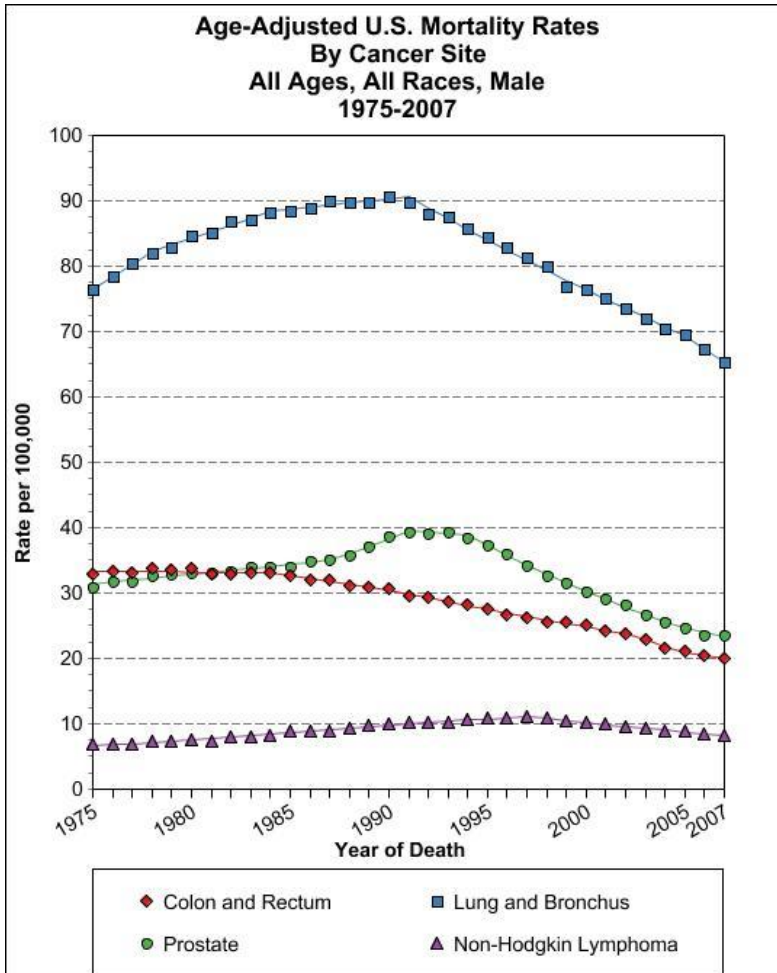


# New Developments in Cancer Treatment

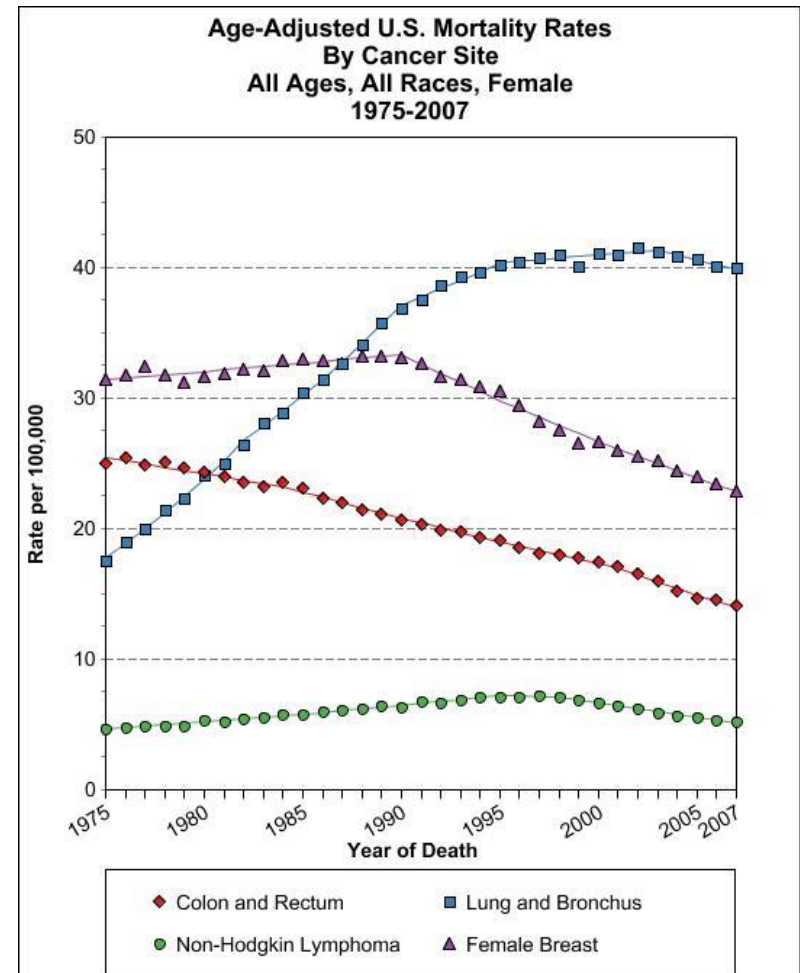
Dulcinea Quintana, MD



# Mortality Rates

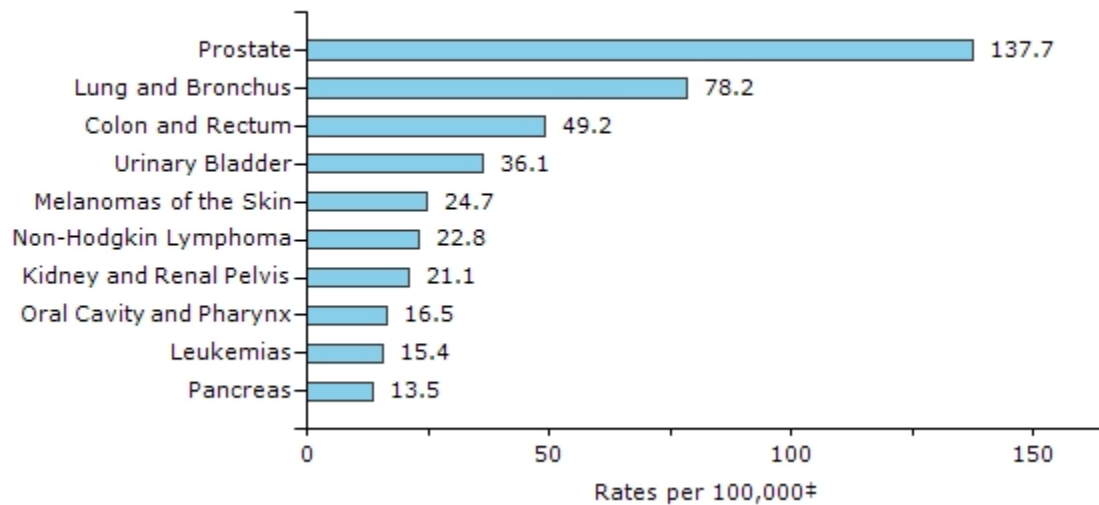


Cancer sites include invasive cases only unless otherwise noted.  
Mortality source: US Mortality Files, National Center for Health Statistics, CDC.  
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.4.3, April 2010, National Cancer Institute.

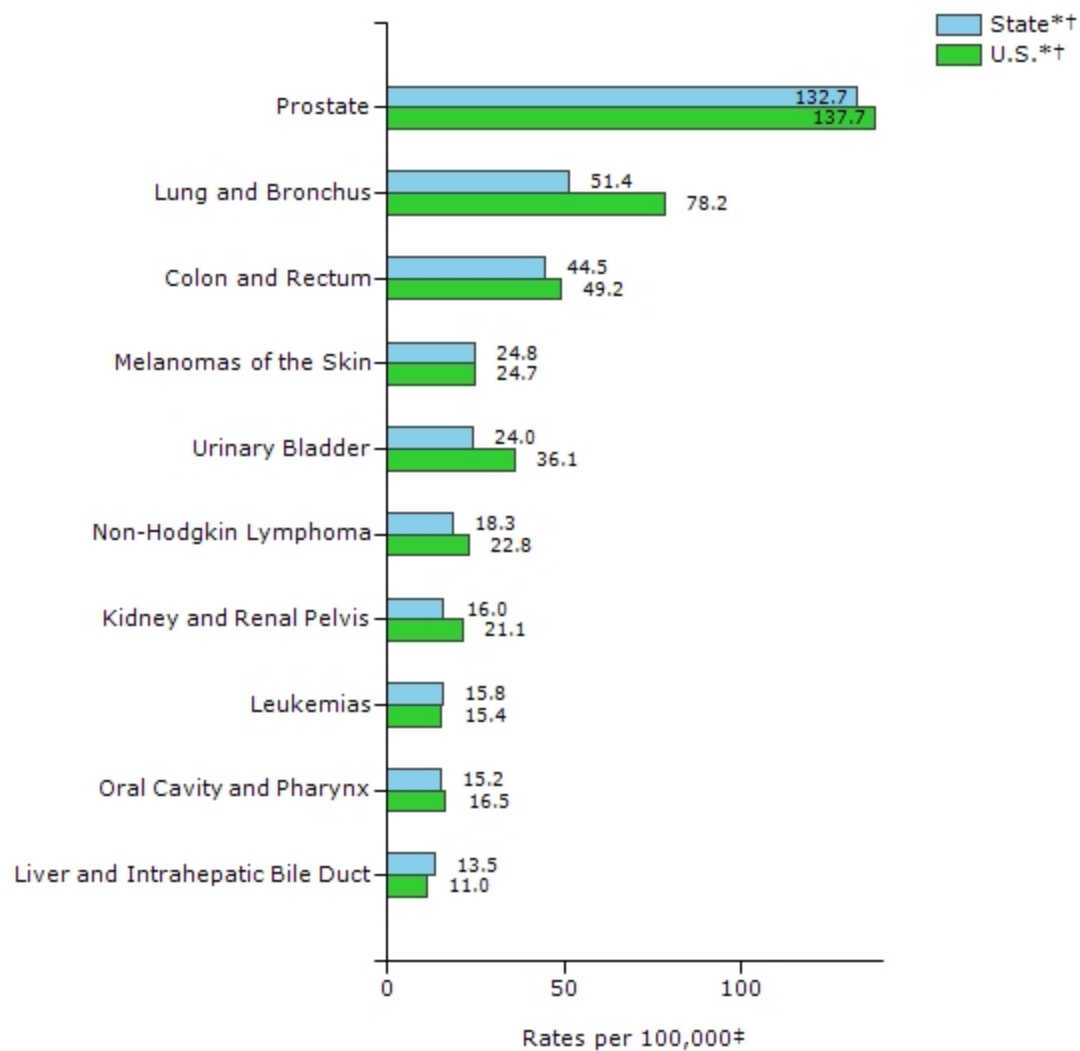


Cancer sites include invasive cases only unless otherwise noted.  
Mortality source: US Mortality Files, National Center for Health Statistics, CDC.  
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.4.3, April 2010, National Cancer Institute.

