Advances In Oncology

Immuno Modulation
A New Frontier in Cancer Treatment

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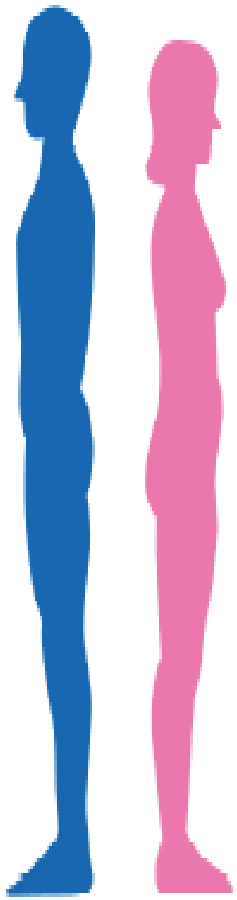
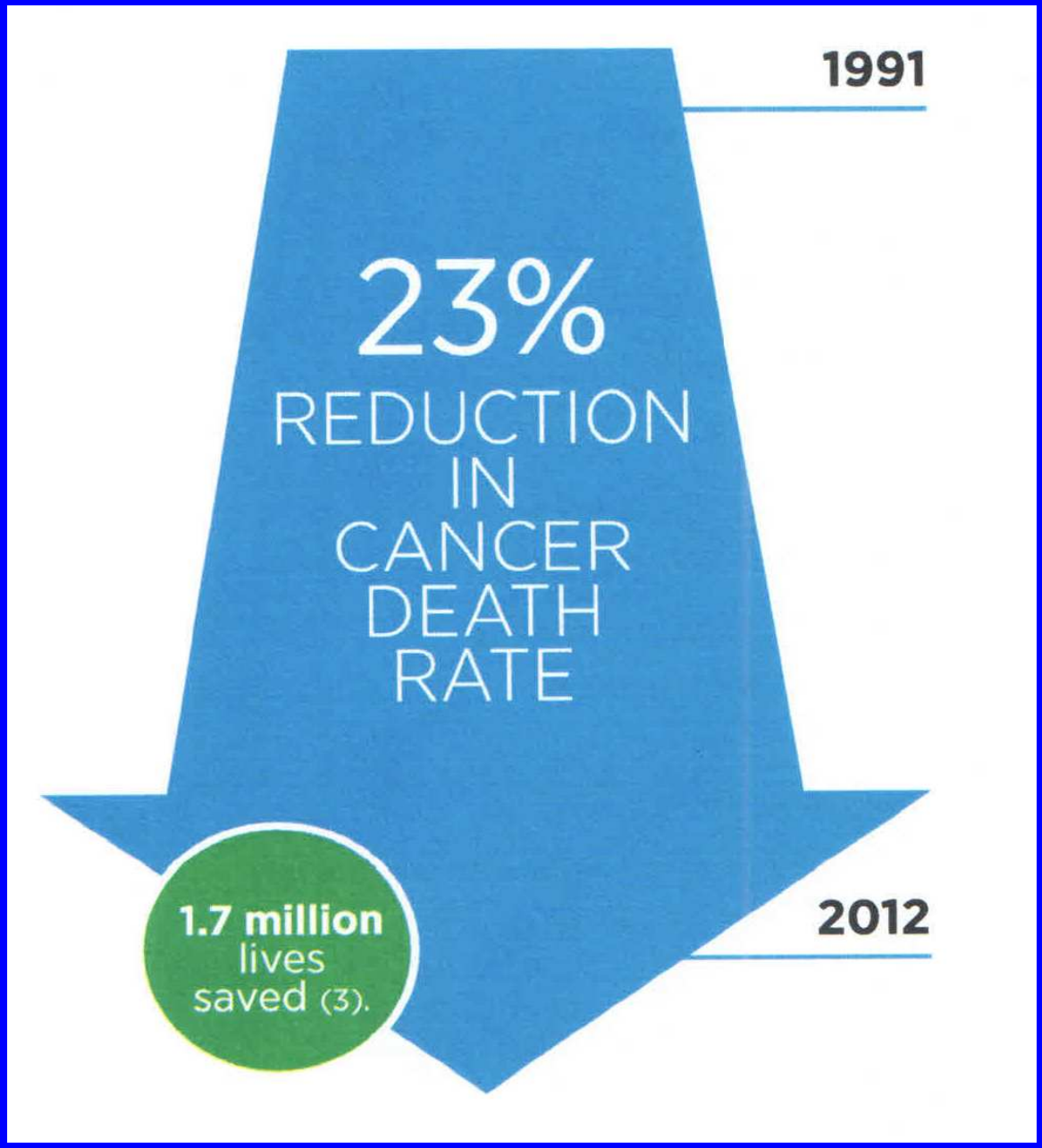
AAPI-QLI - 2018

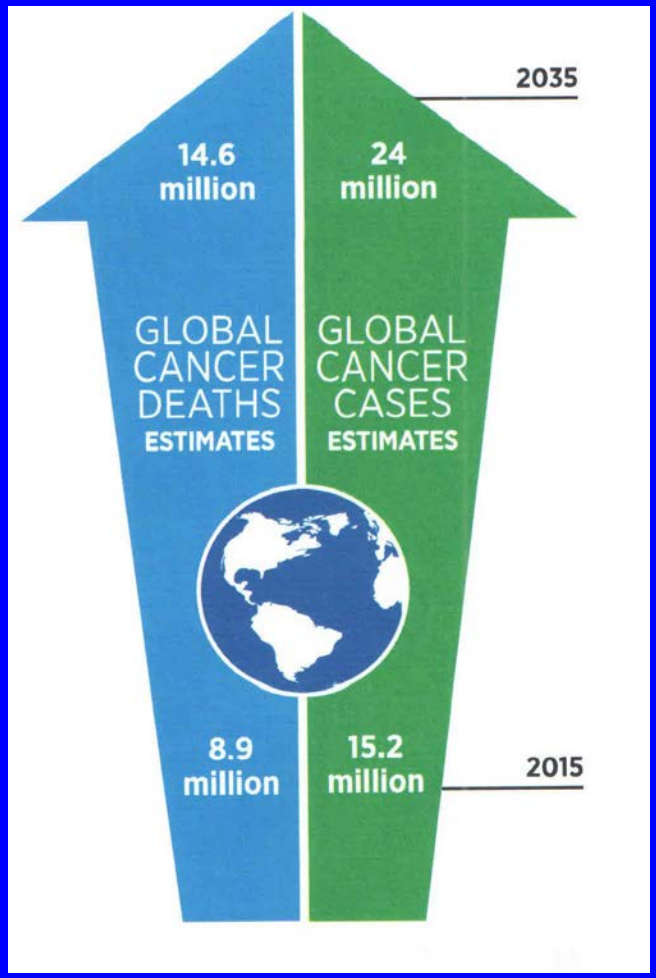
Estimated New Cases*

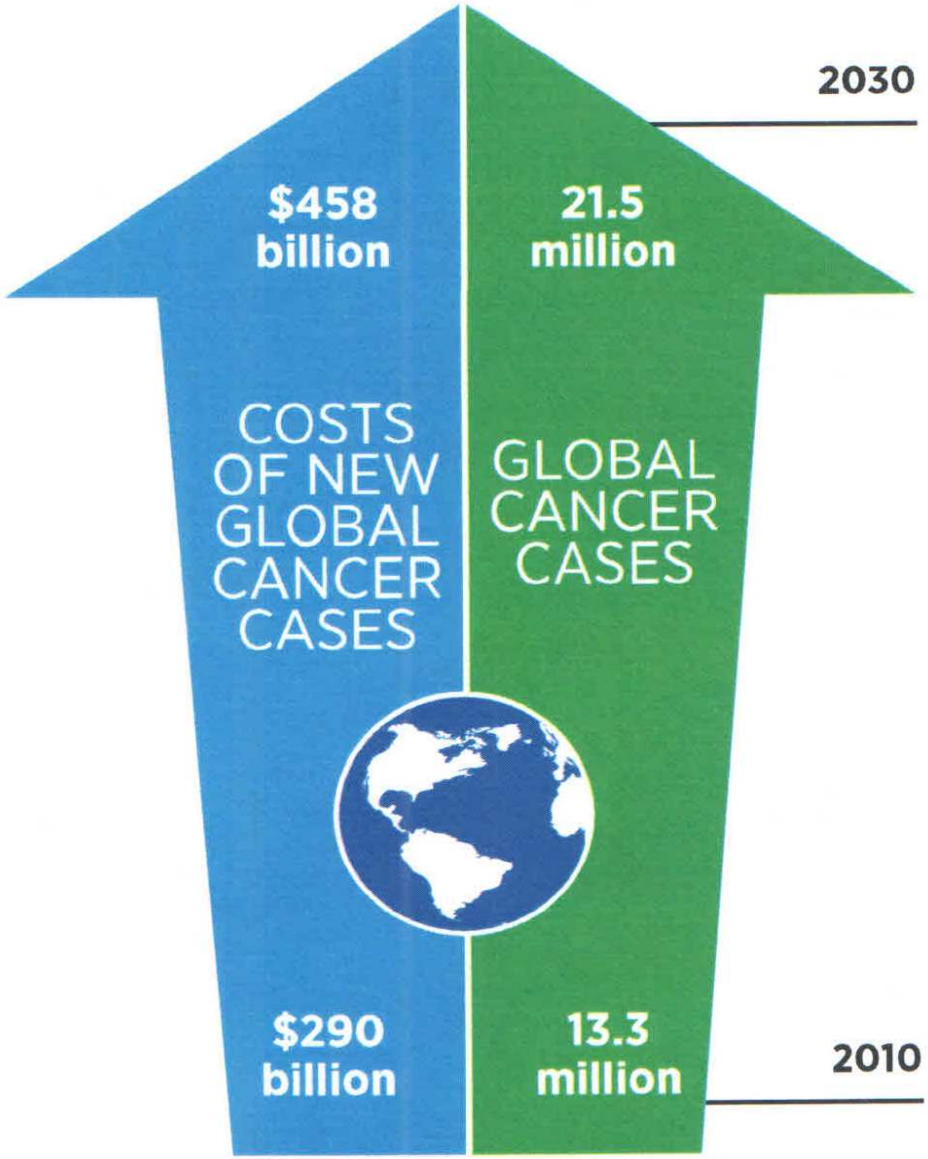
Males			Females		
Prostate	233,000	27%	Breast	232,670	29%
Lung & bronchus	116,000	14%	Lung & bronchus	108,210	13%
Colorectum	71,830	8%	Colorectum	65,000	8%
Urinary bladder	56,390	7%	Uterine corpus	52,630	6%
Melanoma of the skin	43,890	5%	Thyroid	47,790	6%
Kidney & renal pelvis	39,140	5%	Non-Hodgkin lymphoma	32,530	4%
Non-Hodgkin lymphoma	38,270	4%	Melanoma of the skin	32,210	4%
Oral cavity & pharynx	30,220	4%	Kidney & renal pelvis	24,780	3%
Leukemia	30,100	4%	Pancreas	22,890	3%
Liver & intrahepatic bile duct	24,600	3%	Leukemia	22,280	3%
All Sites	**855,220**	**100%**	**All Sites**	**810,320**	**100%**



Seigal et al. Cancer statistics, 2015. CA CANCER J CLIN 2015;64:9–29


1991
23%
REDUCTION
IN
CANCER
DEATH
RATE
2012
1.7 million
lives
saved (3).


