

# **New Oncological Treatments Impacting Palliative Care: Do We Need New Endpoints**

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ESMO Palliative Care Working Group

# Medical Therapy of Cancer

- Conventional chemotherapy:

Shrinkage of tumors.

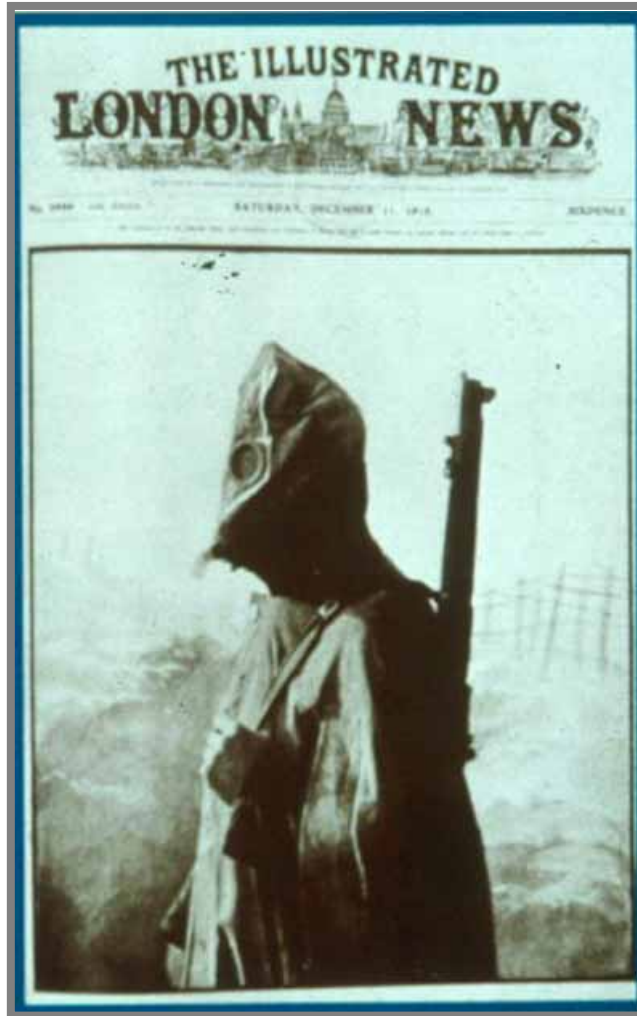
- New targeted therapy:

Stabilization, prevention of relapse,  
emphasis on quality of life.

# Chemotherapy=Cytotoxic Medical Treatment of Cancer

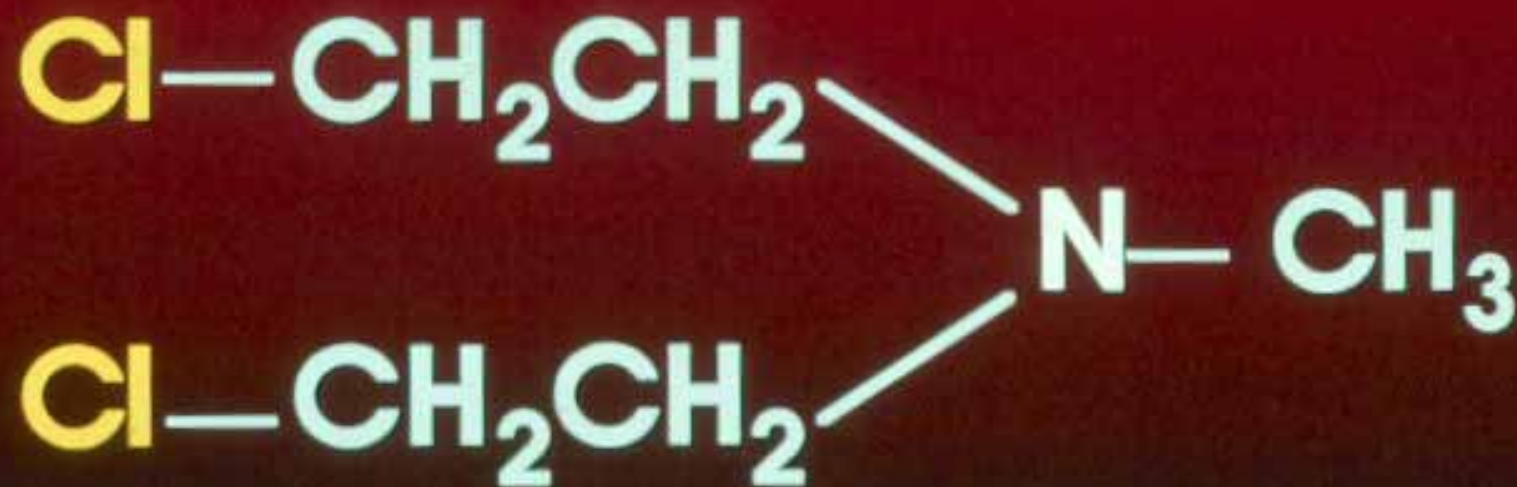
**The name “chemotherapy” was adopted  
for historical reasons**