**Top 10 Cancer Sites: 2009, Male, United States—All Races**



### State vs. National Rates: 2009, Male , New Mexico



# Goals of treatment

1



Cure

# Goal of treatment

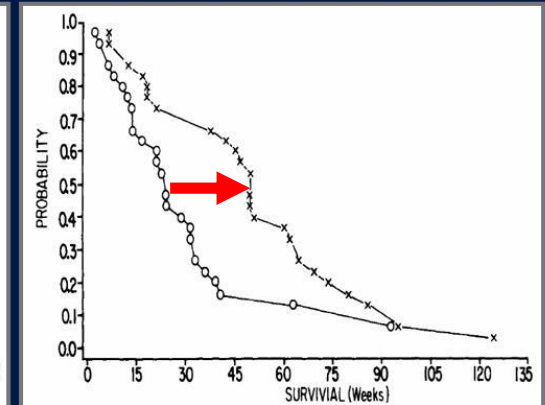
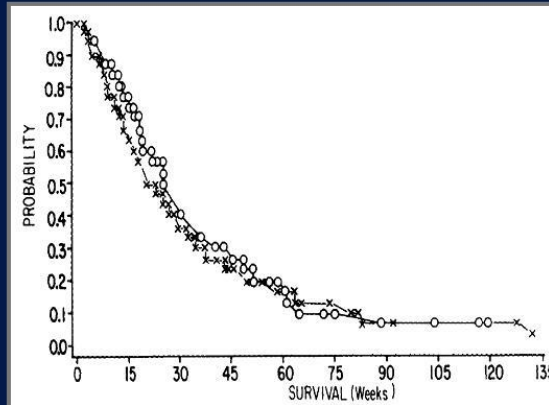
2



## VA Study 75: Coumadin vs. Placebo with Chemo for Various Cancers

NSCLC

SCLC



Zacharski, Cancer 1984

Prolong life

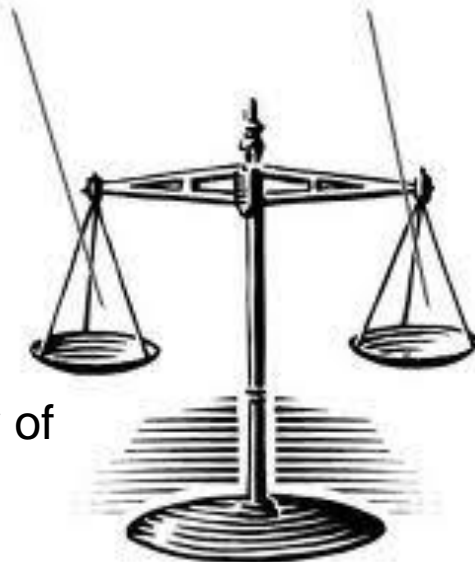
# Goals of treatment



3

Symptoms of progressive cancer

Side-effects of therapy

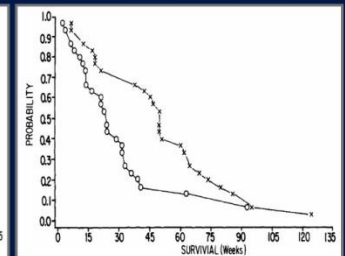
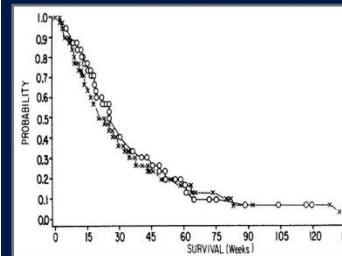


Improve Quality of Life

VA Study 75: Coumadin vs. Placebo with Chemo for Various Cancers

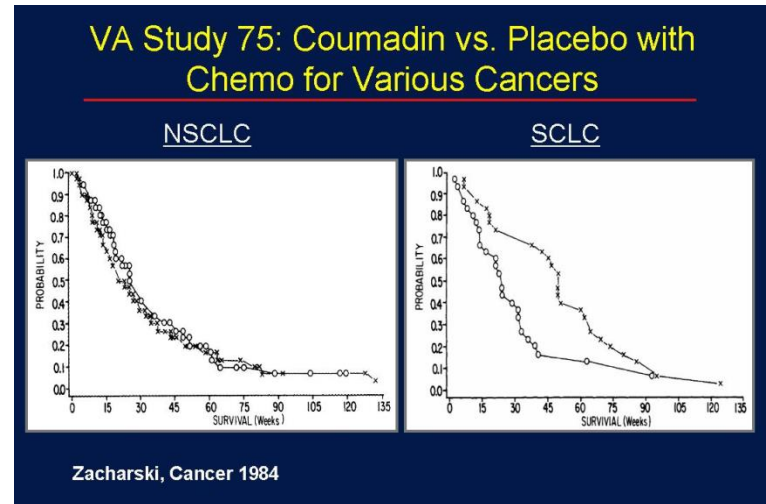
NSCLC

SCLC



Zacharski, Cancer 1984

# Goals of treatment



Symptoms of  
progressive  
cancer

Side-effects  
of therapy



4



Target symptoms  
rather than disease



# Advances can come in two flavors

- Improve the identification of patients likely to benefit from therapy. Response is ~5%



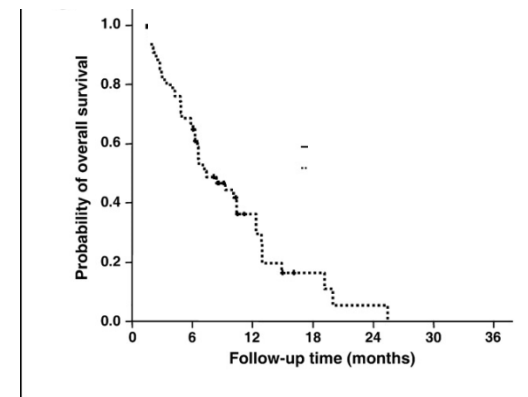
# Advances can come in two flavors

- Improve the identification of patients likely to benefit from therapy. Response 100%.



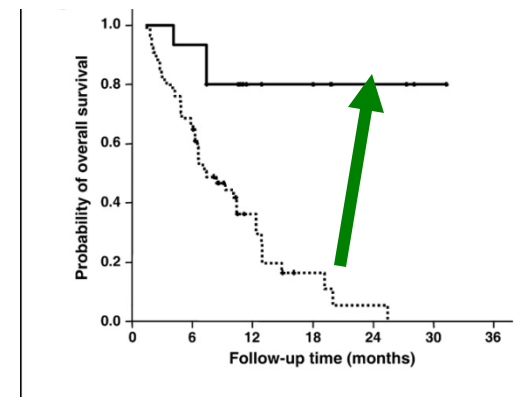
# Advances can come in two flavors

- Improve the identification of patients likely to benefit from therapy. Response 100%.
- Improve response and survival for the whole group



# Advances can come in two flavors

- Improve the identification of patients likely to benefit from therapy. Response 100%.
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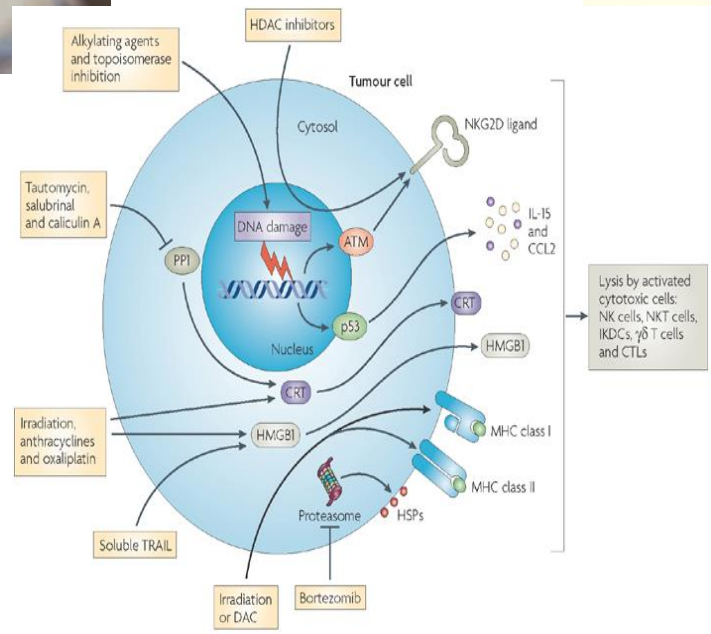


# Treatment Strategies

The old and the new...