2035
14.6 million
24 million
GLOBAL CANCER DEATHS ESTIMATES
GLOBAL CANCER CASES ESTIMATES
8.9 million
15.2 million
2015


2030
$458 billion
21.5 million
COSTS OF NEW GLOBAL CANCER CASES
GLOBAL CANCER CASES
$290 billion
13.3 million
2010

Data from (21)

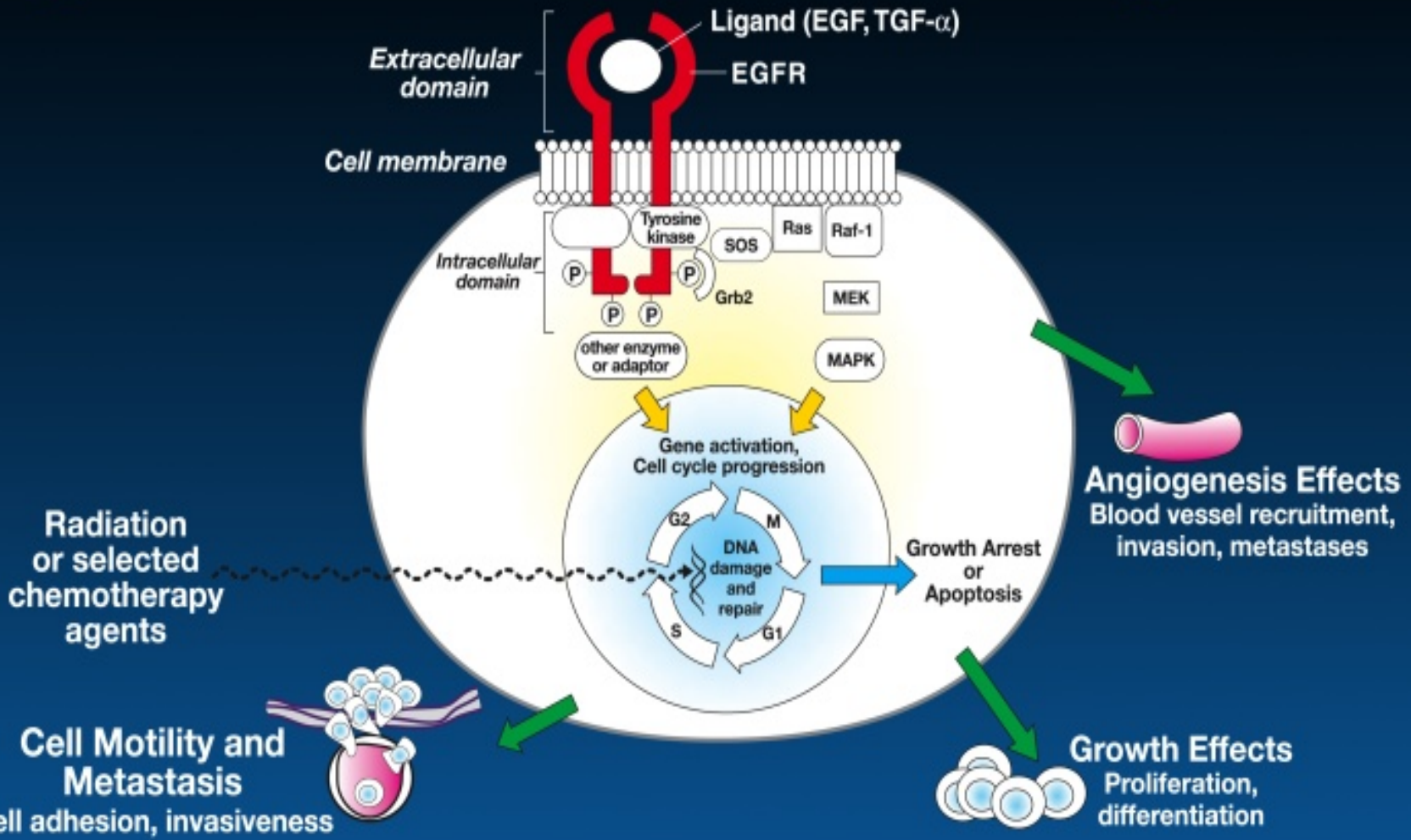
Advances In Oncology

- Evolving Paradigms
- New Discoveries in Cancer
- Advances in Clinical Oncology

Advances in Oncology

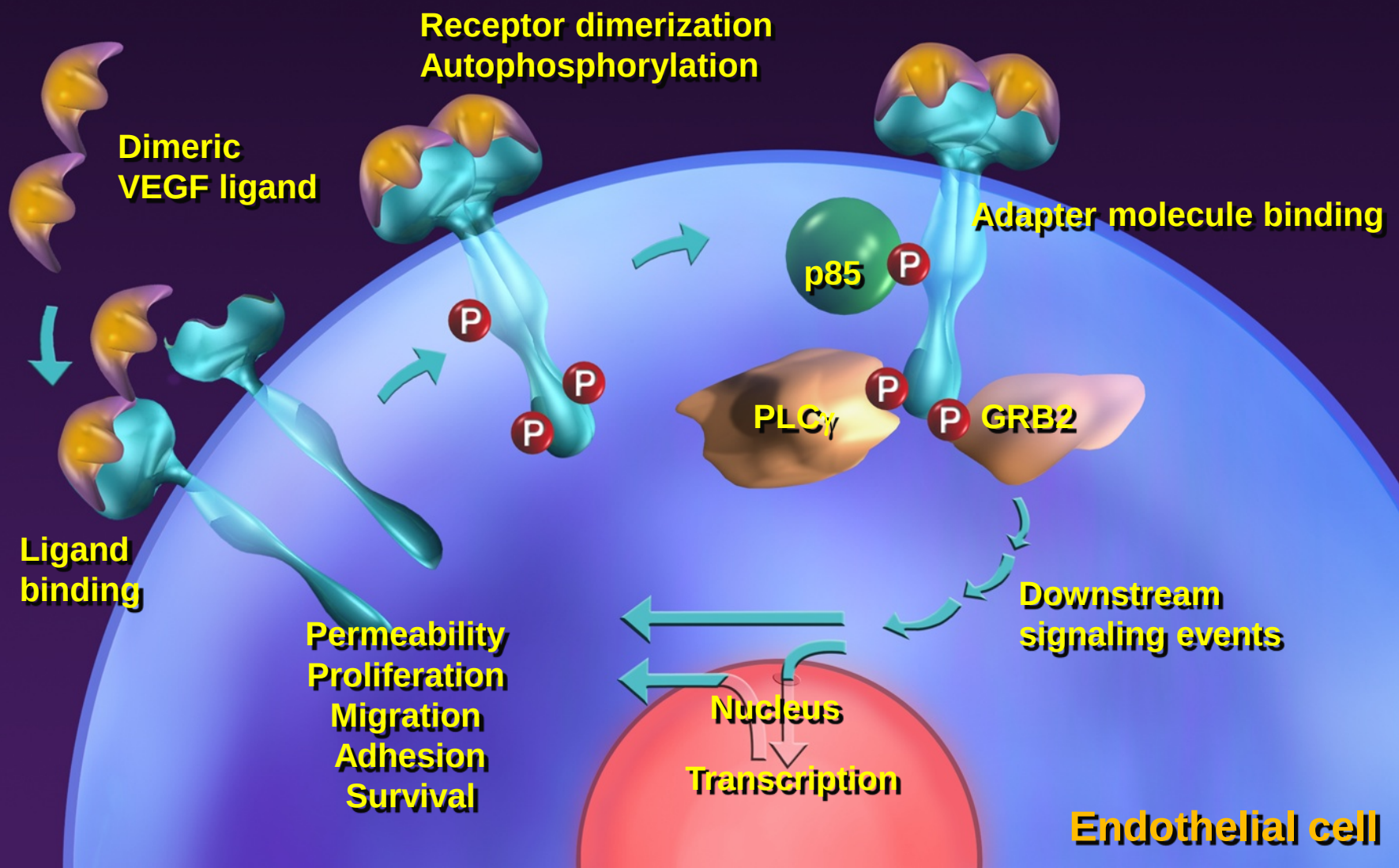
- Predictors of Outcomes
  - Primary Predictors
    - Size
    - Pathology
    - Grade
  - Secondary Predictors
    - Tumor Markers
    - Ploidy
    - Receptors
  - Tertiary Predictors
    - P^{53} Gene Expression
    - EGFR-2 Receptor Expression
    - Molecular & Proteomic Profiling

