Clinical Oncology*

## INTRODUCTION

Prostate-specific membrane antigen (PSMA) is a highly prostate-restricted type II integral membrane cell-surface glycoprotein expressed in both benign and malignant prostate tissue.[1,2] In contrast to other prostate-related antigens such as prostate-specific antigen (PSA), prostatic acid phosphatase (PAP), and prostate secretory protein, PSMA is not secreted. PSMA expression is increased in high-grade cancers, metastatic disease, and hormone-refractory prostate cancer (PC).[1,3,4] Although PSMA has folate hydrolase and neurocarboxypeptidase activity, its function with respect to PC biology is unknown.[5,6] Nevertheless, the expression pattern of PSMA makes it an excellent target for monoclonal antibody (mAb) therapy.

J591 is an anti-PSMA mAb that binds with high affinity (1 nm) to the extracellular domain of PSMA$_{ext}$.[7] The murine antibody J591 was deimmunized to allow for repeated dosing.[8] J591 deimmunization involved genetic engineering into a human immunoglobulin G1 (IgG1) with identical specificity

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Phase I Trial of $^{177}$Lutetium-Labeled J591, a Monoclonal Antibody to Prostate-Specific Membrane Antigen, in Patients With Androgen-Independent Prostate Cancer

*Neil H. Bander, Matthew I. Milowsky, David M. Nanus, Lale Kostakoglu, Shankar Vallabhajosula, and Stanley J. Goldsmith*

From the Department of Urology, Division of Hematology and Medical Oncology; Department of Medicine, Division of Nuclear Medicine; Department of Radiology, Weill Medical College of Cornell University, New York, NY.

Submitted May 21, 2004; accepted October 12, 2004.

Supported in part by National Institutes of Health General Clinical Research Center Program (NCRR grant M01RR00047); the Cancer Research Institute; the David H. Koch Foundation; the Peter Sacerdote Foundation; the Robert H. McCooey Memorial Cancer Research Fund; BZL Biologics Inc; and Millennium Pharmaceuticals Inc.

Presented in part at the 39th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 3, 2003.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Neil H. Bander, MD, Weill Medical College of Cornell University, 525 E 68th St, E-300, New York, NY 10021; e-mail: nhbander@med.cornell.edu.



0732-183X/05/2321-4591/$20.00

DOI: 10.1200/JCO.2005.05.160

A B S T R A C T

**Purpose**

To determine the maximum tolerated dose (MTD), toxicity, human anti-J591 response, pharmacokinetics (PK), organ dosimetry, targeting, and biologic activity of $^{177}$Lutetium-labeled anti–prostate-specific membrane antigen (PSMA) monoclonal antibody J591 ($^{177}$Lu-J591) in patients with androgen-independent prostate cancer (PC).

**Patients and Methods**

Thirty-five patients with progressing androgen-independent PC received $^{177}$Lu-J591. All patients underwent $^{177}$Lu-J591 imaging, PK, and biodistribution determinations. Patients were eligible for up to three retreatments.

**Results**

Thirty-five patients received $^{177}$Lu-J591, of whom 16 received up to three doses. Myelosuppression was dose limiting at 75 mCi/m$^2$, and the 70-mCi/m$^2$ dose level was determined to be the single-dose MTD. Repeat dosing at 45 to 60 mCi/m$^2$ was associated with dose-limiting myelosuppression; however, up to three doses of 30 mCi/m$^2$ could be safely administered. Nonhematologic toxicity was not dose limiting. Targeting of all known sites of bone and soft tissue metastases was seen in all 30 patients with positive bone, computed tomography, or magnetic resonance images. No patient developed a human anti-J591 antibody response to deimmunized J591 regardless of number of doses. Biologic activity was seen with four patients experiencing ≥ 50% declines in prostate-specific antigen (PSA) levels lasting from 3+ to 8 months. An additional 16 patients (46%) experienced PSA stabilization for a median of 60 days (range, 1 to 21+ months).

**Conclusion**

The MTD of $^{177}$Lu-J591 is 70 mCi/m$^2$. Multiple doses of 30 mCi/m$^2$ are well tolerated. Acceptable toxicity, excellent targeting of known sites of PC metastases, and biologic activity in patients with androgen-independent PC warrant further investigation.