# History of Chemotherapy



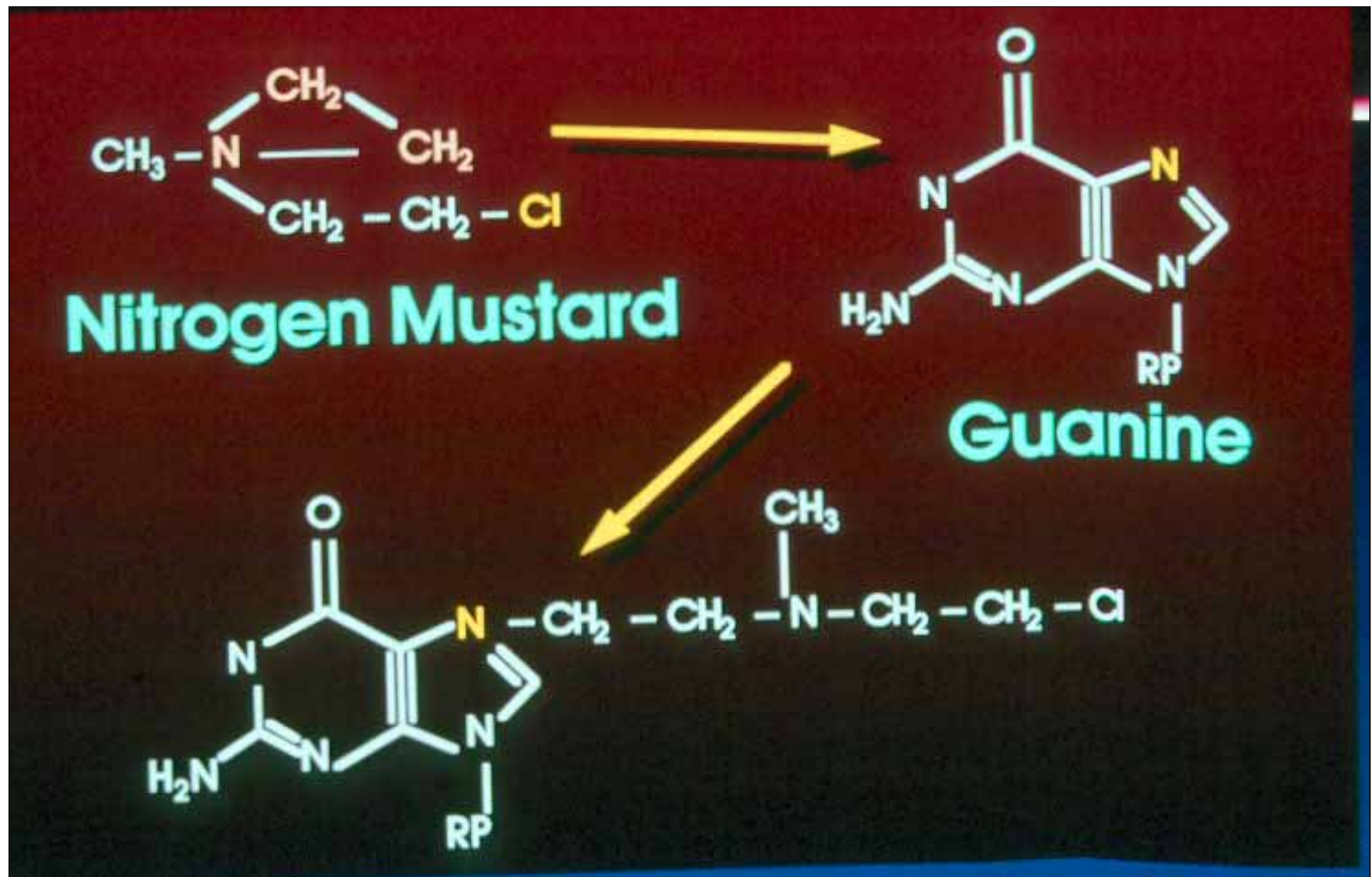
**WW1: chemical warfare**

# Nitrogen Mustard.



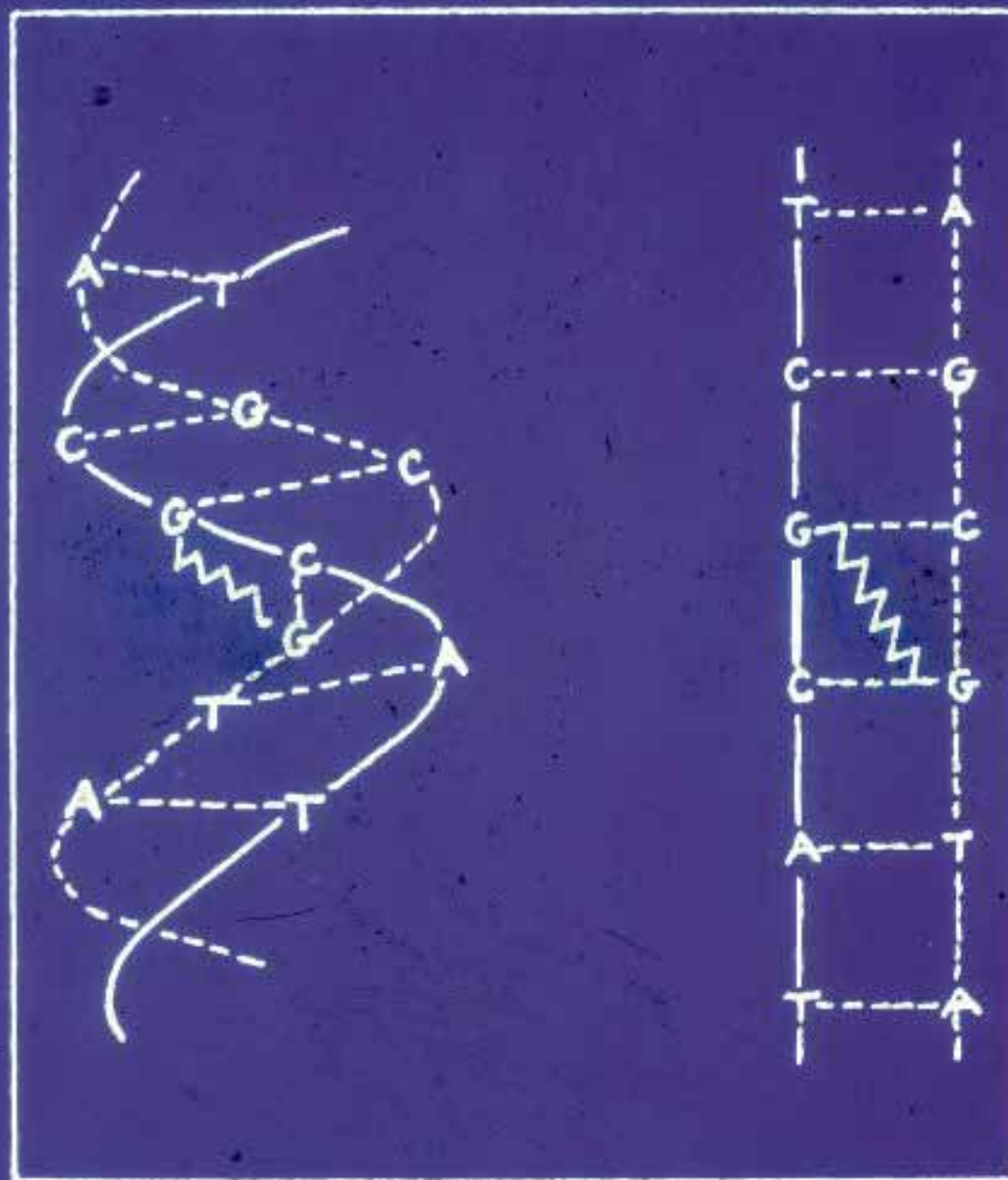