Role of the EGFR in Signal Transduction and Tumor Progression

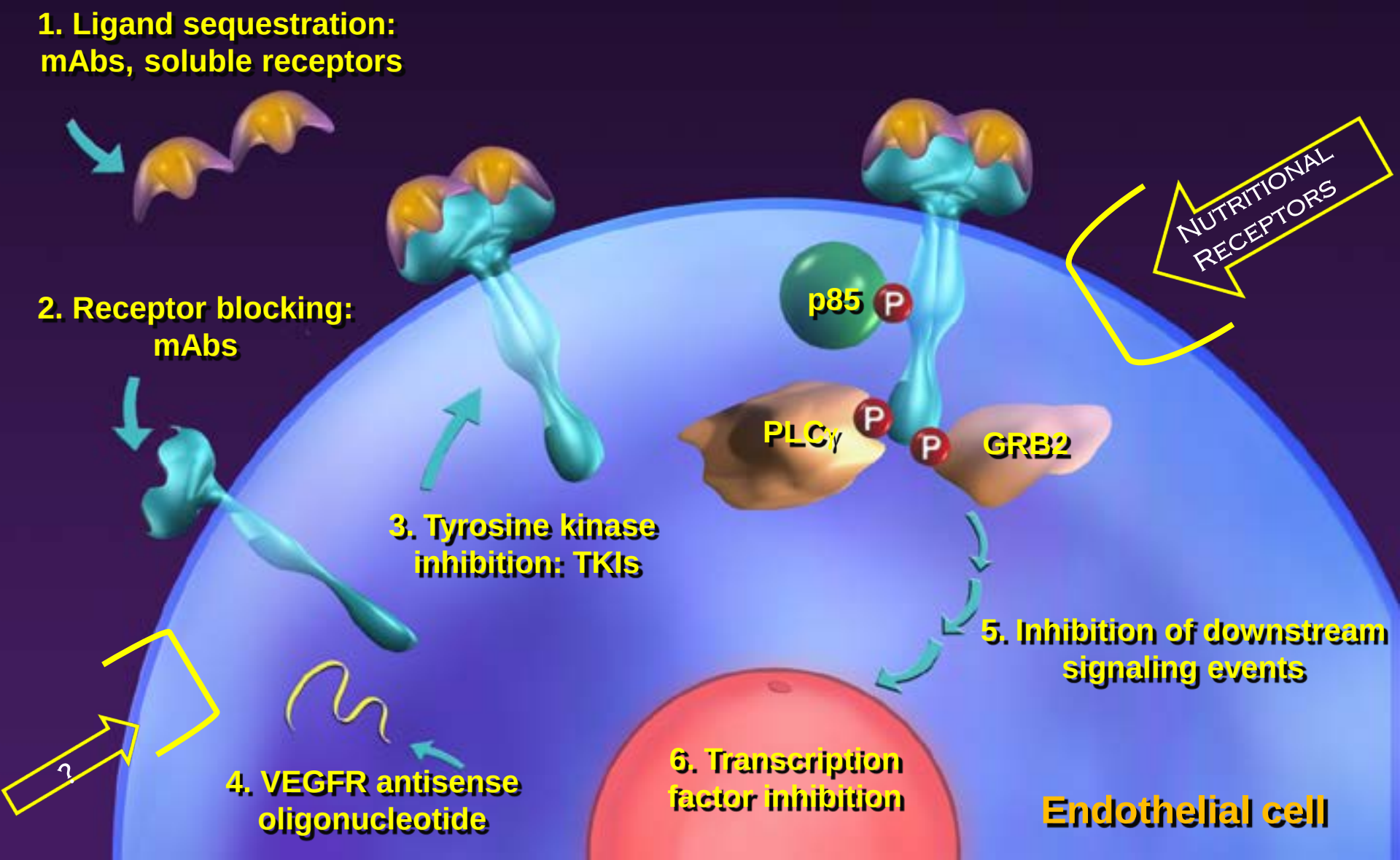


Harari PM, Huang S-M. Clin Cancer Res 6:323, 2000

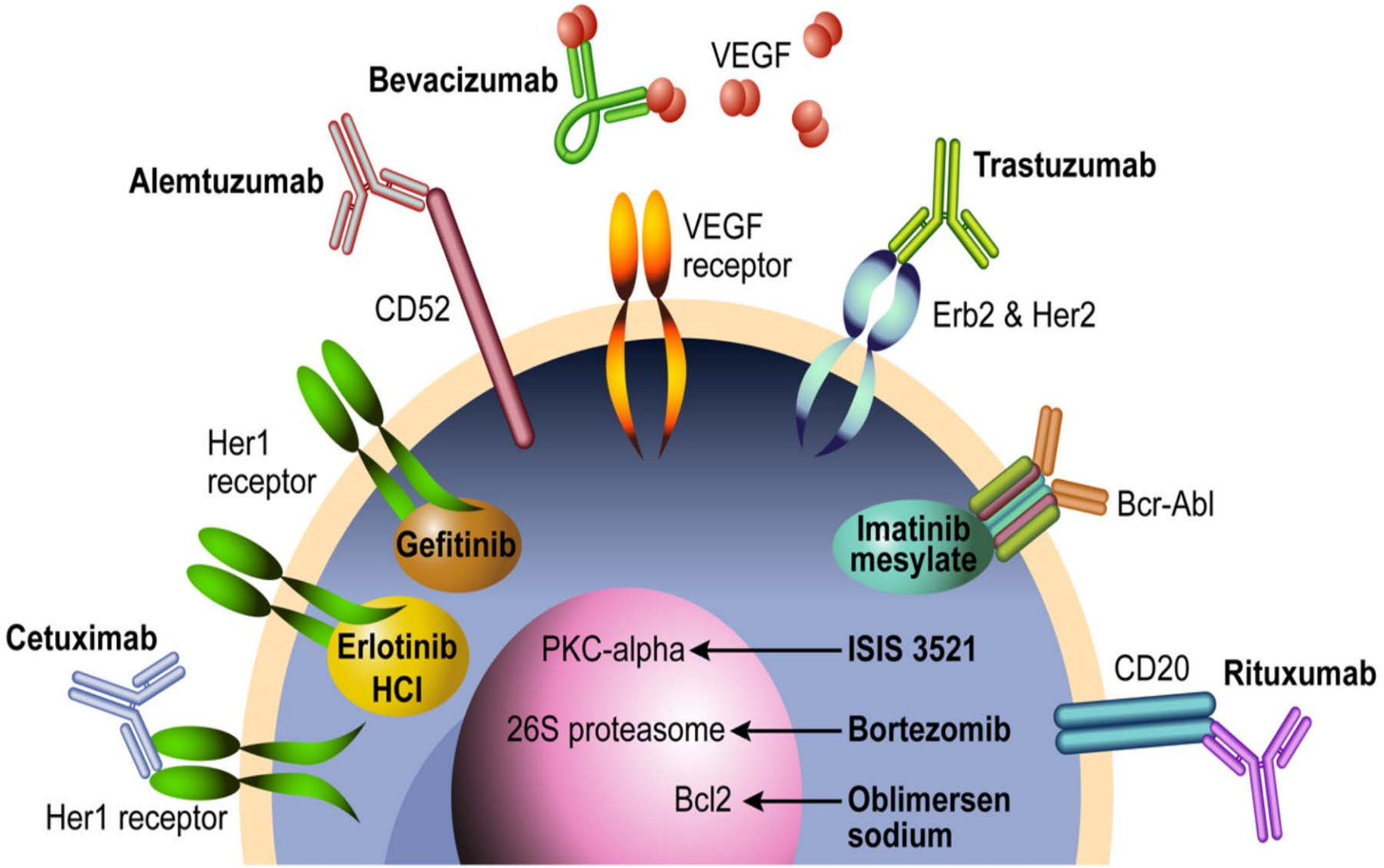
VEGF Receptor Activation



Approaches to VEGF Signal Inhibition



Targeted Therapies



New Discoveries in Oncology

- Targeted Therapies
  - Herceptin for breast cancer
  - Avastin for advanced lung, ovary and colon cancers
  - Rituximab (Rituxan) for B-cell lymphomas
  - Erbitux for head & neck cancers
  - Tarceva for lung Cancer
  - Gleevec for CML

Weill Cornell Medicine

Immuno Modulation-A New Frontier in Cancer Treatment

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Immuno Modulation-A New Frontier in Cancer Treatment

Each stage in the development and progression of cancer is the result of cross-talk between the tumor and the host's immune system.

The escape of tumor cells from immune control plays a significant role in
tumor progression.

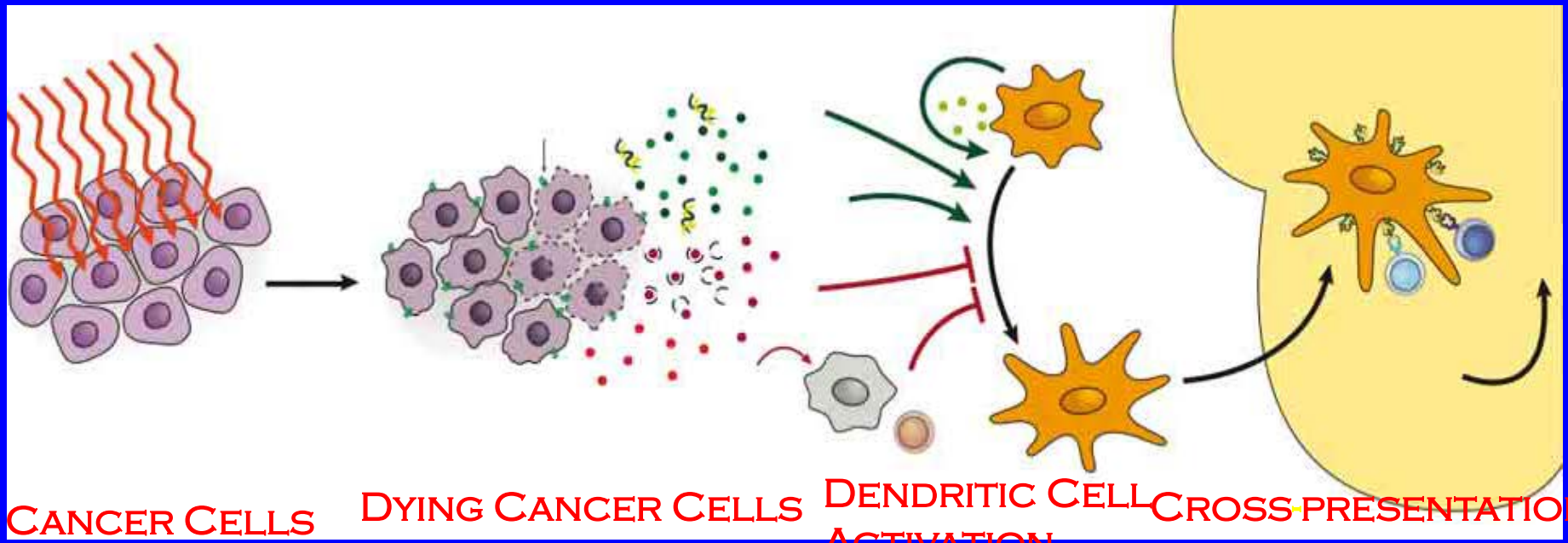
Resistance to immune rejection has been recognized as an essential requirement for tumors to become clinically detectable.

Weill Cornell Medicine

Immuno Modulation-A New Frontier in Cancer Treatment

During the past 5 years, a functional redefinition of cell death,
based on its effects on immune cells (ie, tolerance or activation) has emerged.

Ionizing radiation induces immunogenic cell death.



JAMA Oncology Published online August 13

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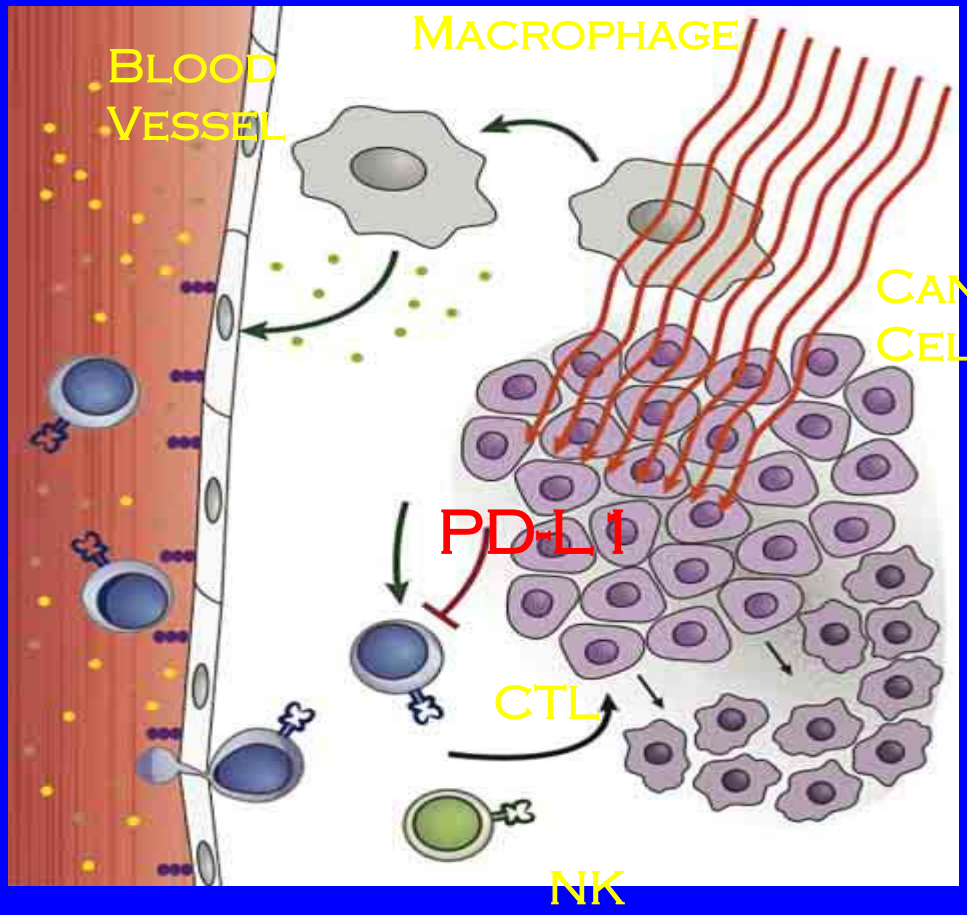
Radiation and Immuno Modulation-A New Frontier in Cancer Treatment

Radiation has complex effects
on the tumor microenvironment.
It can overcome effector T-cell
exclusion or inhibition.