# Chemotherapy -still a very important role...



# But is there a better way?...



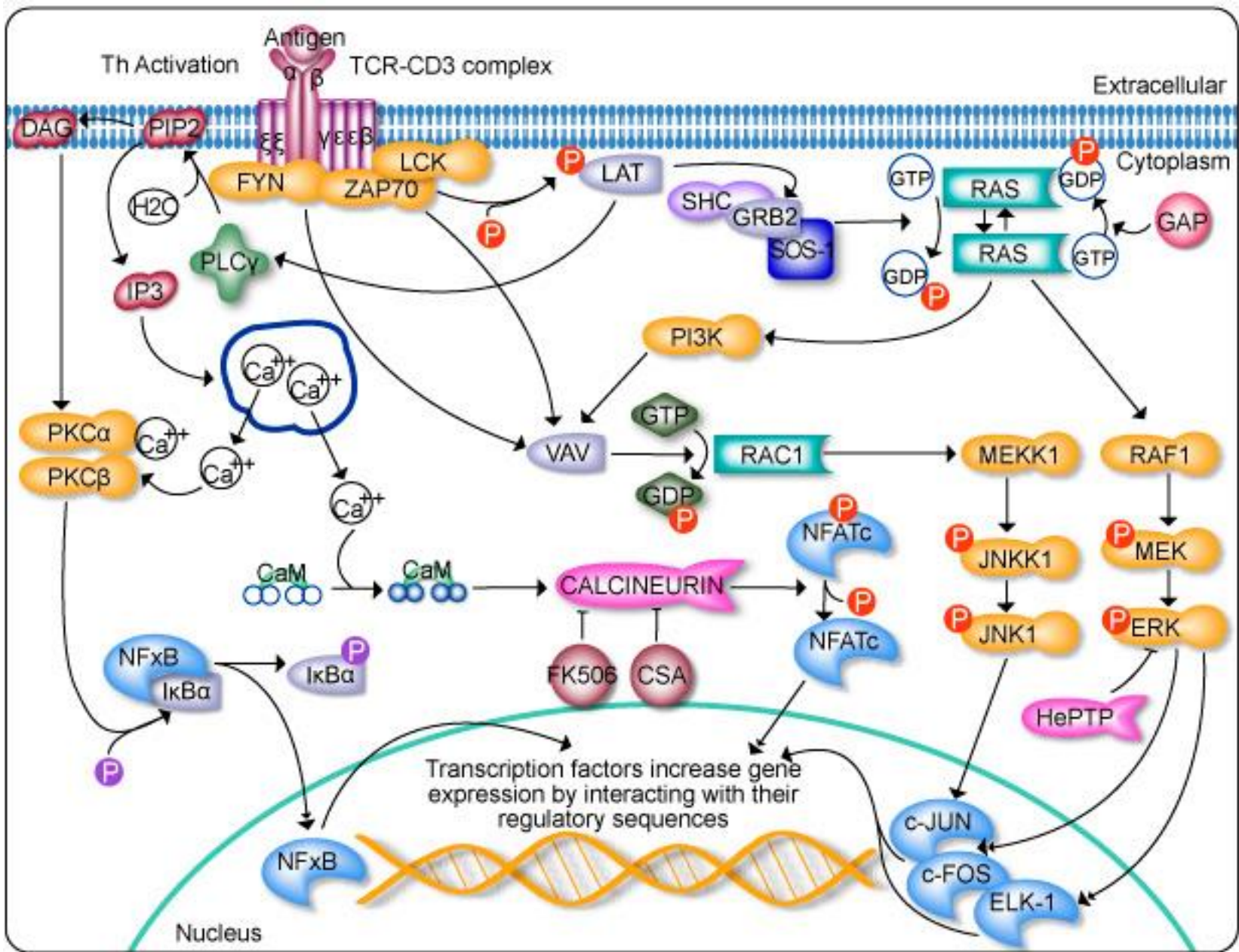


# Targeted Therapies!

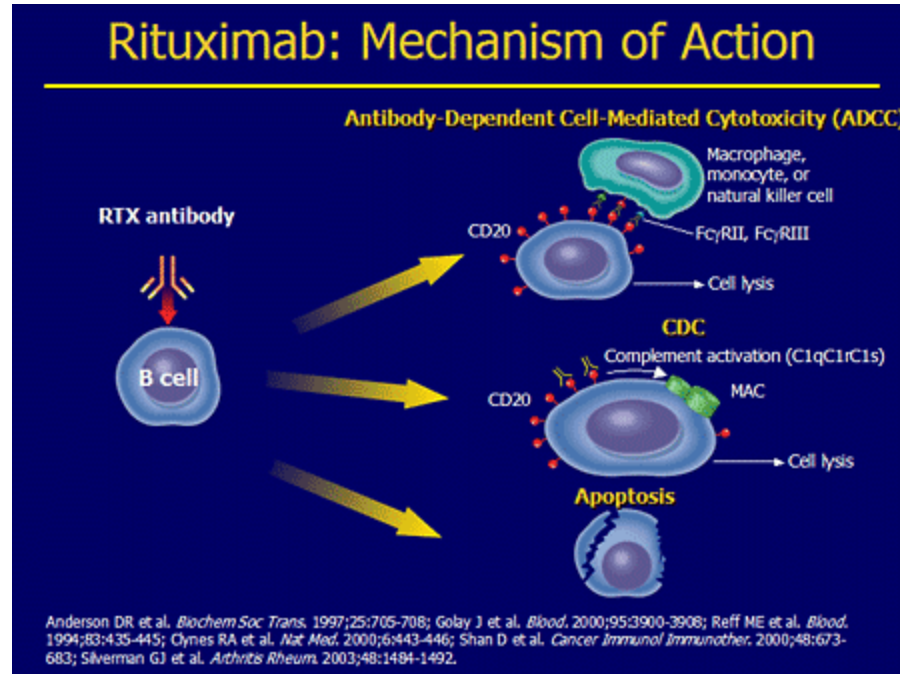
Monoclonal antibodies

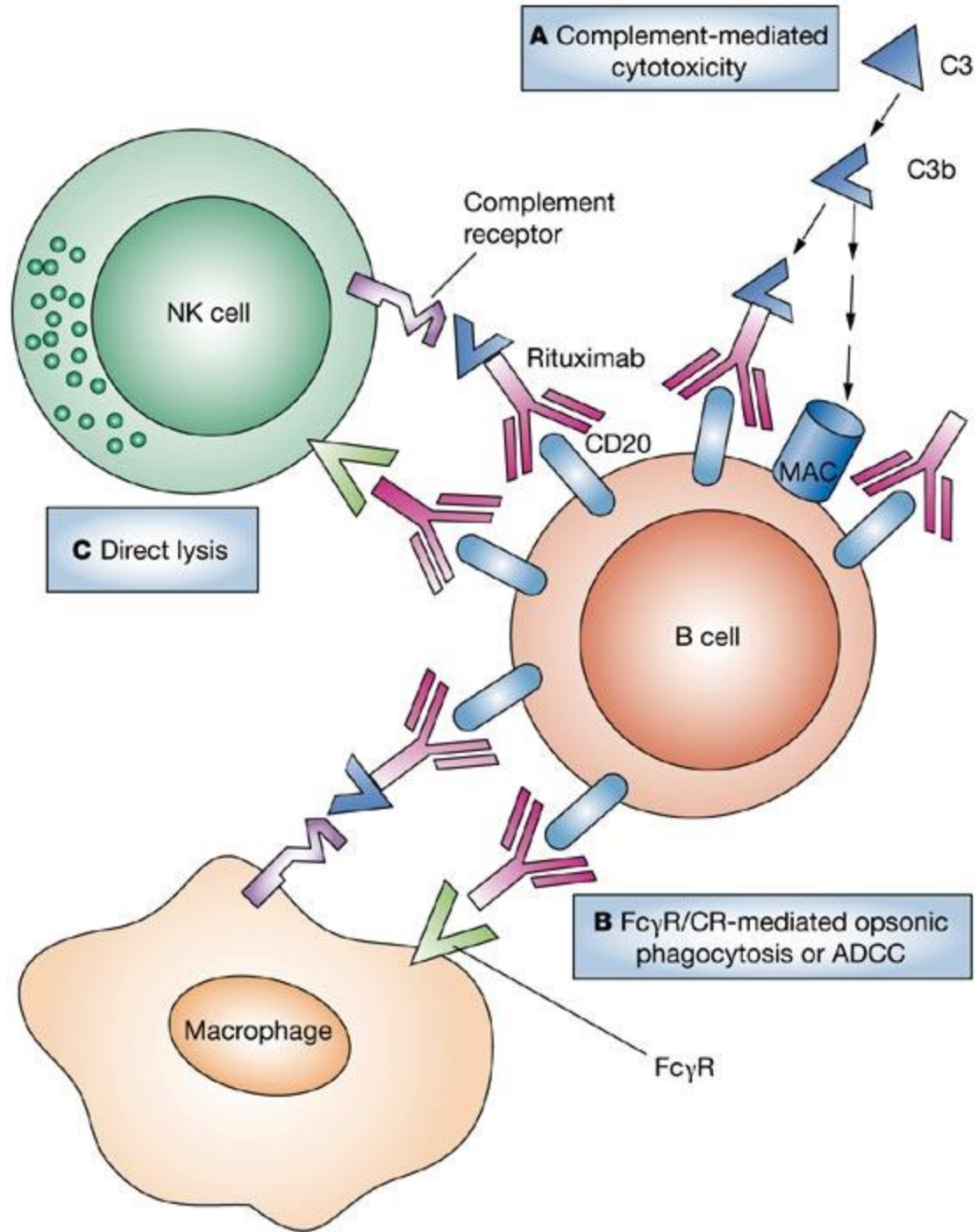
Targeted therapies

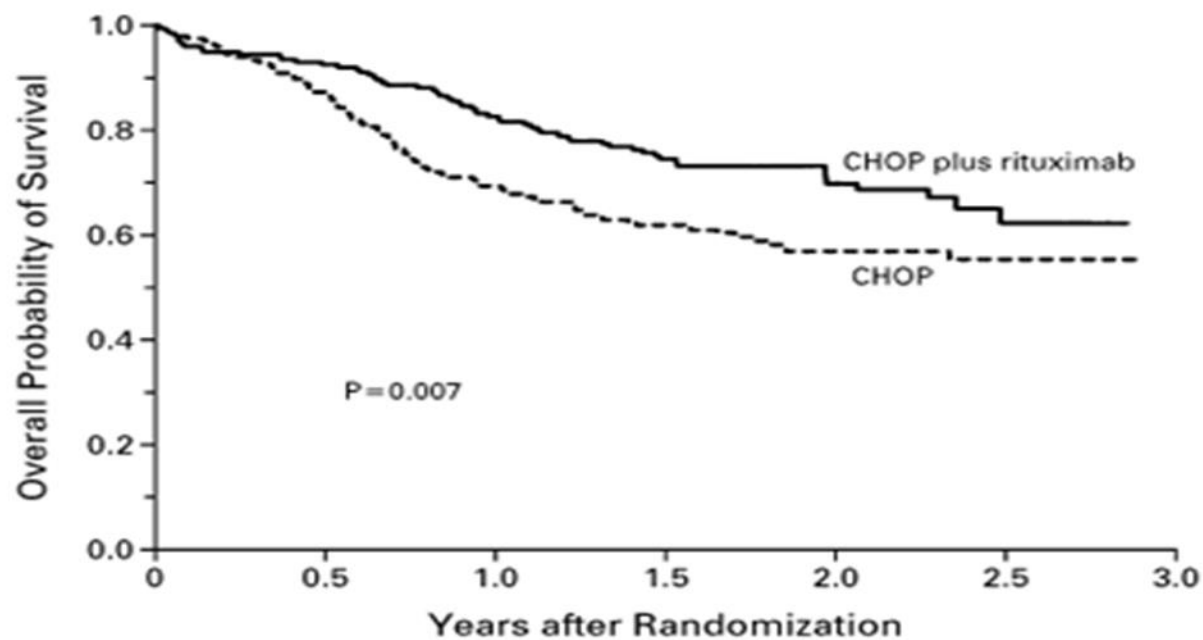
Immunotherapies



# Monoclonal antibodies



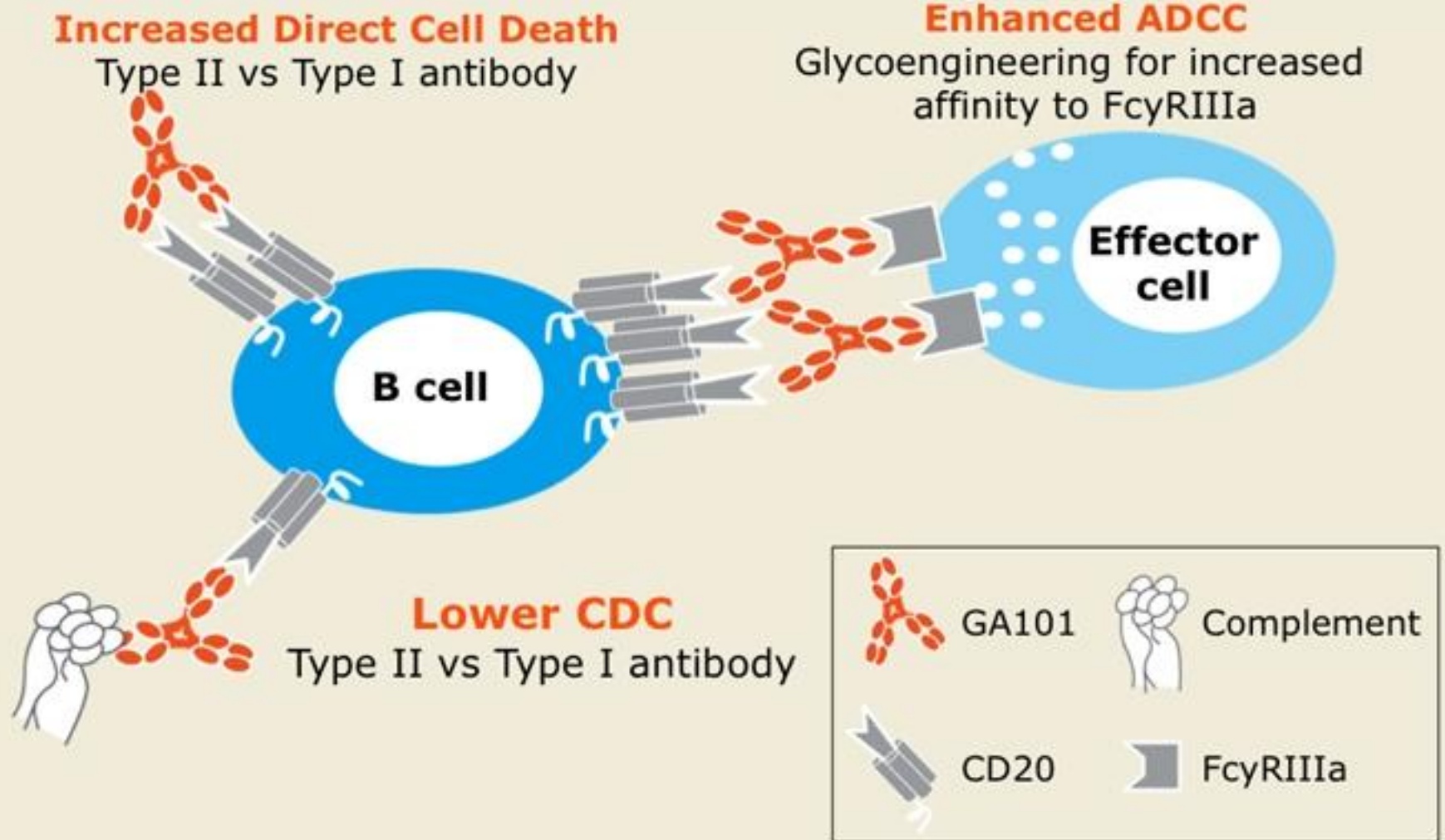




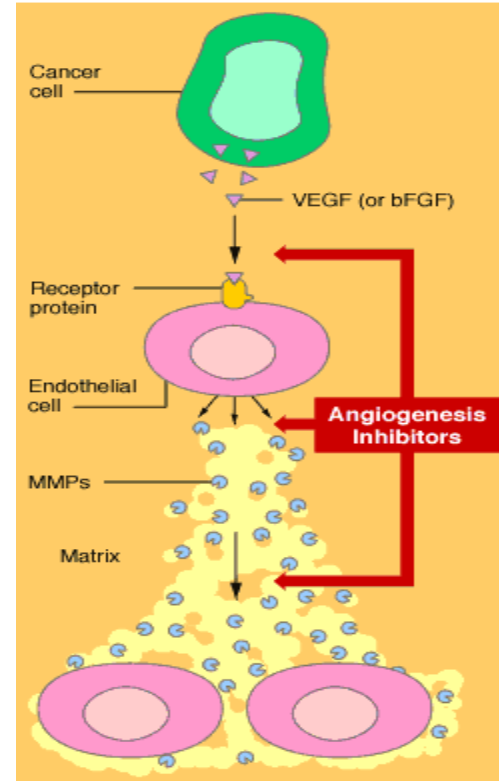
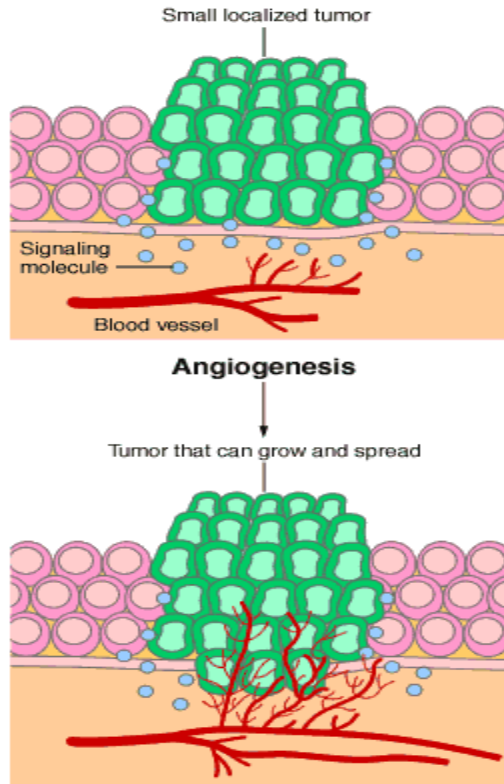
No. AT RISK

CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