**Mechlorethamine**

A secret new weapon developed between the 2 WW

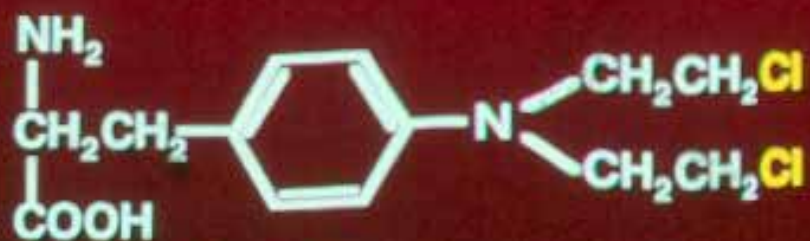


NM: Triangular “ring” formation and binding to guanine

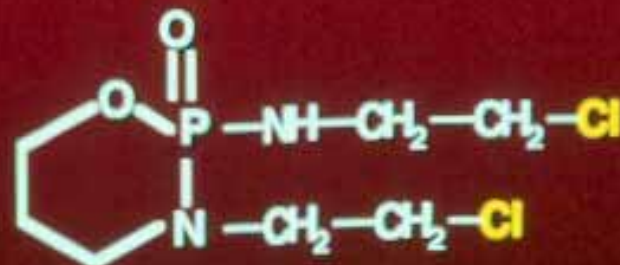




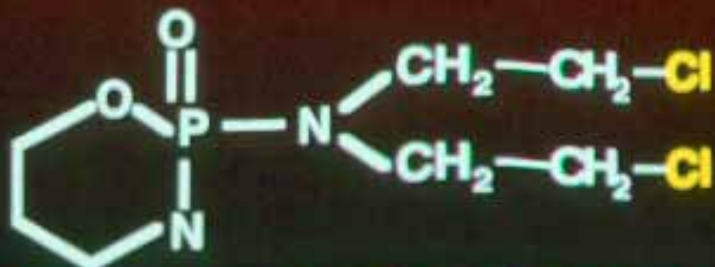
Schematic representation of the mechanism of alkylating agents (cross-linkage).