Radiation can complement the effects of immunotherapy
via a number of different mechanisms to generate robust antitumor T-cell responses.



JAMA Oncology Published online August 13, 20

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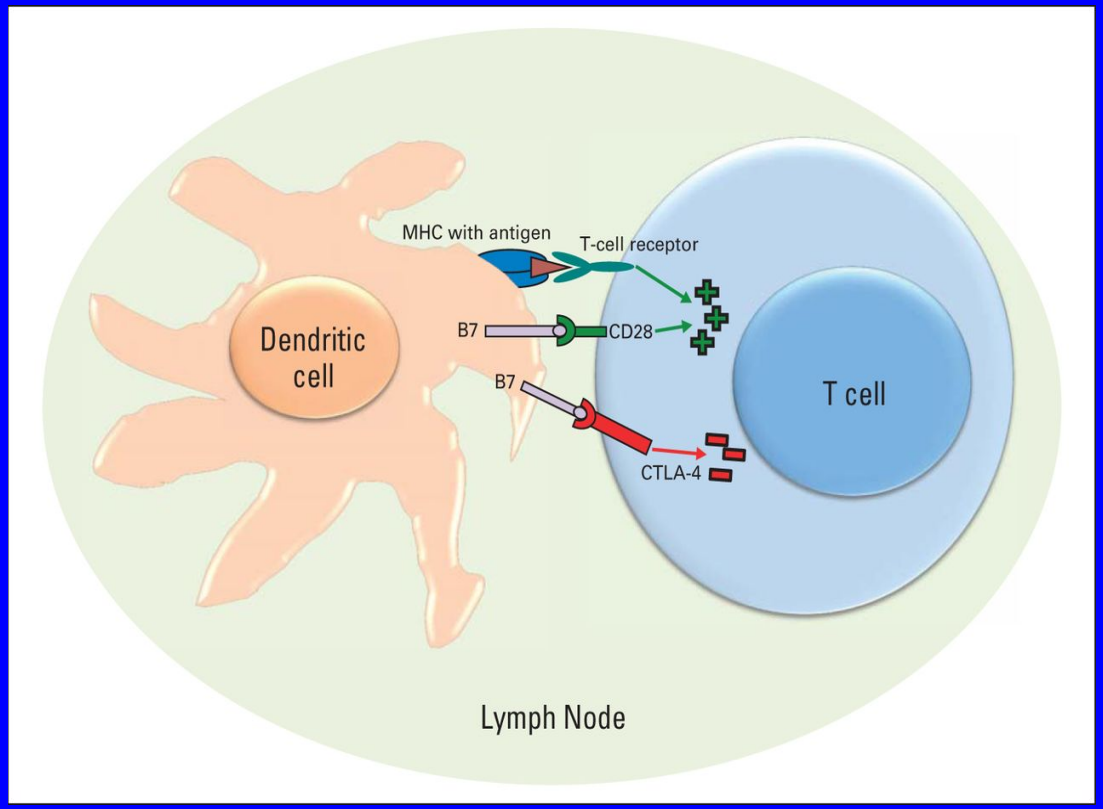
Immuno Modulation-A New Frontier in Cancer Treatment

CTLA-4 (cytotoxic T-lymphocyte-associated protein 4)



CTLA-4 is upregulated on the plasma membrane where it functions to downregulate T-cell function through a variety of mechanisms.

Antibody blockade of CTLA-4 could result in antitumor immunity in preclinical models

J Clin Oncol. 2015 Jun 10;33(17):1974-82..

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Radiation and Immuno Modulation-A New Frontier in Cancer Treatment

Clinical Trials: Melanoma, Bladder, Renal Cancer, NSCLC.

Melanoma Trials:

Table 1 Clinical trials with checkpoint inhibitors

Drug	Study	N	Phase	Line	OR (%)	OS (m)	OS (%)	PFS (m)	PFS (%)
Pembrolizumab	KEYNOTE001 (B1) (8)	135	I	IPI, IPI-N	38 (IPI-N 38)				
	KEYNOTE001 (B1+B2+D) (9)	411	I	190 IPI-N	40 (IPI 28)				
	KEYNOTE002 (10)	540	II	IPI	21-25			2.9	9m
			2 mg/kg 3W						24-29
			10 mg/kg 3W						
			Chemo						
	KEYNOTE006 (11)	834	III	556 IPI-N			OS_{1y}		PFS_{6m}
			10 mg/kg 2W		34		74	5	47
			10 mg/kg 3W		33		68%	4	46
			IPI		12		58	3	26
Nivolumab	Weber (12)	90	I	44 IPI-N	24 (IPI-N 25)				
	Hodi (13)	107	I	IPI-N	30-40	17	OS_{3y}: 40		
	CheckMate037 (14)	405	III	IPI	32			4.7	
	CheckMate066 (15)	418	III	IPI-N	40		OS_{1y}: 73	5	
Nivolumab + ipilimumab	Wolchock (16)	53	I	IPI-N	40-53	40	OS_{2y}: 79		
	CheckMate069 (17)	142	II	IPI-N					
			NIVO + IPI		61			NR	
			IPI		11			4.4	
	CheckMate067 (18)	945	III	IPI-N					
			NIVO + IPI		58			11.5	
			NIVO		44			6.4	
			IPI		19			2.9	
Ipilimumab	MDX010-20 (19,20)	676	III	2nd	11	10	OS_{3y}: 25	2.7	
	024 (16)	502	III	1st	15	11.2	OS_{3y}: 21; OS_{5y}: 18	2.4	

IPI, pretreated with ipilimumab; IPI-N, ipilimumab naïve; 2W, ever 2 weeks; 3W, every 3 weeks.

Ann Transl Med. 2015 Oct;3(18):267.

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Radiation and Immuno Modulation-A New Frontier in Cancer Treatment

CheckMate 017

A phase III study (CheckMate 017) of nivolumab (NIVO; anti-programmed death-1 [PD-1]) vs docetaxel (DOC) in previously treated advanced or metastatic squamous (SQ) cell non-small cell lung cancer (NSCLC).

272 patients: nivolumab, at a dose of 3 mg per kilogram of body weight every 2 weeks, or docetaxel, at a dose of 75 mg per square meter of body-surface area every 3 weeks

Primary end point was overall survival.

The median overall survival was 9.2 months (95% confidence interval [CI], 7.3 to 13.3) with nivolumab versus 6.0 months (95% CI, 5.1 to 7.3) with docetaxel.

Treatment-related adverse events of grade 3 or 4 were reported in 7% of the patients in the nivolumab group as compared with 55% of those in the docetaxel group.

Biomarkers that predict Disease Outcome

Whole-exome sequencing of tumors from patients treated with CTLA-4 blockade
has revealed mutations that lead to neoantigens, which may be immunologically
relevant in responses to immune checkpoint blockade.

Patients whose tumors express PD-L1, as detected by IHC, have numerically higher response rates to PD-1/PD-L1 blockade than patients
who do not express PD-L1.

Progression free survival correlated with intensity of PD-L1 expression.

However, patients who do not express PD-L1 can still have impressive responses
to PD-1 blockade

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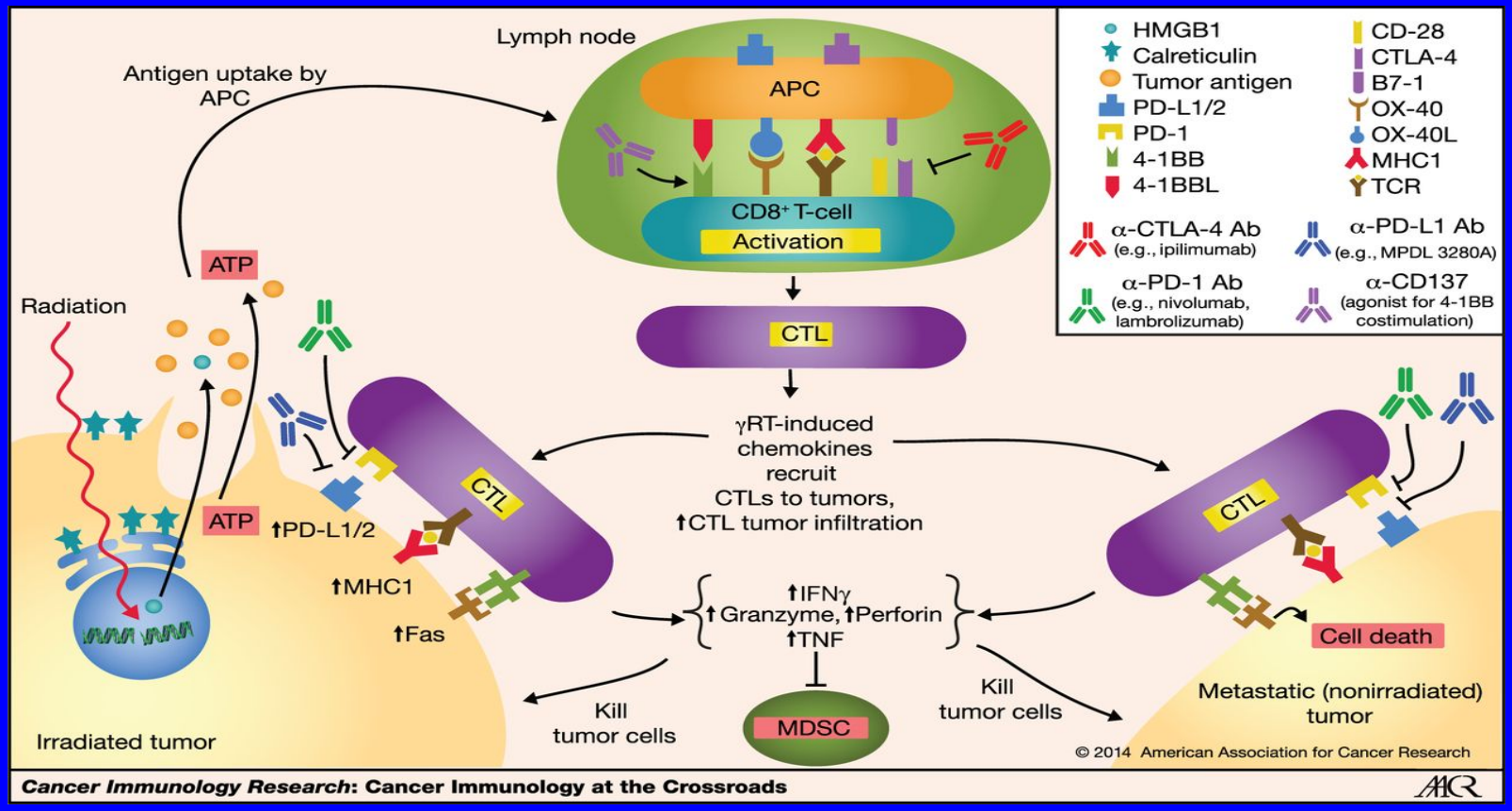
Radiation and Immuno Modulation-A New Frontier in Cancer Treatment

Schematic diagram outlining the antitumor activity and abscopal effect in combining checkpoint inhibitors with radiation-induced immune response.