*J Clin Oncol 23:4591-4601. © 2005 by American Society of Clinical Oncology*

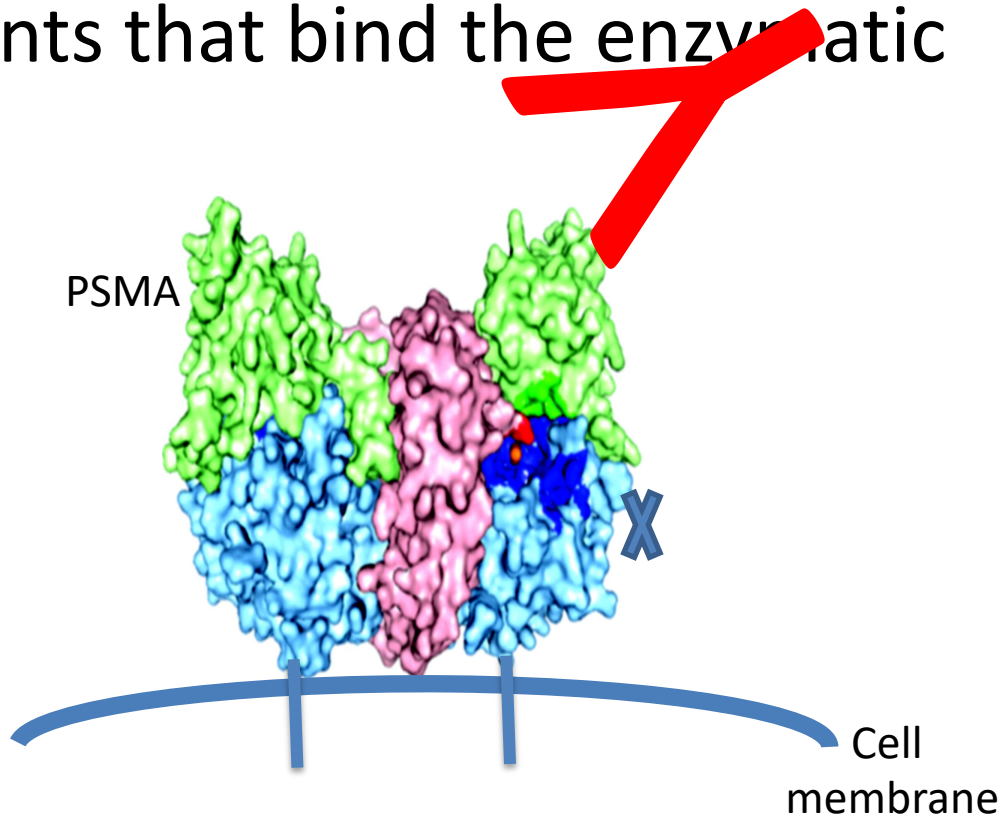
## INTRODUCTION

Prostate-specific membrane antigen (PSMA) is the most well established, prostate cancer (PC) –restricted, cell-surface antigen identified to date.[1] PSMA is a 100-kD type II transmembrane glycoprotein that is expressed by all prostate cancers.[2] The density of PSMA expression progressively increases in higher-grade cancers, metastatic disease, and hormone-refractory PC.[3-6] The 19–amino acid cytoplasmic domain of this nonsecreted protein contains a novel MXXXL internalization motif,[7,8] resulting in its internalization and endosomal recycling. These characteristics make PSMA an ideal target for monoclonal antibody (mAb) therapy.

J591 is an anti-PSMA mAb that binds with 1-nM affinity to the extracellular domain of PSMA.[9,10] Murine J591 antibody

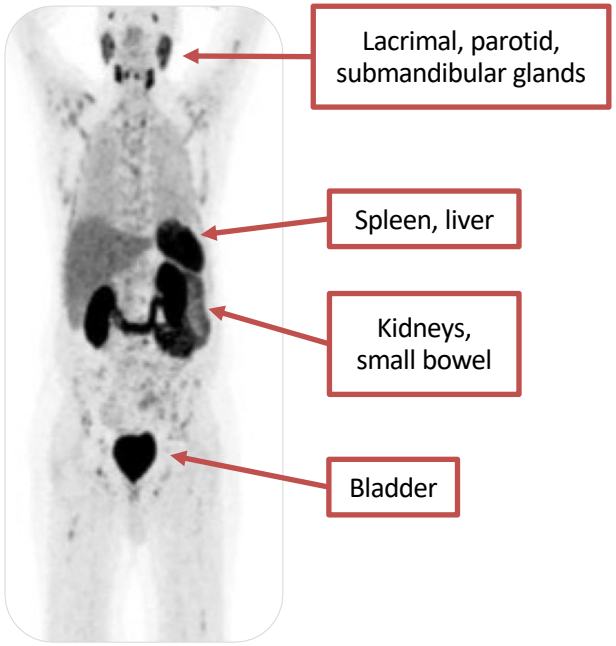
# 2 Ways to Target PSMA

- Abs that bind the molecule (e.g., J591)
- Inhibitors/agents that bind the enzymatic 'pocket'



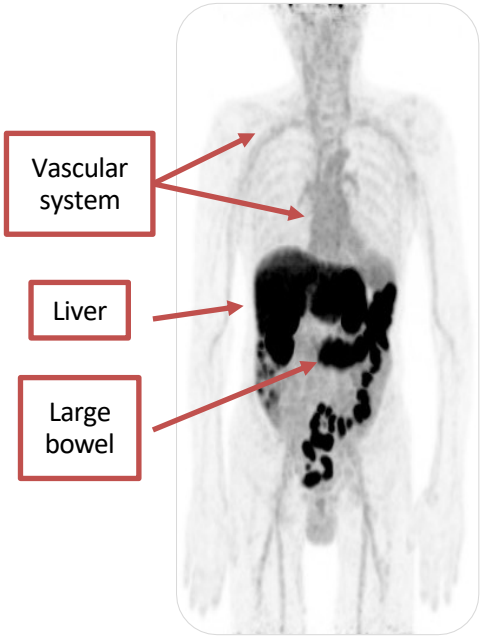
# Radioantibodies and radioligands have differing biodistributions