# Mechanism of Action of Obinutuzumab



# Angiogenesis in tumors



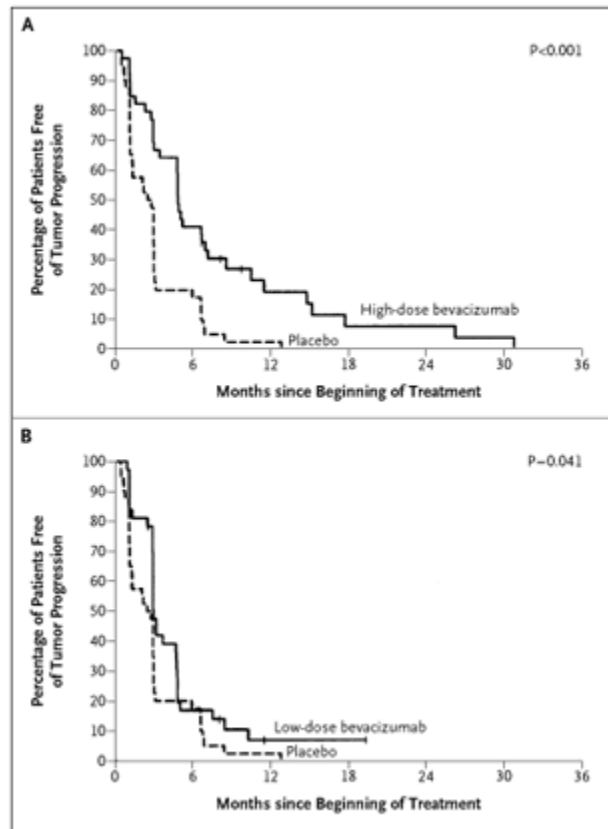
# Bevacizumab

- Improve survival in:
  - Colon cancer
  - Lung cancer
  - Renal cancer





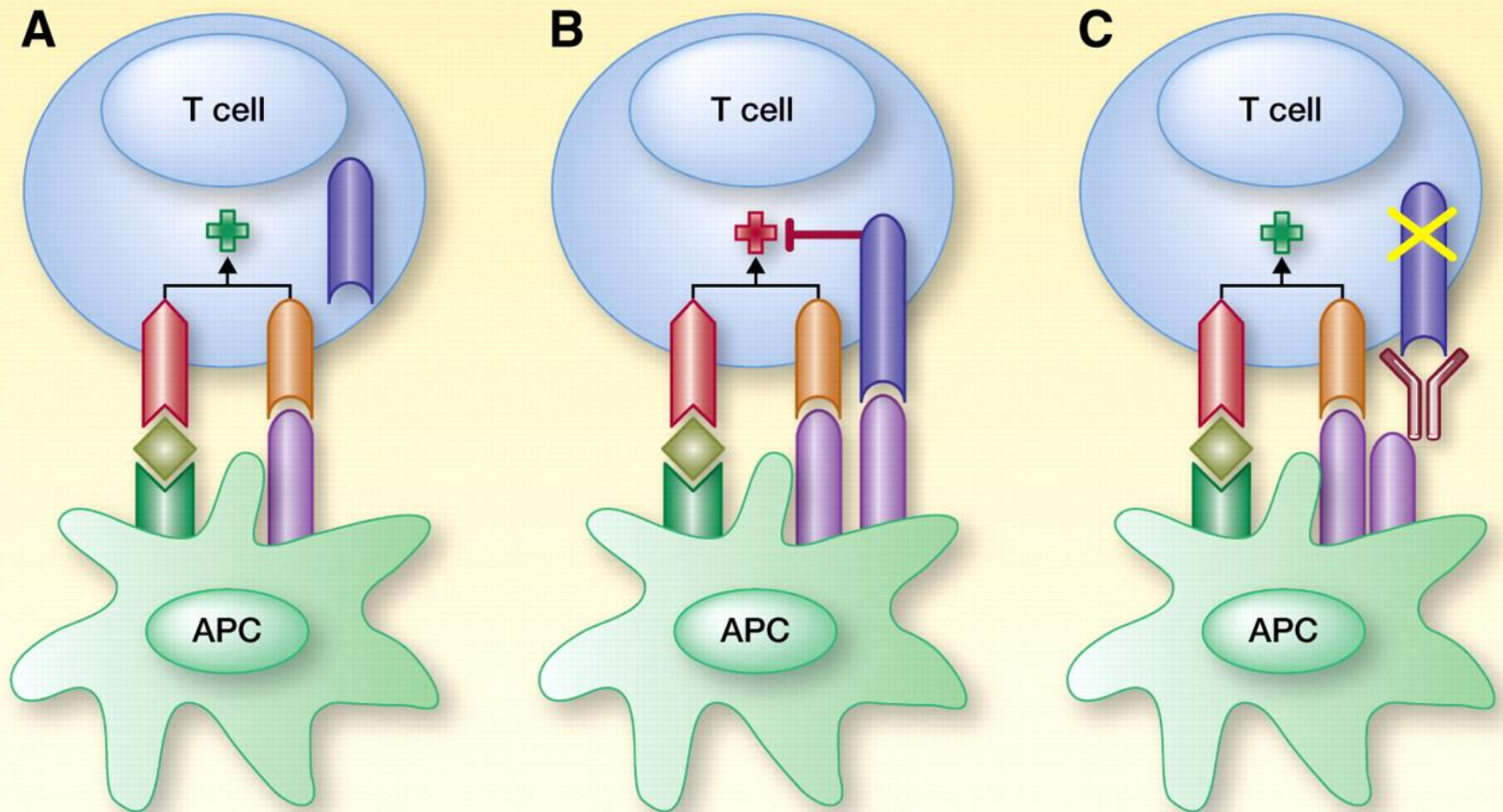
# Bevacizumab in Renal Cancer



- Bevacizumab, a neutralizing antibody against vascular endothelial growth factor
- A randomized, double-blind, phase 2 trial was conducted comparing placebo with bevacizumab at doses of 3 and 10 mg/ kg, given q2 weeks
- After 116 patients randomly assigned to treatment groups, the trial was stopped early