1. Radiation generate immunological cell death.
2. Cytotoxic T lymphocytes (CTL) are activated via radiation and immunotherapy
3. CTLs then attack radiated and nonirradiated tumor cells

Demaria et al. Cancer Immunol Res 2014;2:831-838

Abscopal Effect

Abscopal effect refers to a rare phenomenon of tumor regression at a site distant from the primary site of radiotherapy.

Localized radiotherapy has been shown to induce abscopal effects in several types of cancer, including melanoma, lymphoma, and renal-cell carcinoma.

The combination of radiotherapy with immune modulators can take advantage of abscopal effect and have the capability to escalate antitumor responses to a level that could suppress or eliminate systemic metastasis.

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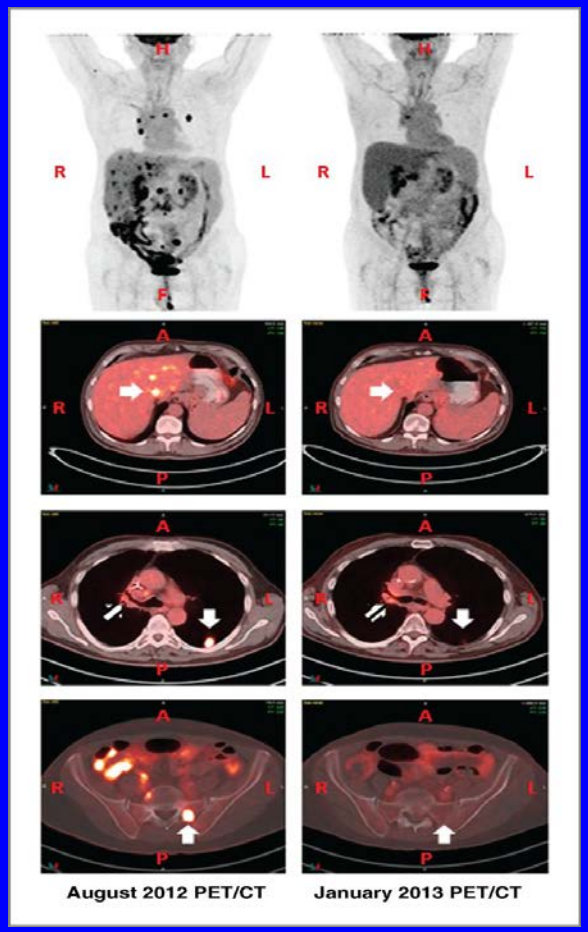
Radiation and Immuno Modulation-A New Frontier in Cancer Treatment

Ipilimumab and local radiotherapy result in an abscopal response.



Ipilimumab and local radiotherapy result in an abscopal response. PET imaging and select fused PET/CT axial images from August 2012 (left) and January 2013 (right) are displayed.

The axial images in the second row reveal the hypermetabolic liver lesion that was t argetedand responded to radiotherapy (white arrows, second row).

An abscopal response was seen in a left lower lobe lung lesion (white arrows, third row) and a left sacral lesion (white arrows, bottom row).
A mixed response was seen in the hilar/mediastinal lymph nodes (striped arrows, third row).

Encouse B. Golden et al. Cancer Immunol Res 2013;1:365-372

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Radiation and Immuno Modulation-A New Frontier in Cancer Treatment

Former US President Jimmy Carter announced that his latest brain scan showed no sign of cancer.

He underwent surgery to his liver and radiation treatments for his brain, along with taking Keytruda.

Keytruda (pembrolizumab) works by blocking what's known as the PD-1 pathway

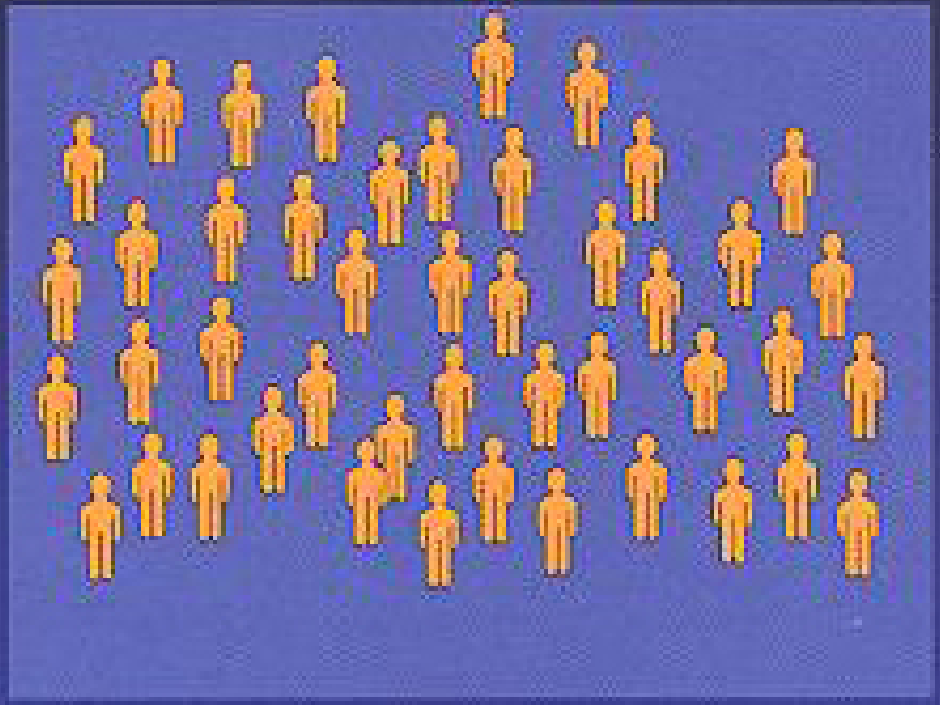
Human Genome

Single Nucleotide Polymorphisms (SNPs) in Human Health & Disease

- An amazing aspect of human Genome is the minimal variation in the DNA sequence in. the Genome of different individuals
- Of the 3.2 Billion bases, roughly 99% are identical between two individuals.
- It is the variation in the remaining tiny fraction of the Genome , 0.1%, that makes a person unique.
- This small amount of variation determines critical attributes of the individuals in developing cancer and response to the treatment.
- The Genome of each individual contains its own pattron SNPs and SNP profile.
- Generic variation in human Genome is an emerging resource for studying cancer.

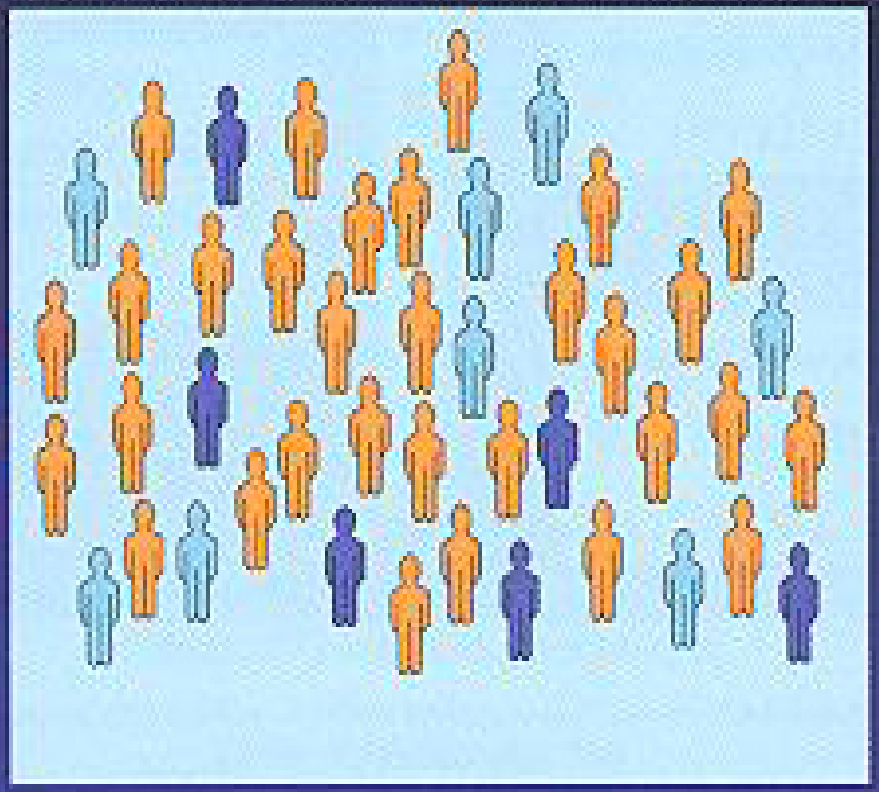
Exploiting the Tumor Molecular Profile of Individual Patients for Selection of Therapy

Patients with the same Diagnosis & Clinical Features
(Stage IV Non-small Cell Lung Cancer)