**RADIOLIGAND**




$^{68}$Ga-PSMA11 at 1 hour

**RADIOANTIBODY**




J591 Ab Zr$^{89}$ at 3 days

- Undetectable uptake in lacrimal and salivary glands
- Excretion through the hepatobiliary system mitigates concerns about renal toxicity associated with radioligands
- Superior uptake and retention in bone lesions and other small volume lesions
- Less normal tissue exposure

Tagawa S, Bander N et al. Weill Cornell Medicine

# Two types of Isotopes: α and β radionuclides

## α particles are significantly more potent and precise than β particles

| | α ($^{225}$Ac) | β ($^{177}$Lu) |
|---|---|---|
| Relative particle mass | 7300 | 1 |
| Max range in tissue (µm) | 50 | 1,700 |
| Linear energy transfer | 100 keV/µm | 0.2 keV/mm |
| Type of DNA damage generated | Double strand breaks | Single strand breaks |
| DNA hits required to kill a cell | 1 | 1000 |

Henriksen G et al. *J Nucl Med.* 2003;44:252-259; Kozempel J et al. *Molecules* 2018, 23, 581-599; Hosono M et al. *Ann Nucl Med.* 2018; 32(3): 217–235; Kassis A *Semin Nucl Med.* 2008;38:358–366;
Nayak T et al. *Cancer Biotherapy & Radiopharm.* 2005; 20 (1) 52-57; Wadas TJ et al. *Am J Roentgenol.* 2014 Aug; 203(2): 253–260.

# VISION Trial: PSMA RL-$^{177}$Lu

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

ABSTRACT

**BACKGROUND**

Metastatic castration-resistant prostate cancer remains fatal despite recent advances. Prostate-specific membrane antigen (PSMA) is highly expressed in metastatic castration-resistant prostate cancer. Lutetium-177 ($^{177}$Lu)–PSMA-617 is a radioligand therapy that delivers beta-particle radiation to PSMA-expressing cells and the surrounding microenvironment.

**METHODS**

We conducted an international, open-label, phase 3 trial evaluating $^{177}$Lu-PSMA-617 in patients who had metastatic castration-resistant prostate cancer previously treated with at least one androgen-receptor–pathway inhibitor and one or two taxane regimens and who had PSMA-positive gallium-68 ($^{68}$Ga)–labeled PSMA-11 positron-emission tomographic–computed tomographic scans. Patients were randomly assigned in a 2:1 ratio to receive either $^{177}$Lu-PSMA-617 (7.4 GBq every 6 weeks for four to six cycles) plus protocol-permitted standard care or standard care alone. Protocol-permitted standard care excluded chemotherapy, immunotherapy, radium-223 ($^{223}$Ra), and investigational drugs. The alternate primary end points were imaging-based progression-free survival and overall survival, which were powered for hazard ratios of 0.67 and 0.73, respectively. Key secondary end points were objective response, disease control, and time to symptomatic skeletal events. Adverse events during treatment were those occurring no more than 30 days after the last dose and before subsequent anticancer treatment.

**RESULTS**

From June 2018 to mid-October 2019, a total of 831 of 1179 screened patients underwent randomization. The baseline characteristics of the patients were balanced between the groups. The median follow-up was 20.9 months. $^{177}$Lu-PSMA-617 plus standard care significantly prolonged, as compared with standard care, both imaging-based progression-free survival (median, 8.7 vs. 3.4 months; hazard ratio for progression or death, 0.40; 99.2% confidence interval [CI], 0.29 to 0.57; P<0.001) and overall survival (median, 15.3 vs. 11.3 months; hazard ratio for death, 0.62; 95% CI, 0.52 to 0.74; P<0.001). All the key secondary end points significantly favored $^{177}$Lu-PSMA-617. The incidence of adverse events of grade 3 or above was higher with $^{177}$Lu-PSMA-617 than without (52.7% vs. 38.0%), but quality of life was not adversely affected.

**CONCLUSIONS**

Radioligand therapy with $^{177}$Lu-PSMA-617 prolonged imaging-based progression-free survival and overall survival when added to standard care in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer. (Funded by Endocyte, a Novartis company; VISION ClinicalTrials.gov number, NCT03511664.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Sartor at Tulane Cancer Center, School of Medicine, Tulane University, New Orleans, LA 70112, or at osartor@tulane.edu.

*The list of the VISION investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Sartor, Morris, and Krause contributed equally to this article.