# Ipilimumab (Yervoy)

- For use in metastatic melanoma
- Interrupts inhibitory mechanism that prevents cytotoxic T lymphocytes from killing cancer cells



TCR



CD28



CTLA-4



T-cell inhibition



Peptide/MHC



B7



Ipilimumab



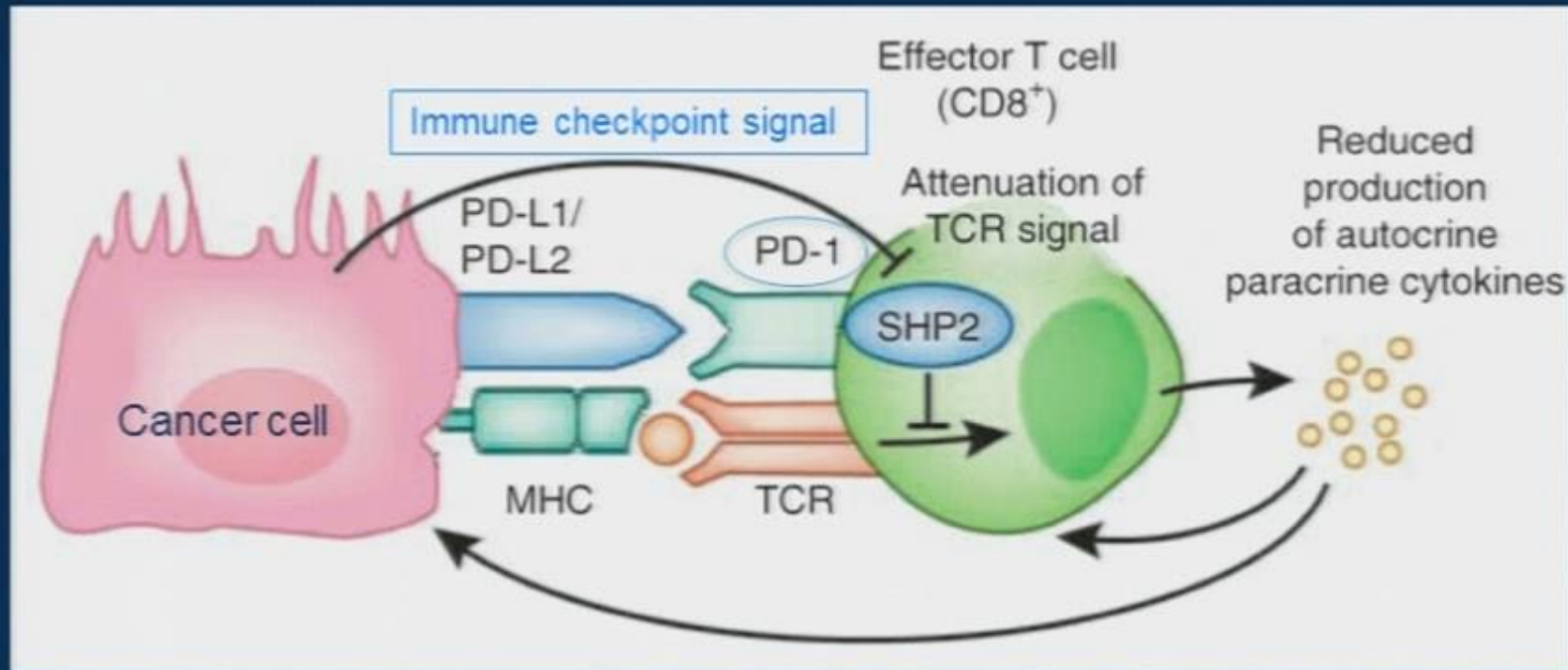
T-cell activation

© 2012 American Association for Cancer Research

# Programmed Cell Death Protein 1 (PD-1)

- New class of drug are inhibitors that activate immune system to attack tumors
- Pembrolizumab FDA approved Sept 2014 for metastatic melanoma
- Nivolumab FDA approved Dec 2014 for metastatic melanoma

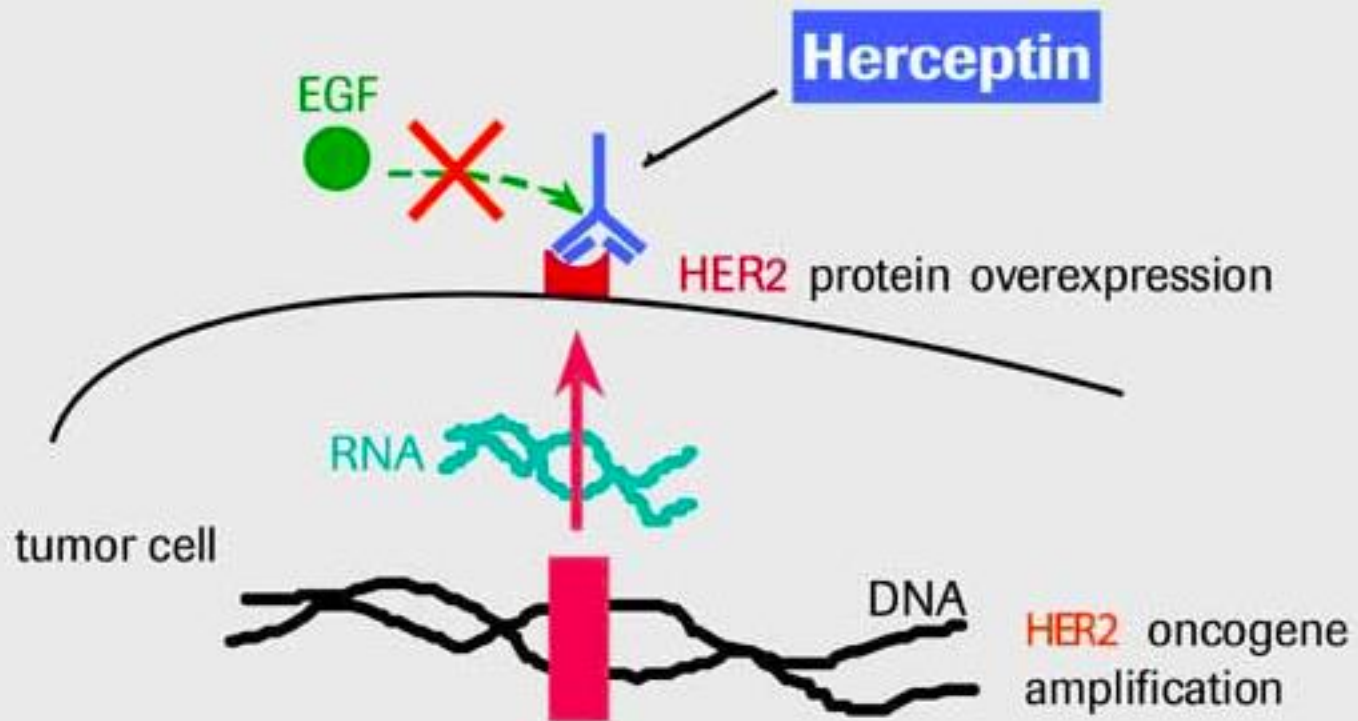
# PD-1/ PD-L1 pathway in suppressing anti-tumor immunity



(Okazaki, Honjo et al. Nat Rev Immunol 2013, modified)

# HER-2 A Target for Breast Cancer

- Human epidermal growth factor receptor 2
- Overexpressed in 25% of breast cancers
- Historically associated with more aggressive course