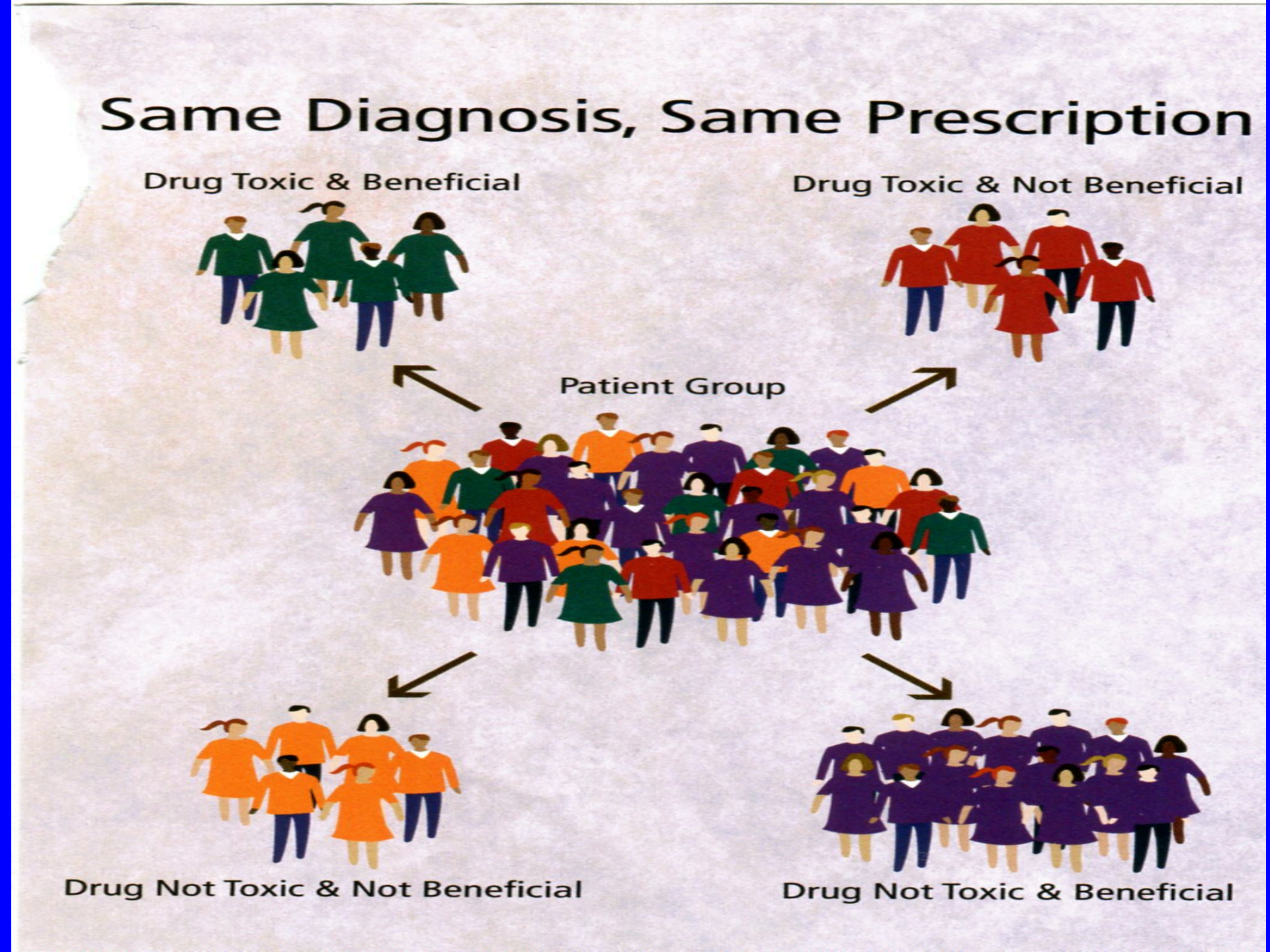


Exploiting the Tumor Molecular Profile of Individual Patients for Selection of Therapy

Patients with same diagnosis, but different Molecular Profiles



Same Diagnosis, Same Prescription



Advances In Oncology

- Advances in Clinical Oncology

FEBRUARY 18, 2002

www.time.com AOL Keyword: TIME

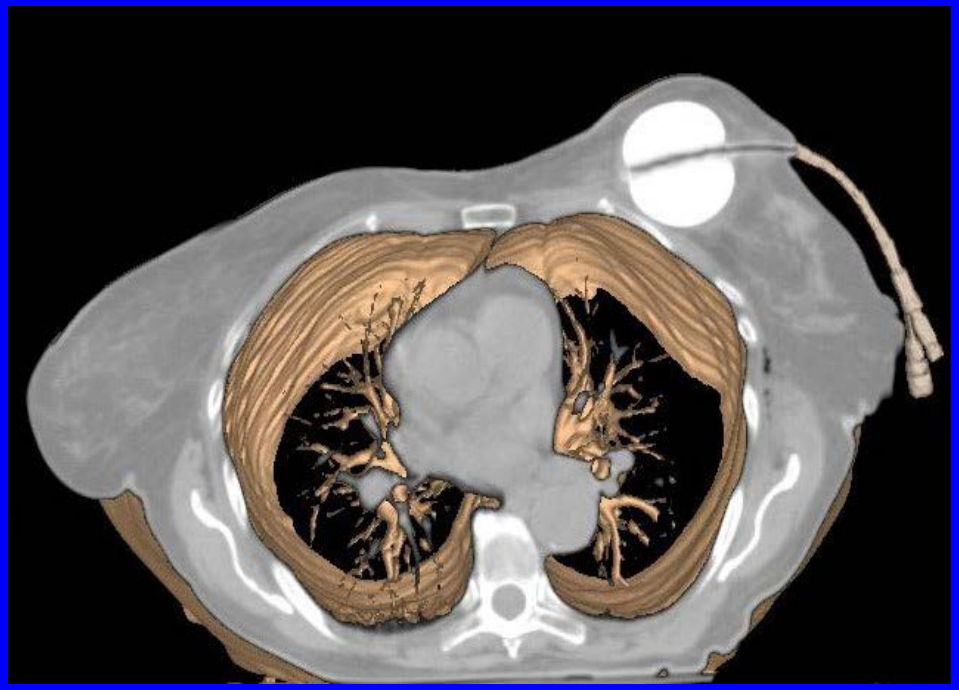
TIME

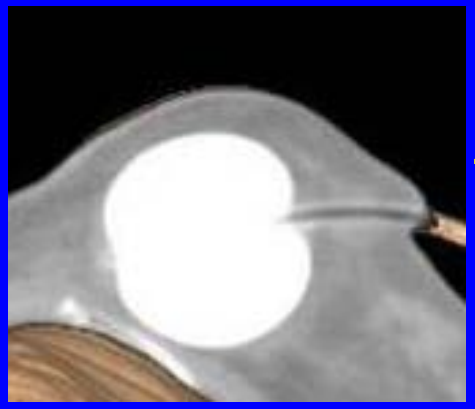
THE NEW THINKING ON BREAST CANCER

- The Smartest Drugs
- The Gentlest Treatments
- The Latest on Mammograms

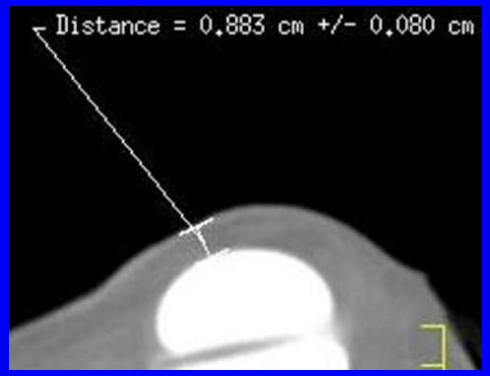
$3.95US
07
10090
0 925679 8

CT Image of MammoSite

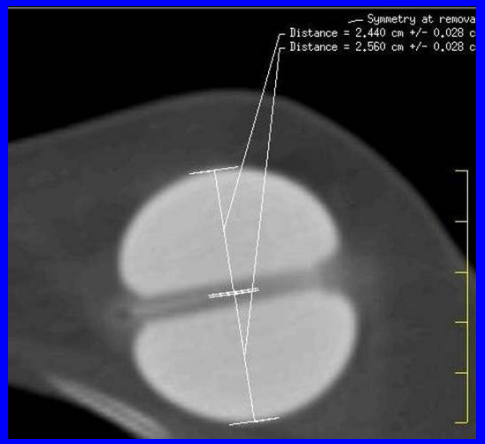




Tissue Conformance

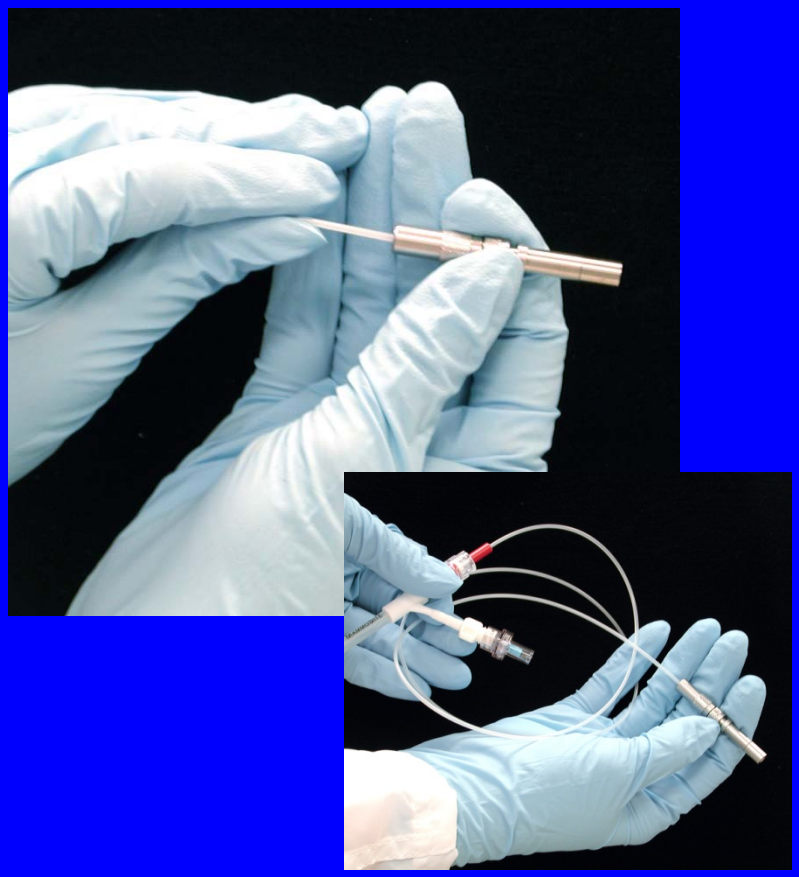


Skin Spacing

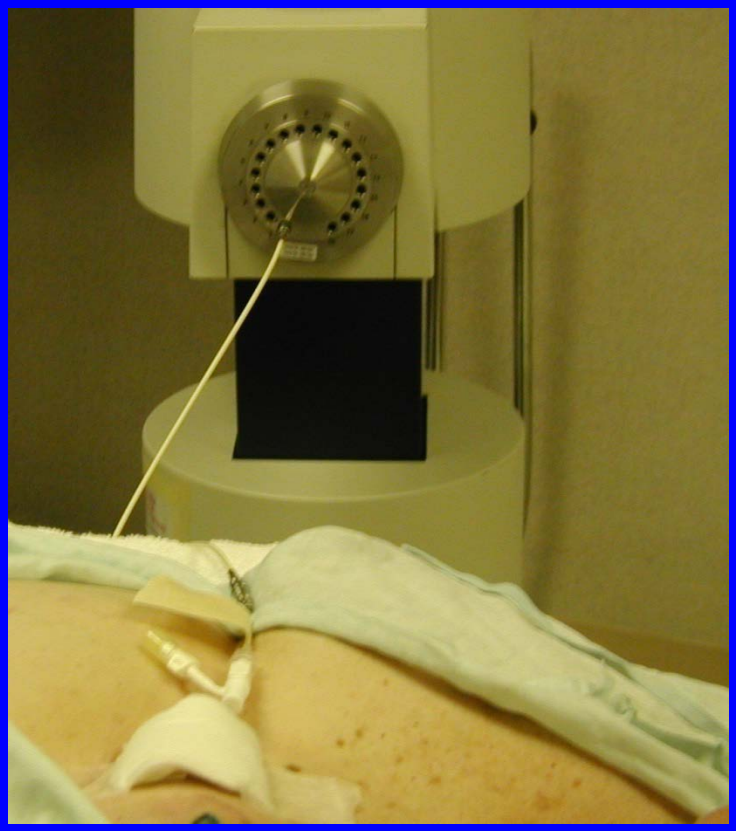


Balloon Diameter & Symmetry

HDR Radiation Treatment



Connect MammoSite to HDR afterloader



Deliver radiation using any commercially available HDR afterloader (Nucletron, Varian, Gamma Med®)