This article was published on June 23, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2107322



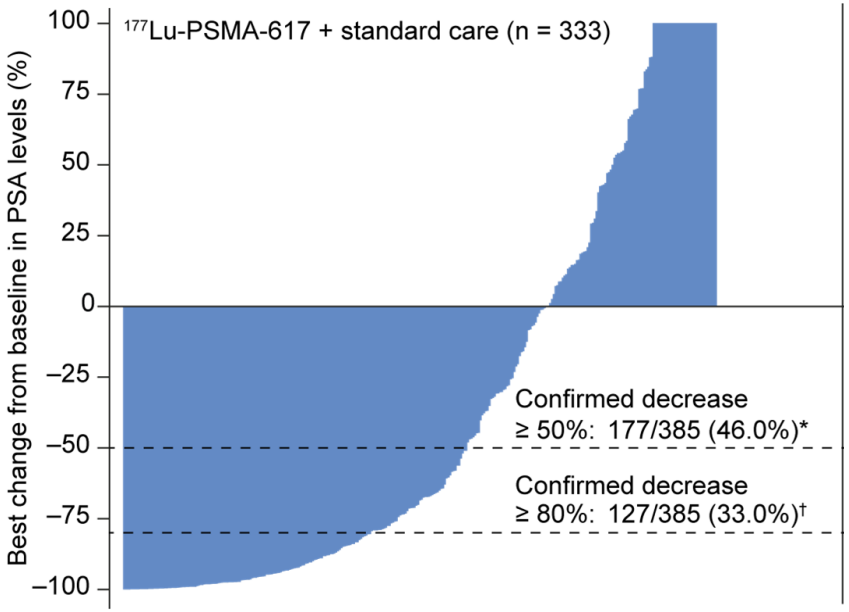




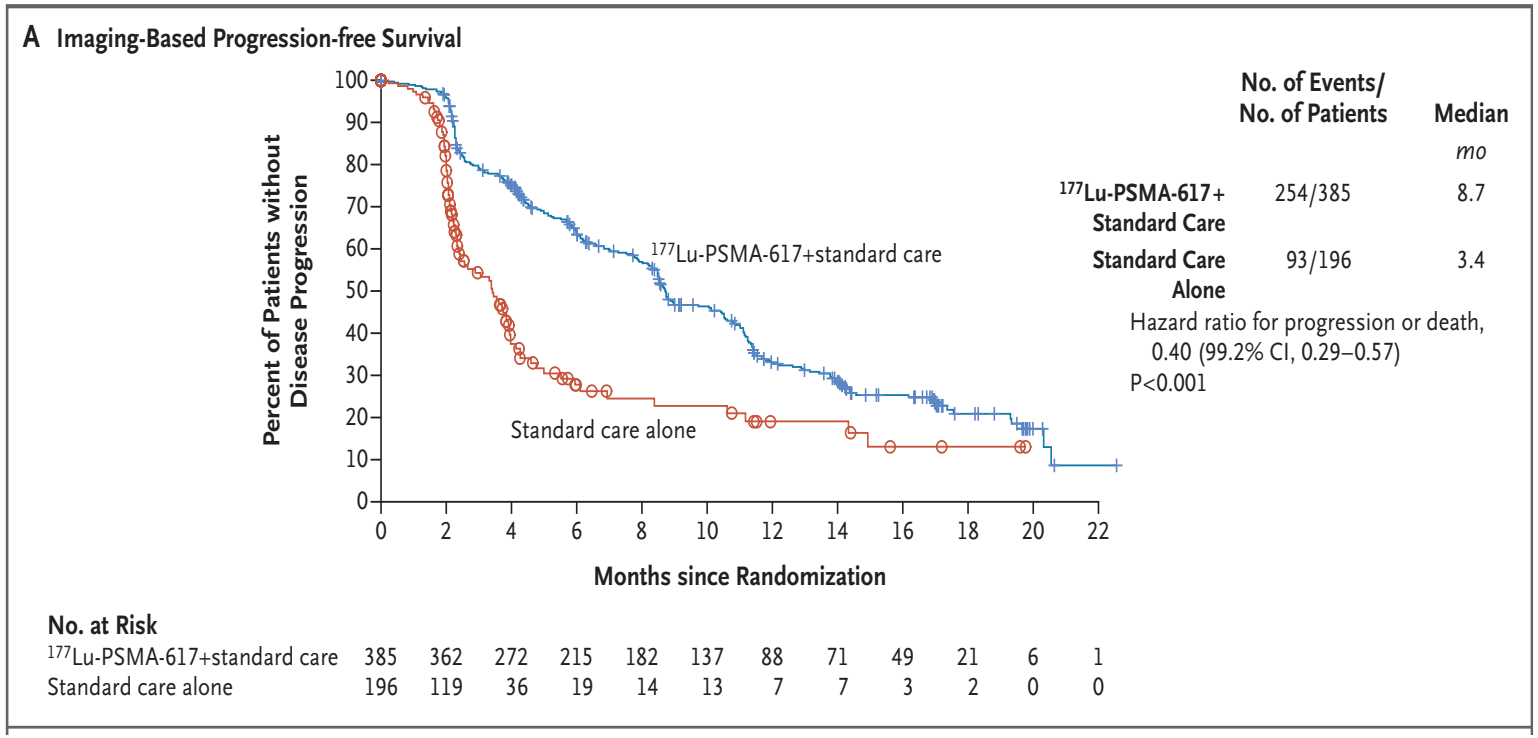
$^{177}$Lu-PSMA-617 every 6 weeks for 4-6 cycles plus protocol-permitted standard care vs standard care alone (Cabazitaxel prohibited)