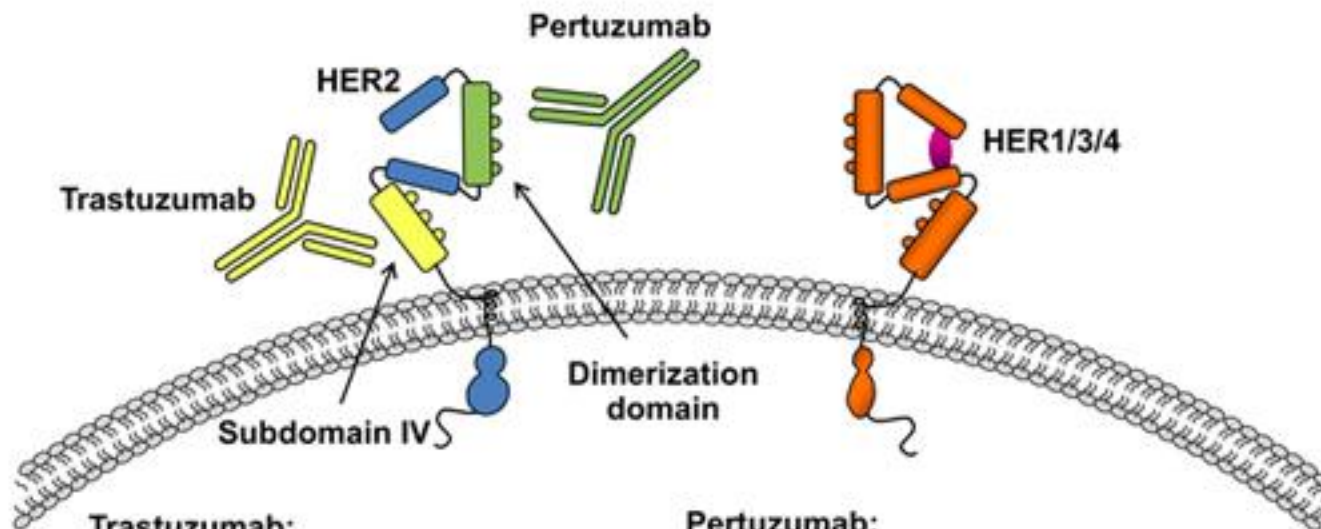


**HER2:** Human Epidermal Growth Factor Receptor-2

**EGF:** Epidermal Growth Factor

# Pertuzumab and Trastuzumab

## *Complementary Mechanisms of Action*



### **Trastuzumab:**

- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

### **Pertuzumab:**

- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

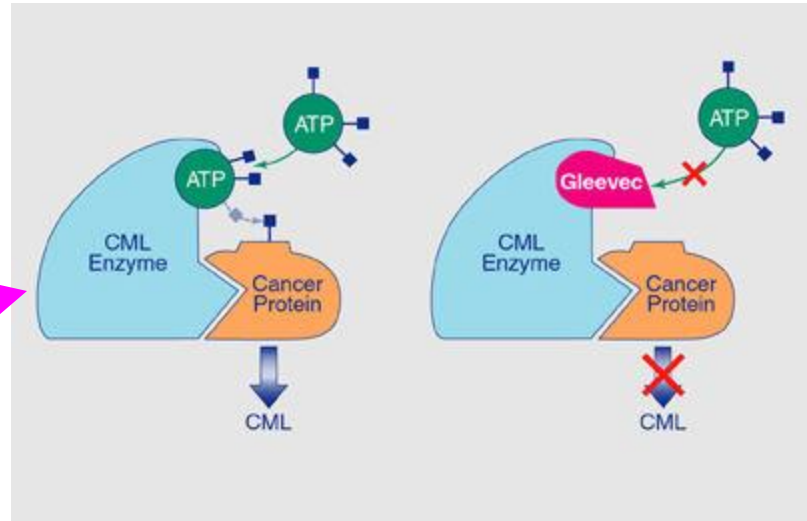
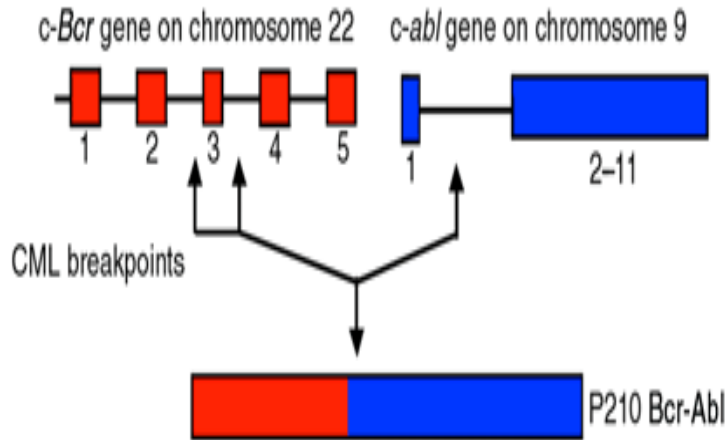


Source: Food and Drug Administration (FDA), Center for Drug Evaluation and Research

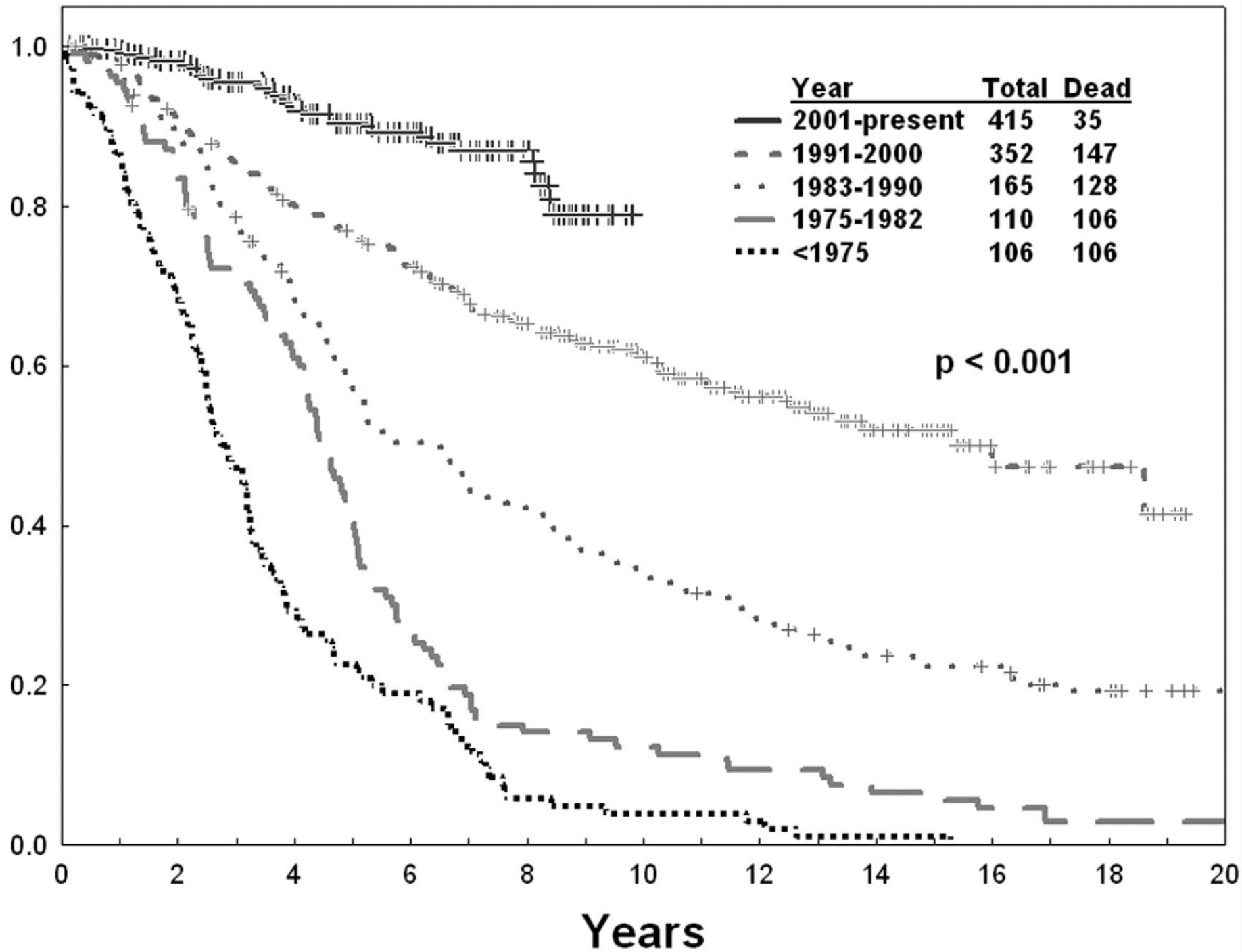
## FDA-approved monoclonal antibodies for cancer treatment

<b>Name of drug</b>	<b>Type of cancer it treats</b>
Alemtuzumab (Campath)	Chronic lymphocytic leukemia Brain cancer
Bevacizumab (Avastin)	Colon cancer Kidney cancer Lung cancer
Cetuximab (Erbix)	Colon cancer Head and neck cancers
Ibritumomab (Zevalin)	Non-Hodgkin's lymphoma
Ofatumumab (Arzerra)	Chronic lymphocytic leukemia
Panitumumab (Vectibix)	Colon cancer
Rituximab (Rituxan)	Chronic lymphocytic leukemia Non-Hodgkin's lymphoma
Tositumomab (Bexxar)	Non-Hodgkin's lymphoma
Trastuzumab (Herceptin)	Breast cancer Stomach cancer

# Targeted therapy (Imatinib)



Survival Probability



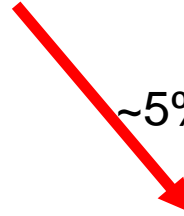
# Targeted therapy in Lung cancer

10% of patients



- Patients with NSCLC expressing mutated epidermal growth factor receptors (EGFRs) were randomly assigned to receive either the EGFR kinase inhibitor gefitinib or standard chemotherapy.
- The gefitinib group had a higher response rate (73.7%, vs. 30.7%) and significantly longer median survival (30 vs. 23 months). (NEJM June 2010)

~5% of patients



- A small group of patients with NSCLC have genetic lesions that activate anaplastic lymphoma kinase (ALK).
- Crizotinib, an oral ALK kinase inhibitor, produced a 57% response rate in this subgroup, (NEJM Oct 2010)

CT scan in a representative ALK +ve patient  
at baseline  
and after two cycles of therapy.