New Innovations In the Treatment of Breast Cancer

- IMRT (6 Weeks)
- APBI (3 Weeks)
- BRT (1 Week)
- IORT (1 Day)

Local Recurrence with MammoSite Brachytherapy

Institution/Study	# of Patients	Follow-up (Months)	Local Recurrence (%)
ASBS registry trial*	1449	63	2.8
NYP/Weill Cornell medical center*	650	72	2.4
William Beaumont*	678	62.8	1.7
Medical University of South Carolina	90	24	2.2
Rush university medical center	70	22	

*2016 UPDATE

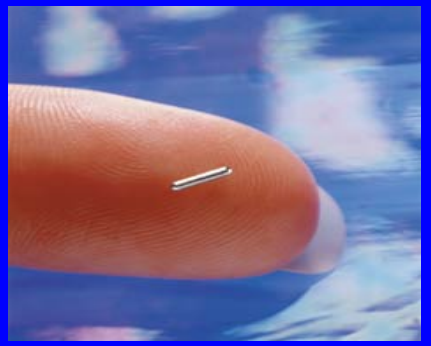
Cosmetic Outcomes with MammoSite Brachytherapy

Institution/Study	# of Patients	Follow-up (Months)	Good or Excellent comesis (%)
ASBS registry trial*	1449	63	90.6
NYP/Weill Cornell medical center*	650	72	96
William Beaumont*	678	62.8	88
Medical University of South Carolina	90	24	90
Rush university medical center	70	22	93

*2016 UPDATE

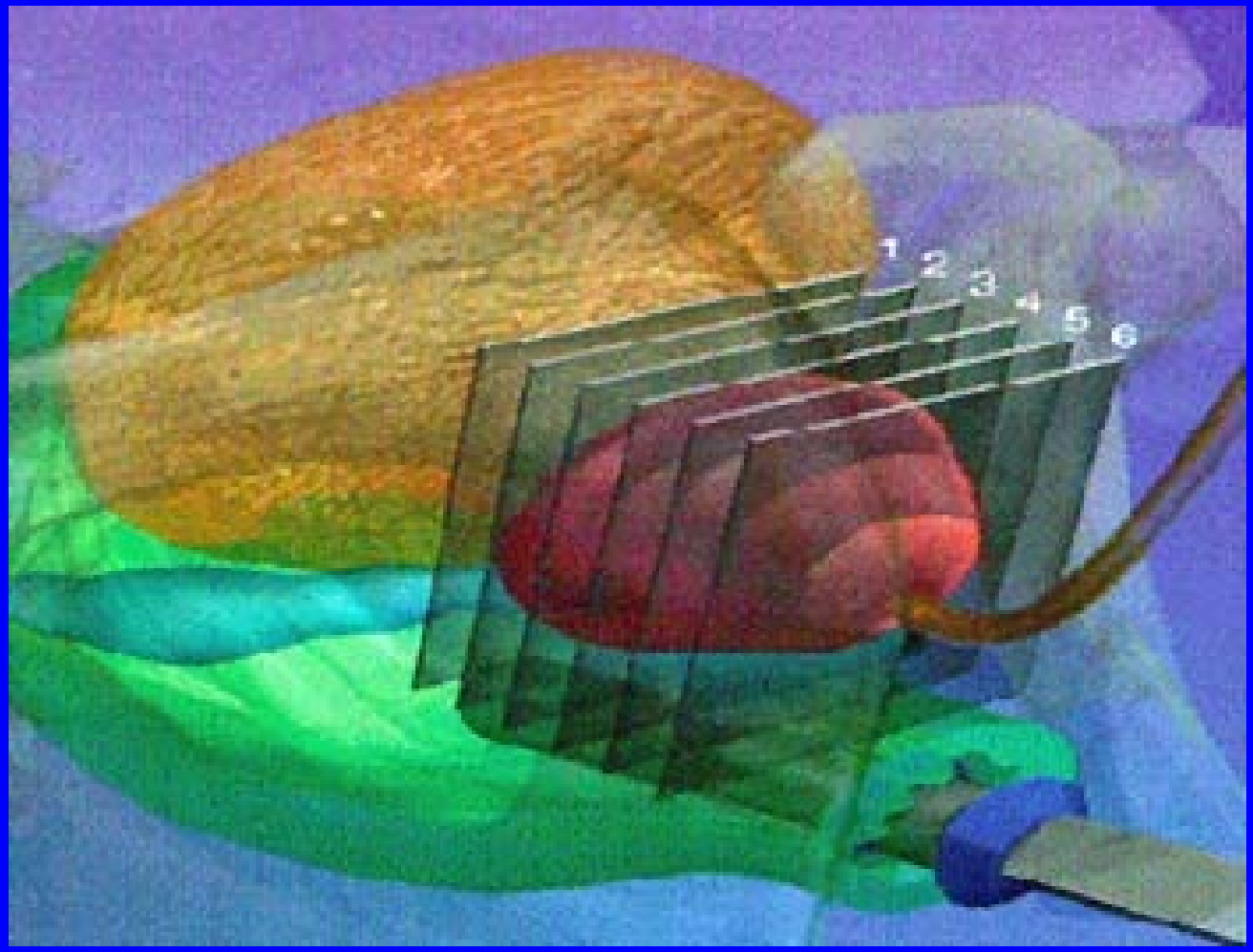
Minimally Invasive Dose & Image-guided Outpatient Brachytherapy for Early Stage Prostate Cancer

Prostate Brachytherapy



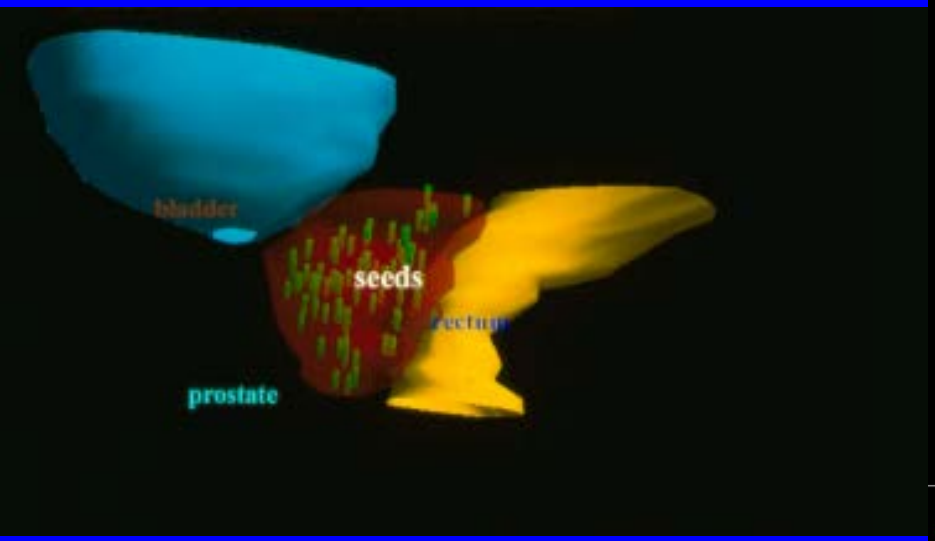
- Higher radiation doses –
  - Lower PSA levels – better biochemical control
  - Lower positive biopsy results
  - Better local control ⇓ distant metastasis
- Brachytherapy delivers highest dose of radiation compared to other radiation modalities
  - 80 Gy EBRT = BED 153
  - I-125 180 Gy = BED 190
  - Pd-103 100Gy + 45Gy EBRT = BED 198
  - Proton therapy (78 Gy in 2 Gy fractions) = BED 156

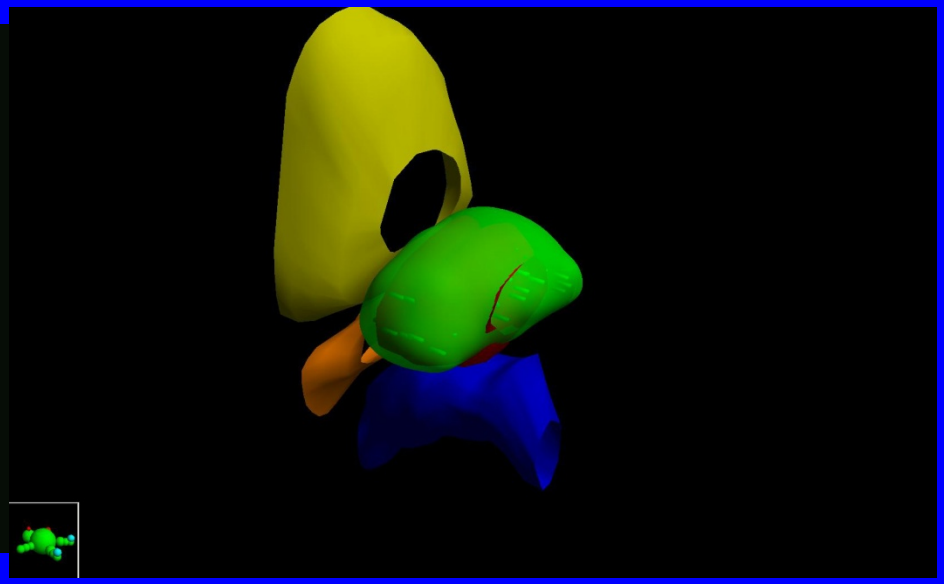
Dose & Image-guided Brachytherapy Planning