- mCRPC post-chemotherapy
- Post-ARSI
- PSMA PET-pos

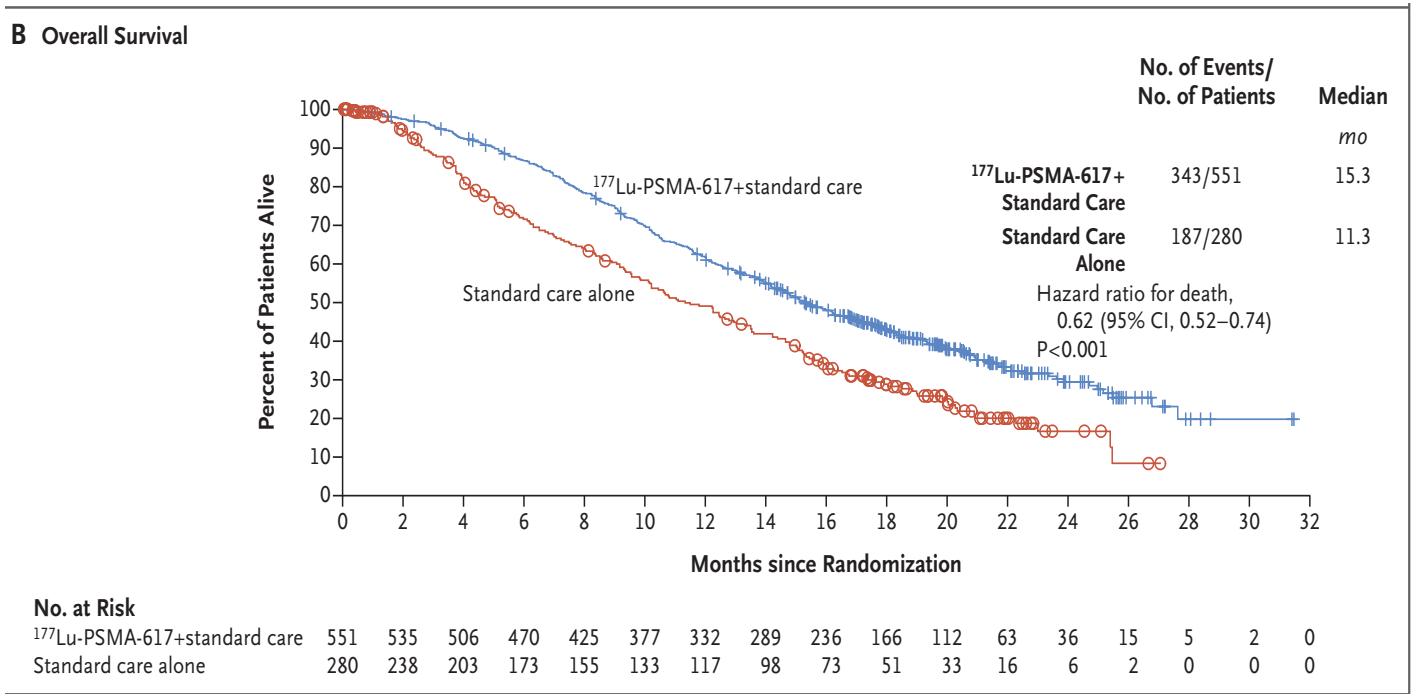
# VISION Trial: PSMA RL-$^{177}$Lu PSA Waterfall Plot



# VISION Trial: PSMA RL-$^{177}$Lu rPFS

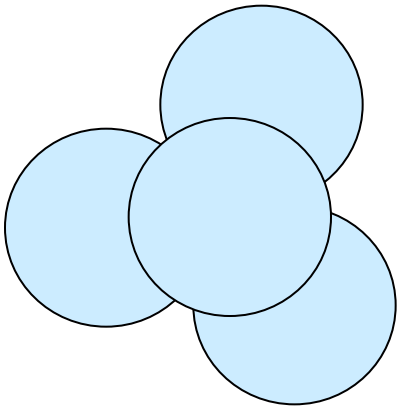


# VISION Trial: PSMA RL-$^{177}$Lu Overall Survival



# From Beta to Alpha

# Alpha- vs. Beta-Particles



**Alpha** **Beta**

| | α | β |
|---|---|---|
| **Relative particle mass** | **7300** | **1** |
| **Initial energy (MeV) per particle** | **3-8** | **0.01-2.5** |
| **Range in tissue (μm)** | **40-100** | **50-5000** |
| **LET (KeV/μm)** | **60-230** | **0.015-0.4** |
| **DNA hits to kill cells** | **1-10** | **≥ 1000's** |

LET = linear energy transfer.