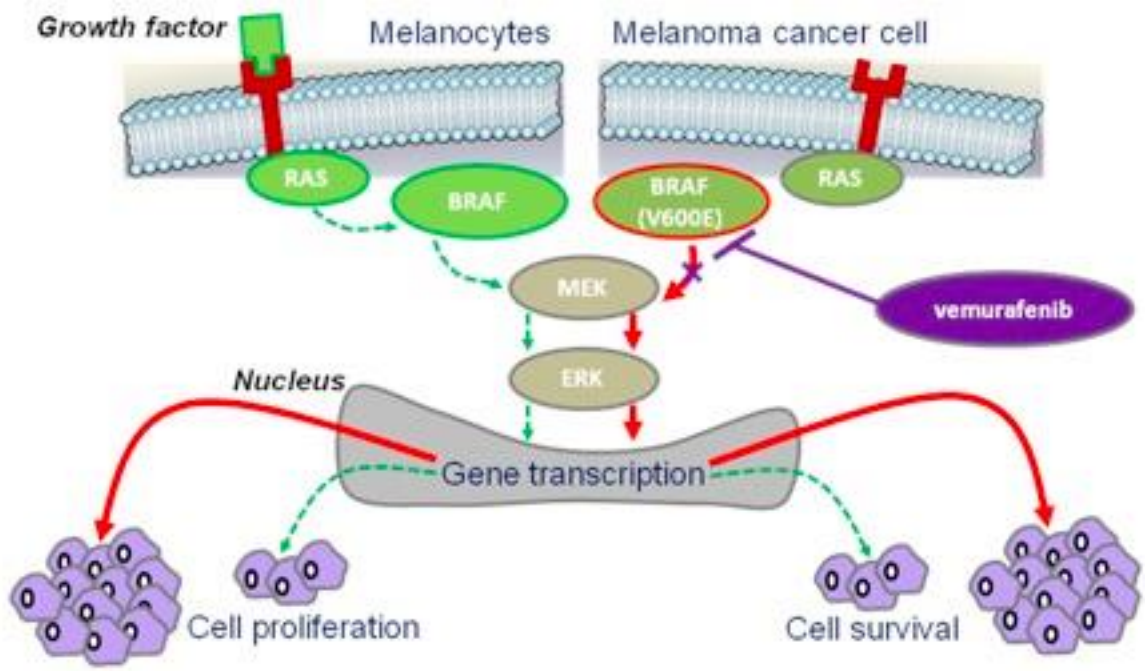


Crizotinib



# Vemurafinib

- For melanoma patients with b-raf mutation
- Interrupts B-Raf/MEK/ERK pathway



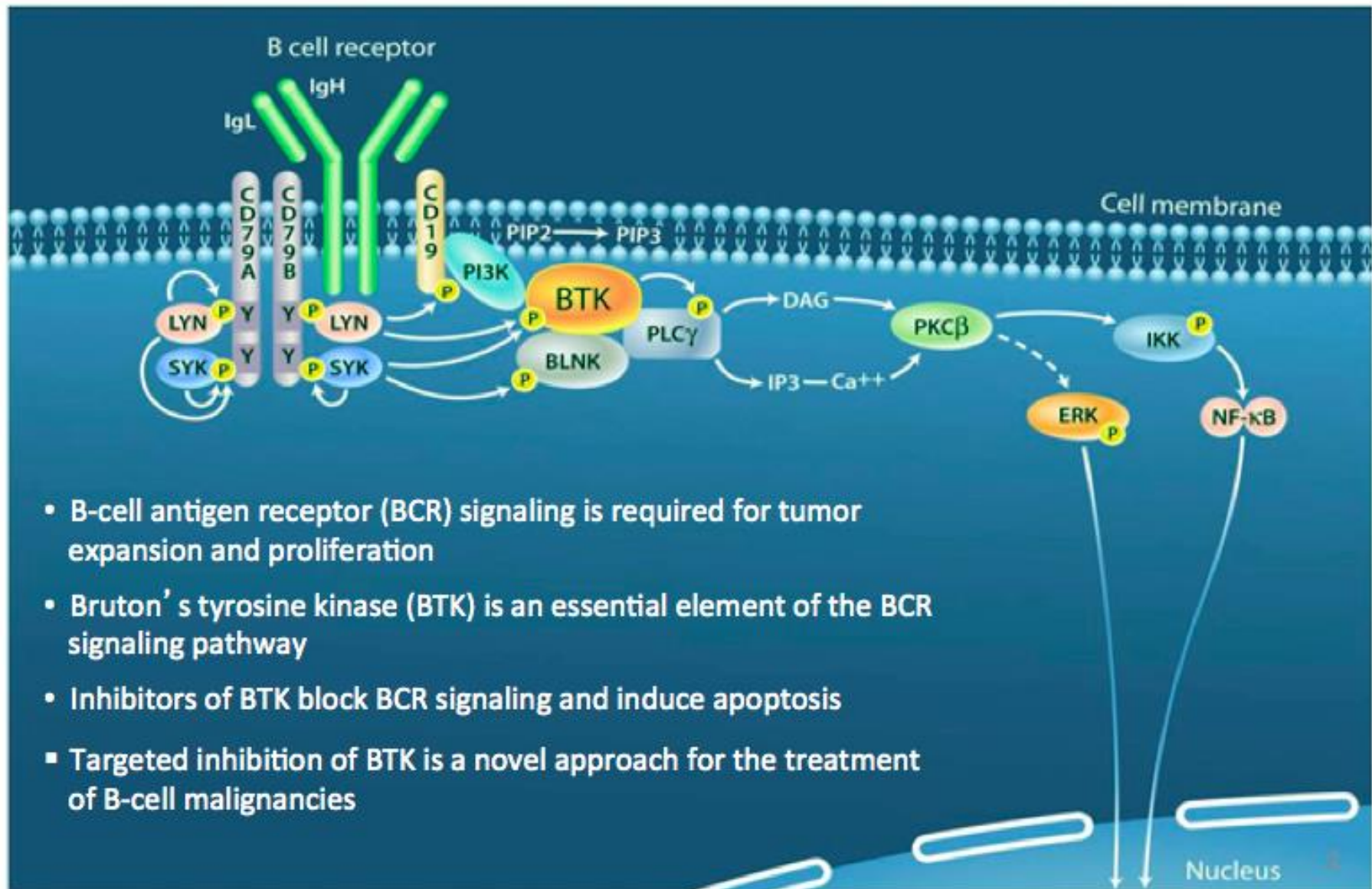
# Ibrutinib (Ibruvica)

- Newly approved last year for use in relapsed/refractory CLL and mantle cell lymphoma
- Novel Bruton's tyrosine kinase inhibitor



# Bruton's Tyrosine Kinase (BTK)

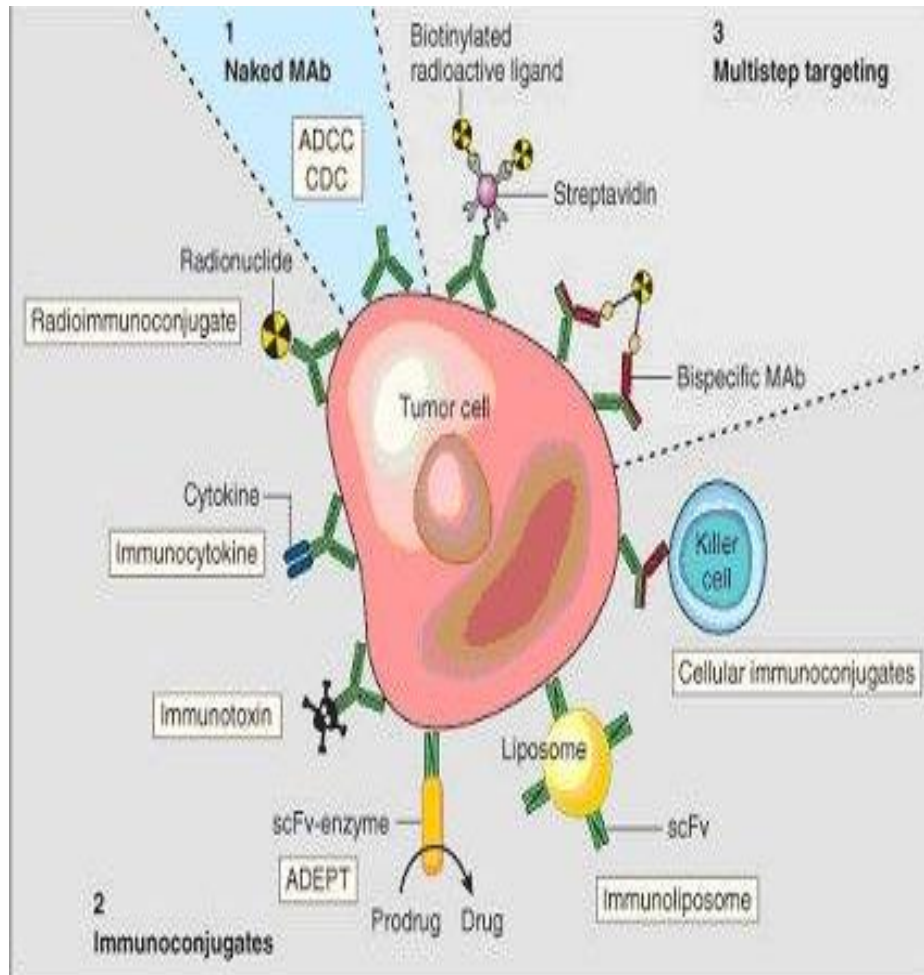
A critical kinase for lymphoma cell survival and proliferation



# Immunotherapy

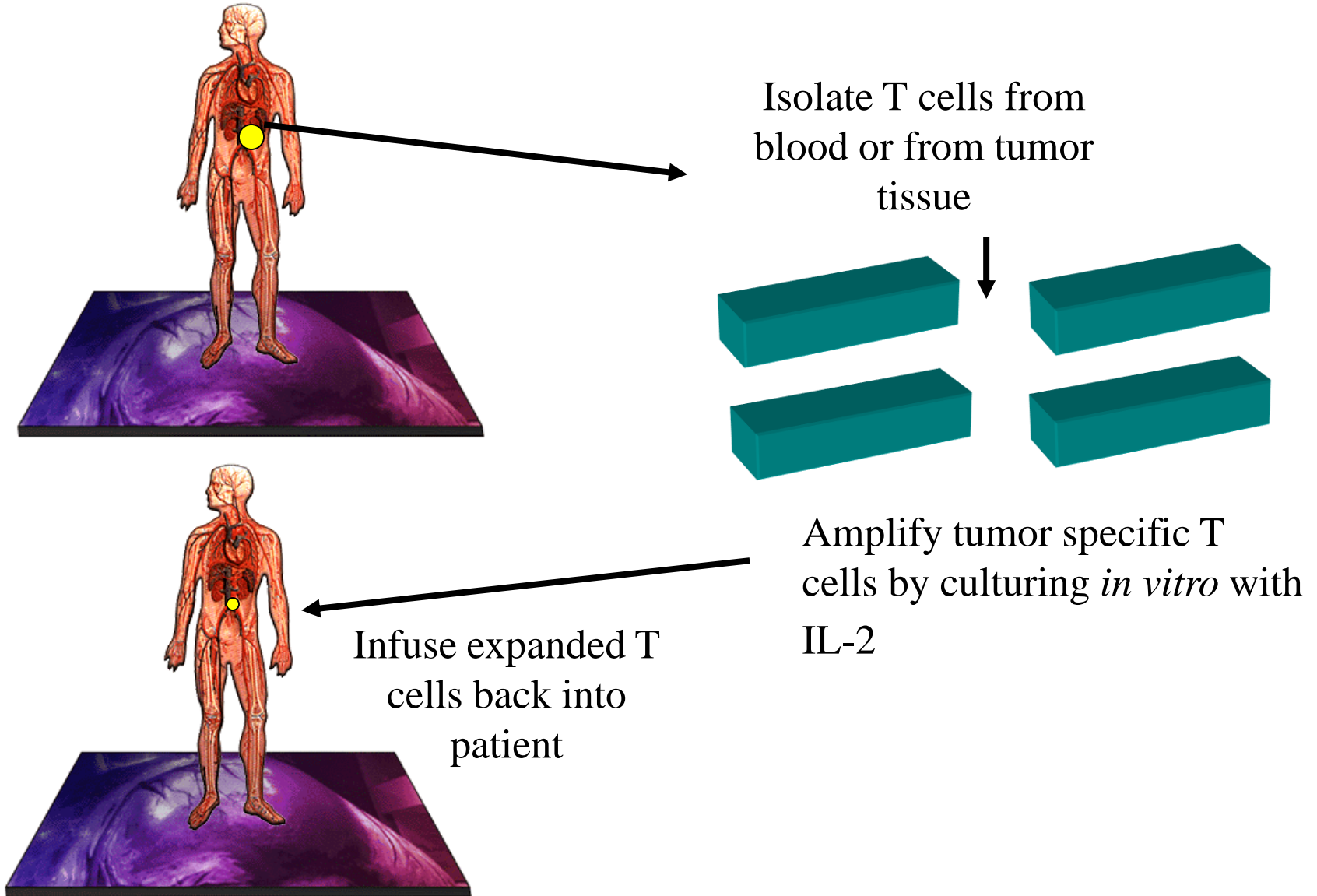
- Use the immune system to prevent or treat neoplasms.
- Goal is to enhance the body's immune response against weakly immunogenic tumors