Weill Cornell Prostate Brachytherapy Center

3D Trans-rectal Ultrasound Evaluation

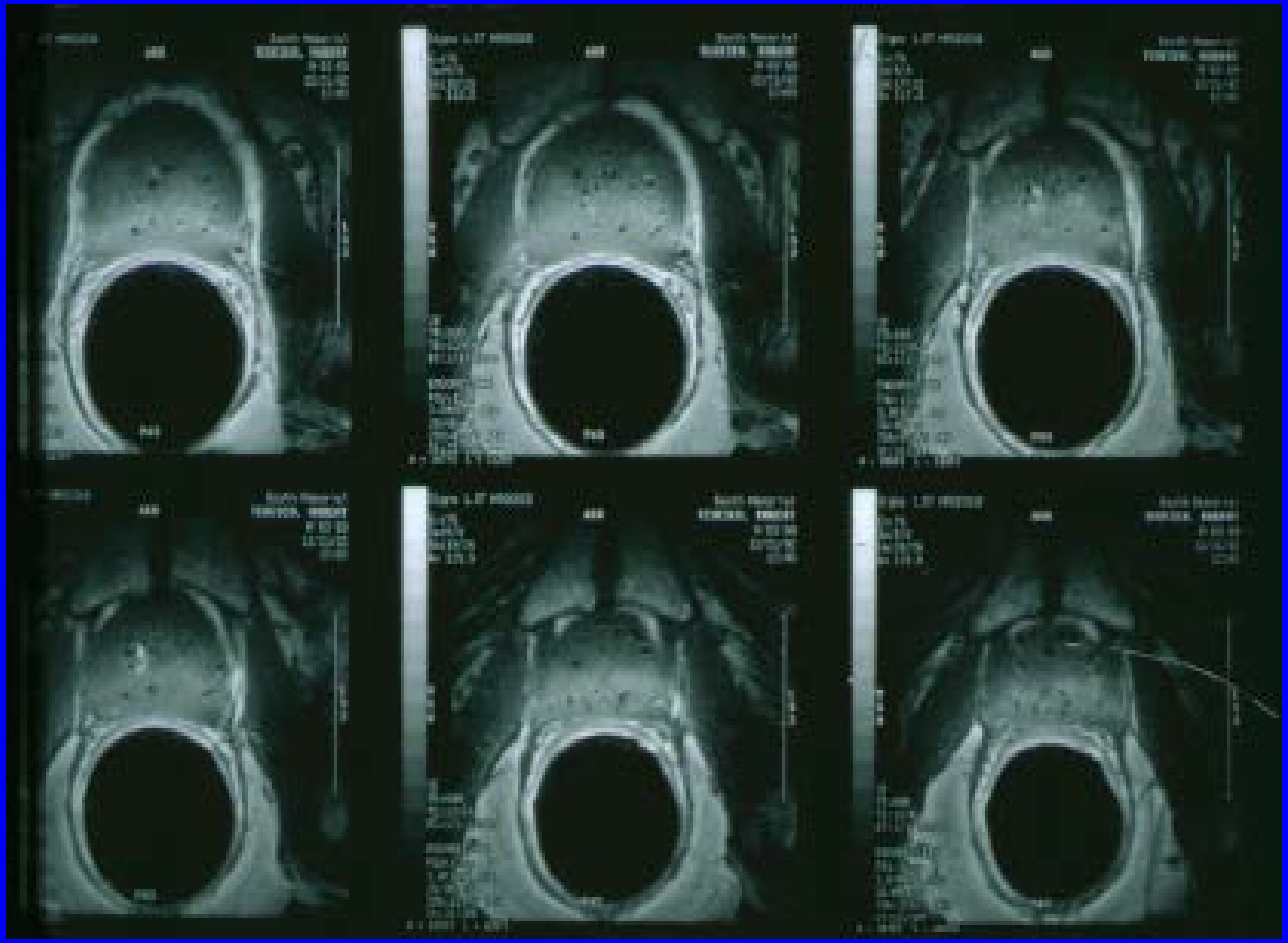




Nori D. M.D.,

Cornell, 2016

Transrectal MRI Evaluation



Brachytherapy Outcomes

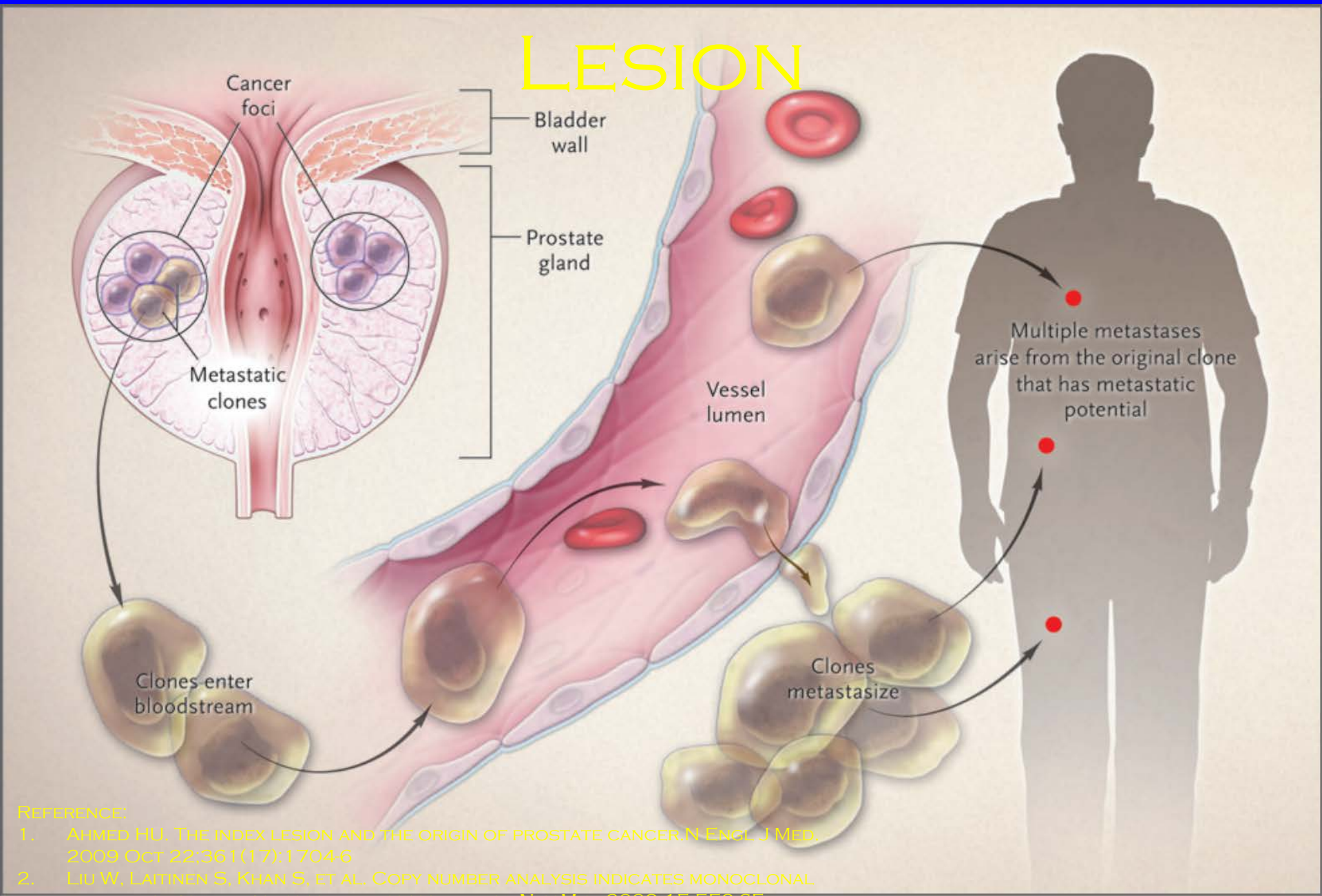
Institution	Stage	Outcome	Result (%)
University of Washington, Seattle	Low	12-yr bNED	90
Utrecht, Netherlands	Low	10-yr bNED	88
Mount Sinai School of Medicine	Low	8-yr bNED	88
NYP – Weill Cornell	Low	10-yr bNED	90

Side Effects Are Fewer In Therapy With Pellets

"Like other prostate cancer patients deciding on treatment, Mayor Rudolph W. Giuliani had to weigh both medical and personal factors. In choosing to have radioactive pellets implanted in his prostate . . . he selected an effective treatment with far fewer side effects than surgery."

~The New York Times

Prostate cancer – Index Lesion



Reference:

1. Ahmed HU. The index lesion and the origin of prostate cancer. N Engl J Med. 2009 Oct 22;361(17):1704-6
2. Liu W, Laitinen S, Khan S, et al. Copy number analysis indicates monoclonal

Prostate cancer – Index Lesion

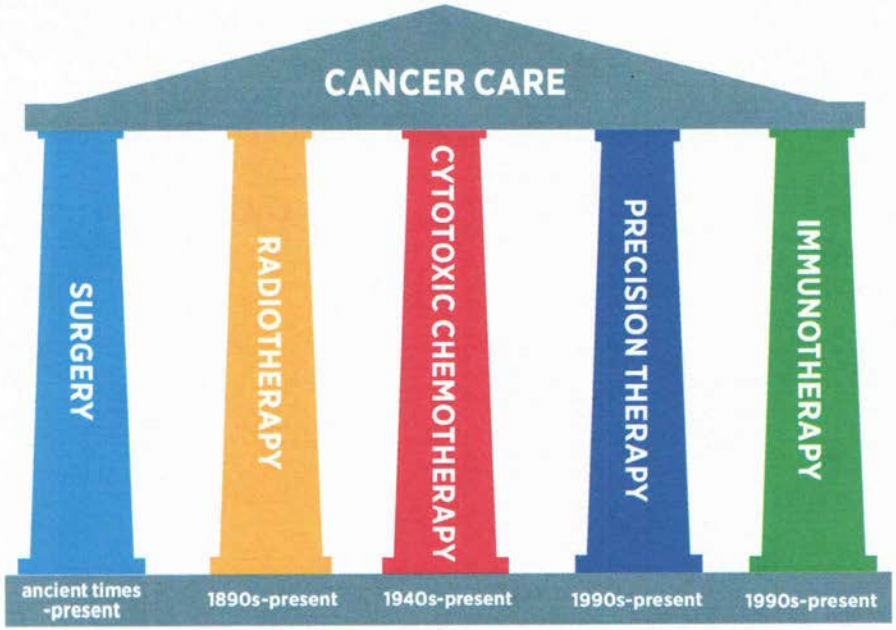
- The largest tumor focus within the prostate
  - Driver of natural history of the prostate cancer
  - Generally indicates the prognosis
  - May harbor clonogen that is responsible for metastasis
  - Increased interest in focal therapy
  - preservation of normal prostate and surrounding structures, “organ-preservation approach”

Reference:

1. Ahmed HU. The index lesion and the origin of prostate cancer.N Engl J Med. 2009 Oct 22;361(17):1704-6
2. Liu W, Laitinen S, Khan S, et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. Nat Med 2009;15:559-65. [Erratum, Nat Med 2009;15:819.]

FIGURE 12

MORE OPTIONS FOR CANCER CARE



Physicians often refer to the "pillars" of cancer treatment. For thousands of years, there was only one treatment pillar: surgery. In 1896, a second pillar, radiotherapy, was added (117). The foundations for the third treatment pillar, cytotoxic chemotherapy, were laid in the early 1940s when a derivative of nitrogen mustard was explored as a treatment for lymphoma. These three pillars—surgery, radiotherapy, and cytotoxic chemotherapy—continue to be the mainstays of cancer care. However, in the late 1990s, the first precision therapeutics were introduced, leading to the fourth pillar, precision therapy, which continues to grow. Likewise, the late 1990s laid the groundwork for the fifth treatment pillar, immunotherapy. The number of anticancer therapeutics that form the most recent pillars of cancer care has increased dramatically in the past 5 years.

Figure adapted from Ref. (24)

Advances In Oncology

- Summary & Future Directions
  - Progress in cancer treatment will increasingly utilize individualized treatment strategies based on complex biology of most cancers.
  - Modern pathological characterization will determine which tumors respond best to a particular therapeutic approach.
  - Targeted therapies with drugs aim at EGFR receptors, tumor environment, angiogenesis
  - Immno Modulation Treatments either alone or combination with Radiation will enhance the outcomes in majority of cancers

Steps to Achieve Caner Moonshot

1. Increase Federal Funding for Cancer Laboratory Research
2. Fund Basic Cancer Screening for Early Detection
3. Open Up Access to Stat-of-the Art Cancer Care
4. Rationalize the Cost of Cancer Drugs
5. Develop a Better Coordinated Care System
6. Speed Up the Sharing of Electronic Medical Records

President Obama 2016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