Henriksen et al. *J Nucl Med*. 2003;44:252-259

21. Local zones of higher respiratory activity may be important, however, as evidenced by higher levels of the respiratory enzyme cytochrome oxidase in the subsets of cells with nitrogenase than in those without (*40*). Deployment of oxygen and reactive oxygen species detoxification systems (such as Mehler, thioredoxin peroxidases, and catalase) also aid in providing a microanaerobic environment around cells fixing nitrogen. Colony formation may further reduce ambient oxygen concentrations (*5*, *8*), enabling the higher $N_2$ fixation rates (per unit of chlorophyll a) observed in colonies as compared to single trichomes (*41*).
22. In mature heterocysts, PSI is the only active photosynthetic reaction center and is important in providing the extra ATP for $N_2$ fixation through cyclic electron transport. In *Trichodesmium*, high Mehler activity has also previously been invoked in supplying ATP (*42*, *43*).
23. Antibodies to D1 fragments and to dinitrogenase reductase raised in rabbits were conjugated to fluorescent probes Alexa 488 and Alexa 568, respectively (Molecular Probes) and labeled sequentially (nitrogenase followed by D1) in cells fixed in 100% ethanol and permeabilized with 0.5% dimethyl sulfoxide in phosphate buffer. Samples were viewed on a confocal laser microscope ( Zeiss LSM410) at 488/528 nm and 568/600 to 620 nm bandpass excitation/emission for the D1 and nitrogenase, respectively. The results obtained for cultures grown in several conditions and at several points during the diel cycle show that D1 occurs in most cells in a trichome and co-occurs in the same cells as nitrogenase.
24. Z. Krupa, G. Öquist, P. Gustafsson, *Plant Physiol*. **93**, 1 (1990).
25. *Trichodesmium* colonies were stained with 3,3-diaminobenzidine (DAB), which polymerizes, in the presence of peroxidases, with intracellular $H_2O_2$ produced by reduction of oxygen in PSI, to form brown deposits (*44*). The final concentration of DAB used was 1 mg/ml. No external peroxidases were added, indicating the presence of active peroxidases involved in the antioxidative pathways [Web fig. 2 (*19*)]. Negative controls of dark-incubated *Trichodesmium* trichomes showed low DAB staining throughout the trichomes.
26. Trichomes were filtered, embedded in 1% agarose (melting point 25°C) in sea water, and placed in a cellophane-sealed thermostated chamber pumped through with medium (100 ml $min^{-1}$ at 25°C, saturated with air). To reduce artifacts caused by handling, fresh samples were prepared for each time point. Samples were viewed with a microscope for two-dimensional measurements of in vivo chlorophyll fluorescence kinetics (*45*). Measurements were done with 30-$\mu$s flashes of nonactinic measuring light, 1000 $\mu$mol of quanta $m^{-2}$ $s^{-1}$ of actinic light, and 10,000 $\mu$mol of quanta $m^{-2}$ $s^{-1}$ saturating multiturnover flashes. Fluorescence kinetics were measured simultaneously on 300 $\times$ 400 pixels.
27. A circadian pattern temporally separates the abundance of mRNA for nifH (nitrogenase), psbA (encoding for PSII) and psaB (encoding for PSI) in *Trichodesmium* strain IMS101 (*46*, *47*).
28. In *Trichodesmium*, high external concentrations of molecular oxygen affect nitrogenase activity within ~15 min (*48*), whereas Western and Northern blots of nitrogenase and nifH (*49*) revealed that the enzyme and transcript levels are not much affected 2 hours after addition of DCMU and DBMIB, indicating that the loss of activity is not due to the loss of the enzyme but rather to a posttranslational inactivation of the enzyme by oxygen.
29. In most cyanobacteria, dark respiration rates are generally <10% of the gross oxygen evolution rates (*50*). In *Trichodesmium*, dark respiration ranged from 13 to 46% of the maximum gross oxygen evolution rate, with a mean of 23% and consisting, in the dark, of approximately 30% of the absolute magnitude of maximal gross photosynthesis. Moreover, at low light intensities (typical of those found for depth-adapted populations or cultured populations), more oxygen was consumed than evolved (*51*, *52*).
30. Phylogenetic analyses suggest a single ancestral origin for the catalytic subunits of the enzyme complex responsible, namely nitrogenase (*53*).
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# Tumor Therapy with Targeted Atomic Nanogenerators


**Michael R. McDevitt,[1] Dangshe Ma,[1] Lawrence T. Lai,[1] Jim Simon,[2] Paul Borchardt,[1] R. Keith Frank,[2] Karen Wu,[1] Virginia Pellegrini,[1] Michael J. Curcio,[1] Matthias Miederer,[1] Neil H. Bander,[3] David A. Scheinberg[1]***