# Antibodies recognizing tumor associated antigens

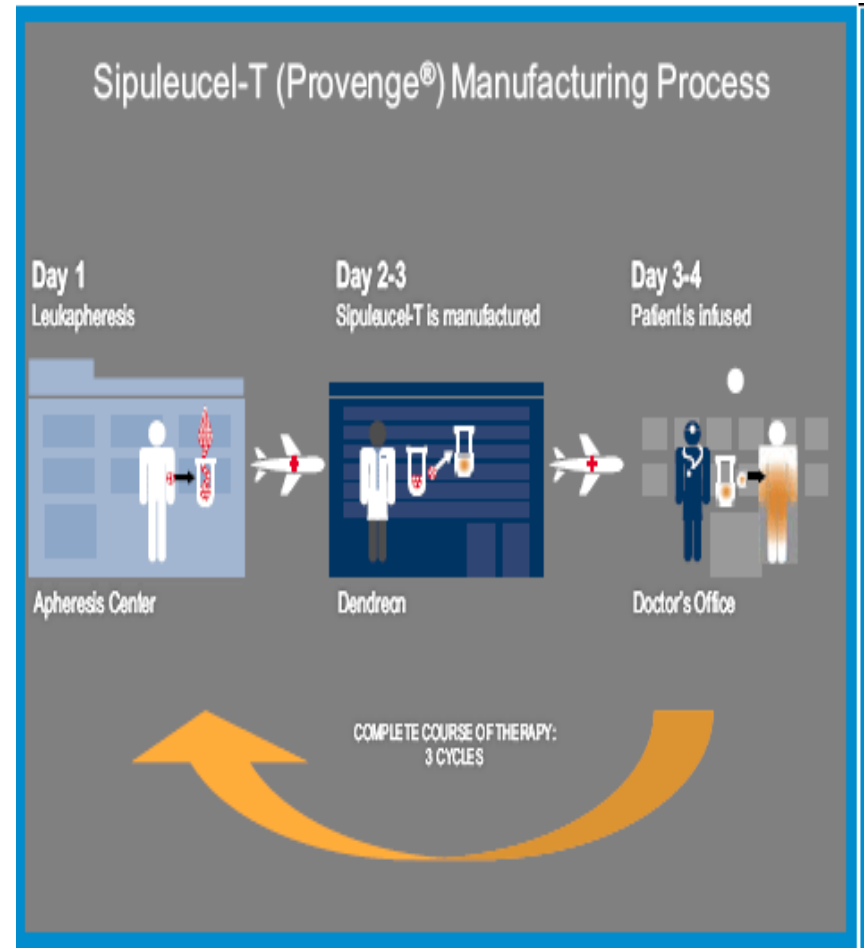
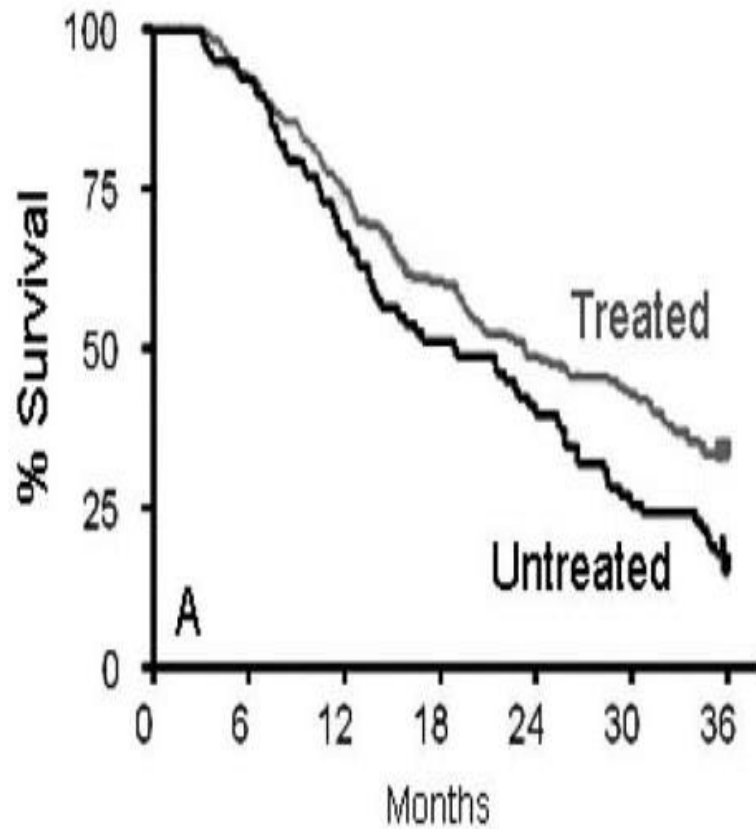


- Breast cancer, *Herceptin* useful in ~30% of patients
- B cell lymphoma, *Rituximab* used as a single agent or in combination with chemotherapy.
- *Zevalin* and *Bexxar* are radio-labelled conjugates of CD20
- CLL, *Campath-H1*, active in pretreated patients
- AML, *Mylotarg*, Moab conjugated with the cytotoxic antibiotic calicheamicin

# Adoptive Transfer

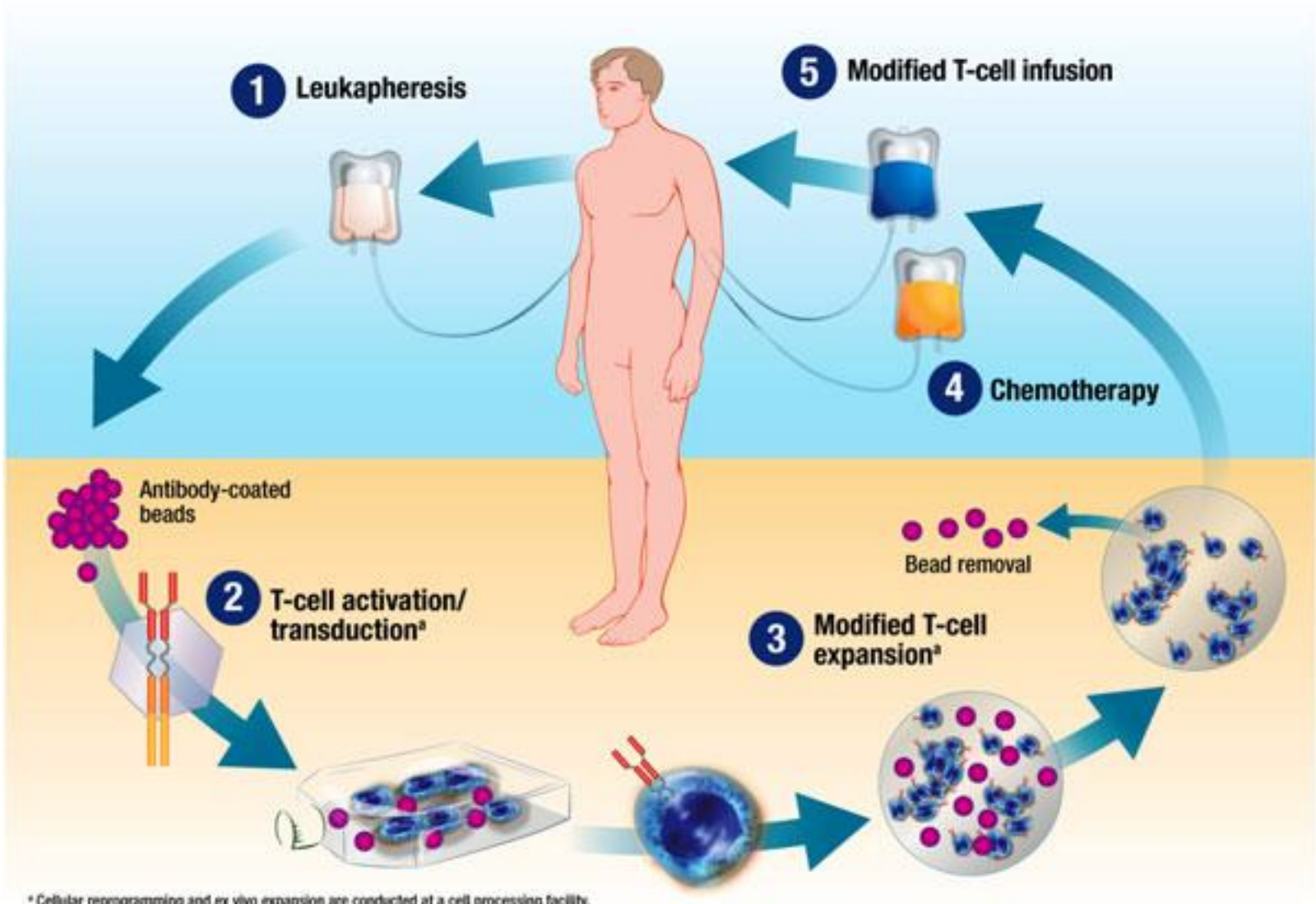


# Vaccine as therapy: Provenge



# CAR-T Therapy

- Chimeric Antigen Receptor T-Cell Immunotherapy



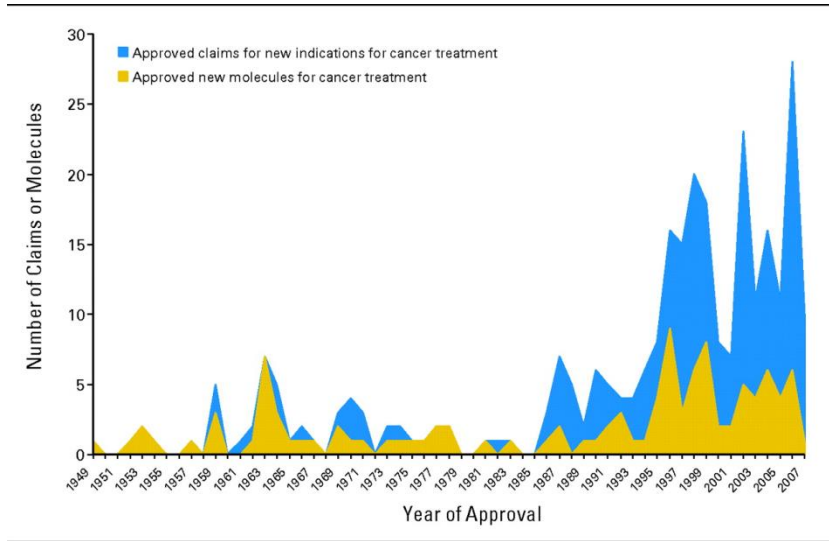
<sup>a</sup> Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

# Cost of Genome Sequencing

- Human Genome Project cost U.S. taxpayers, about \$2.7 billion in FY 1991 dollars.
- Cost of this AML project ~\$20 million
- Cost of sequencing a human genome today is ~\$10-30K and falling
- Predicted to cost \$1000-\$5000



# Hope is on the way



## Winning the War on Cancer

A blitz of medical breakthroughs may end this deadly disease once and for all

BY LORI MILLER KASE

As a nurse, Ginger Empey knew how grim her prognosis was when, at 30, she was diagnosed with breast cancer that had already spread to other parts of her body. She had a mastectomy, but when chemotherapy failed to touch the golf-ball-sized tumors on her liver, the doctors told her to "get her affairs in order."

"I couldn't believe that, three months into the disease, there was nothing available to me," Empey recalls.

Fortunately for her, however, Dr. Dennis Slamon from the University

of California, Los Angeles (UCLA), a pioneer in the use of the next generation of cancer treatments, was about to begin recruiting patients for the final stage of a study to test a new breast cancer drug, Herceptin, which targets the gene defect that is responsible for about a quarter of all breast cancer cases, would supposedly fix the biological problem at the root of Empey's disease.

It worked. Today, little evidence can be found of the aggressive cancer that led doctors to give Empey a death

# CANCER RESEARCH & TREATMENT CENTER

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