**A single, high linear energy transfer alpha particle can kill a target cell. We have developed methods to target molecular-sized generators of alpha-emitting isotope cascades to the inside of cancer cells using actinium-225 coupled to internalizing monoclonal antibodies. In vitro, these constructs specifically killed leukemia, lymphoma, breast, ovarian, neuroblastoma, and prostate cancer cells at becquerel (picocurie) levels. Injection of single doses of the constructs at kilobecquerel (nanocurie) levels into mice bearing solid prostate carcinoma or disseminated human lymphoma induced tumor regression and prolonged survival, without toxicity, in a substantial fraction of animals. Nanogenerators targeting a wide variety of cancers may be possible.**


Alpha particles are high-energy, high linear energy transfer helium nuclei capable of strong, yet selective, cytotoxicity (*1*). A single atom emitting an alpha particle can kill a target cell (*2*). Monoclonal antibodies conjugated to alpha particle–emitting radionuclides ($^{213}$Bi and $^{211}$At) are starting to show promise in radioimmunotherapy (*3*, *4*). The conjugates [$^{213}$Bi]-HuM195 (*2*) and [$^{213}$Bi]J591 (*5*, *6*) have been used in preclinical models of leukemia and prostate cancer, respectively, and in a phase I human clinical trial, [$^{213}$Bi]HuM195 was active against leukemia, with no significant toxicity (*3*). Astatine-211–labeled antibodies to tenascin (anti-tenascin) have been used clinically to treat malignant gliomas in humans (*4*) in a phase I trial. For clinical use of $^{213}$Bi, we developed a therapeutic dose-level $^{225}$Ac/$^{213}$Bi generator device, approximately 1 cm by 6 cm in size,


[1]Molecular Pharmacology and Therapeutics Program, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA. [2]The Dow Chemical Company, Freeport, TX 77541, USA. [3]Department of Urology, New York Presbyterian Hospital-Weill Medical College of Cornell University, 525 East 68th Street, New York, NY 10021, USA.

*To whom correspondence should be addressed. E-mail: d-scheinberg@ski.mskcc.org

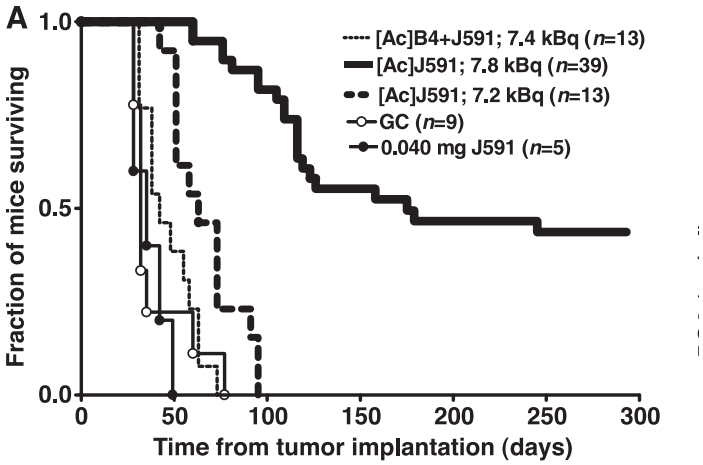



**Fig. 2.** (**A**) Kaplan-Meier plot showing survival of mice bearing i.m. LNCaP tumor xenografts treated intraperitoneally in several therapy/control experiments. The 39 animals that received 7.8 kBq [$^{225}$Ac]J591 were treated on day 12, and the 13 animals that received 7.2 kBq [$^{225}$Ac]J591 were treated on day 15. Animals were killed when tumor area was $\geq$2.5 cm$^2$. Median survival versus time was evaluated using a log-rank test ($P < 0.0001$). (**B**) Individual serum PSA values of the 39 mice treated with a 7.8 kBq dose of [$^{225}$Ac]J591 on day 12 in the therapy experiment with LNCaP model (Fig. 2A). The median was marked with a solid line. (Note the split scale of PSA levels.) PSA values were evaluated using an unpaired *t*-test with two-tailed *P* values (95% co

## J591-$^{225}$Ac prolonged survival and cured approximately 45% of the animals

# Phase 1 Single Ascending Dose clinical trial

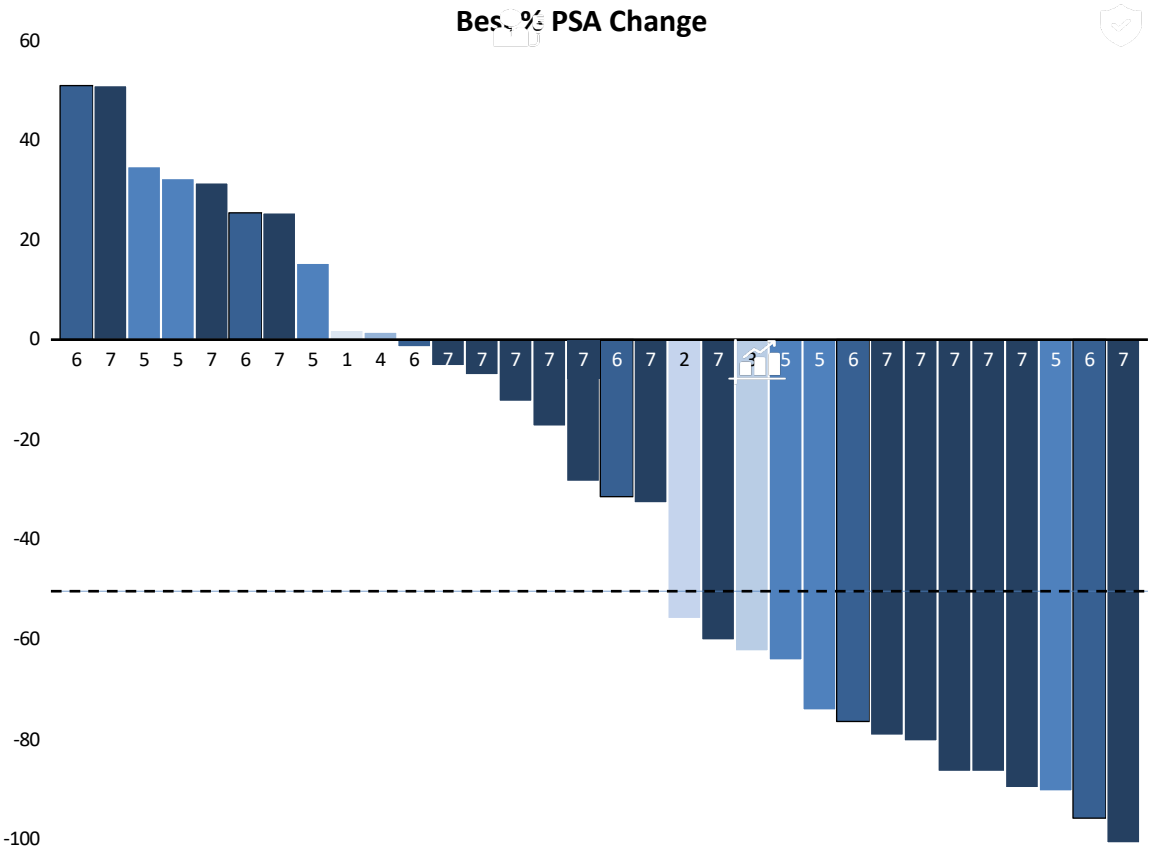
| Patient Population |
| --- |
| **Heavily pre-treated patients with NO PSMA-PET pre-selection** |
| • 100% >/= 1 ARSI<br>• 63% received prior chemotherapy<br>• 45% received prior $^{177}$Lu-PSMA-RL<br>• 28% received prior $^{223}$Ra |

| **Cohort** | **Treatment Dose** (KBq/Kg) |
| --- | --- |
| 1 | 13.3 |
| 2 | 26.7 |
| 3 | 40.0 |
| 4 | 53.3 |
| 5 | 66.7 |
| 6 | 80.0 |
| 7 | 93.3 |

mCRPC
**No** PSMA PET exclusion

# Phase 1 Single Ascending Dose clinical trial

*J591-α POC data supports its superior clinical activity among late-stage metastatic prostate cancer patients*



# Phase 1 Single Ascending Dose clinical trial

*J591-α POC data supports its superior clinical activity among late-stage metastatic prostate cancer patients*

| Safety |
| --- |
| **Well-tolerated** |
| • 12 grade 1 xerostomia, 7 of 12 had prior $^{177}$Lu-PSMA-RL<br>• 1 DLT (platelets)<br>• MTD not reached |

| Efficacy |
| --- |
| **Patients experienced strong dose-dependent efficacy response, with significant reduction in PSA levels in nearly half of patients** |
| • **69% experienced some PSA decline**<br>• **PSA50 response** = 14/31* (**45%**)<br>  • 8/18 (44%) patients without prior $^{177}$Lu-PSMA-RL<br>  • 6/13 (46%) patients with prior $^{177}$Lu-PSMA-RL<br>  • *1 patient treated a second time after long initial response |

# Ongoing Trials

- Multiple Ascending Dose Trial
- Re-treatment Trial
- J591-$^{225}$Ac + $^{177}$Lu-PSMA I&T
- J591-$^{225}$Ac + Pembrolizumab®

# Conclusions

- PSMA is an ideal PC-specific molecular target
- Multiple ways to therapeutically target PSMA
  - Radioactive isotopes
    - $^{177}$Lu [beta emitter]
    - $^{225}$Ac [alpha emitter]
  - Drug conjugates
  - Immuno-potentiators
  - All promising and all under active study
- The picture has never looked brighter for PC patients!