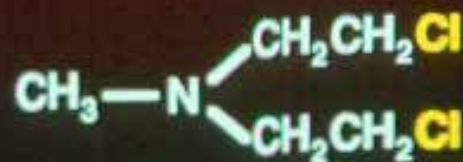
**Melphalan**



**Ifosfamide**



**Cyclophosphamide**



**Nitrogen Mustard**

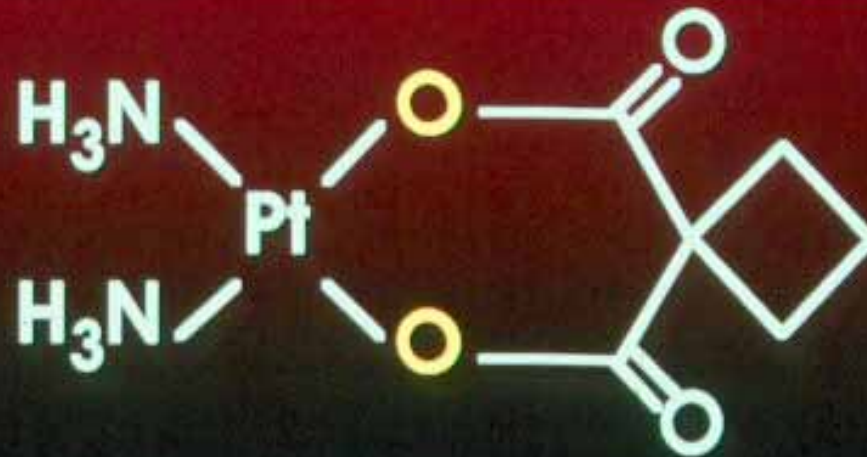
**Nitrogen Mustard derivatives**



**Cisplatin**

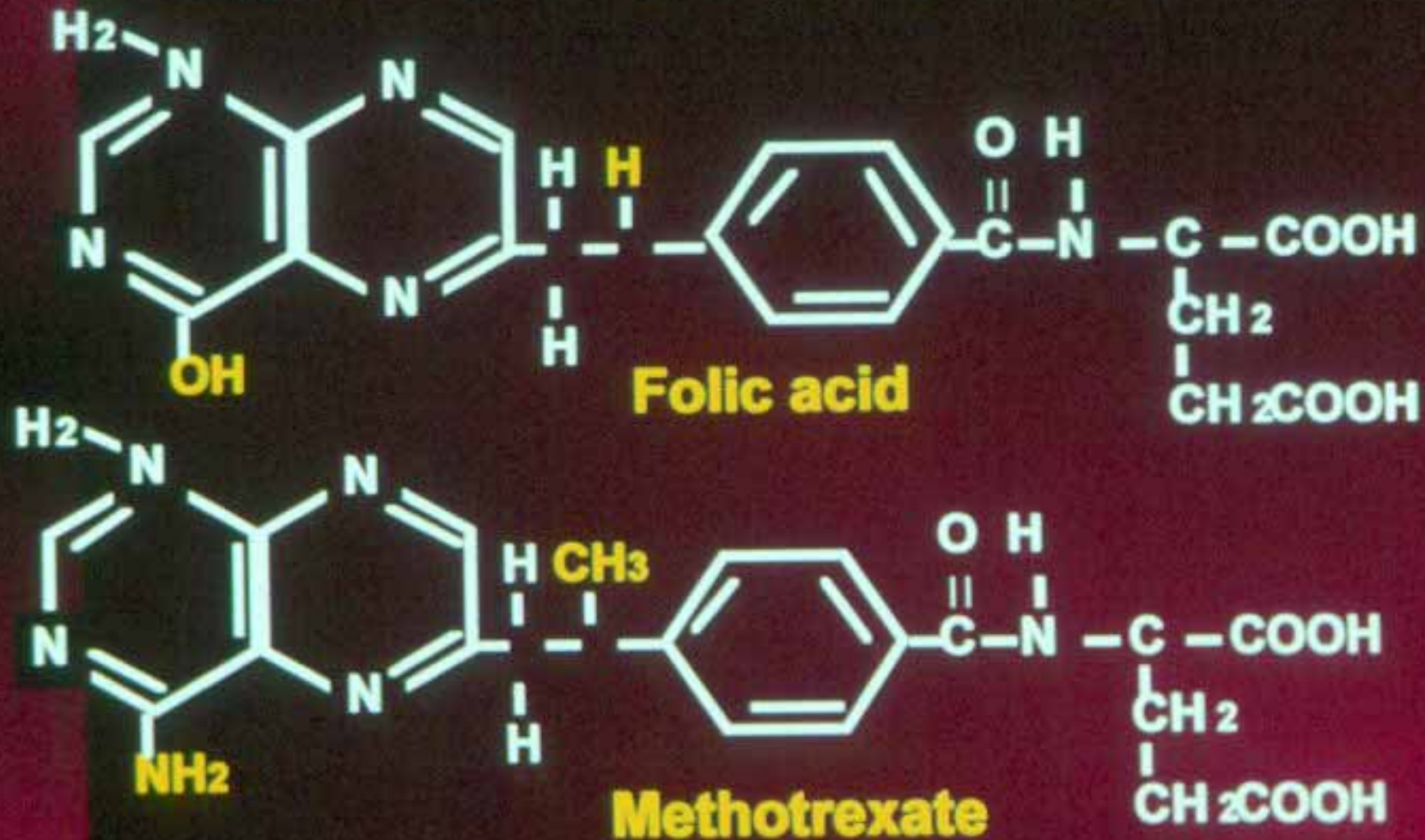


**Carboplatin**

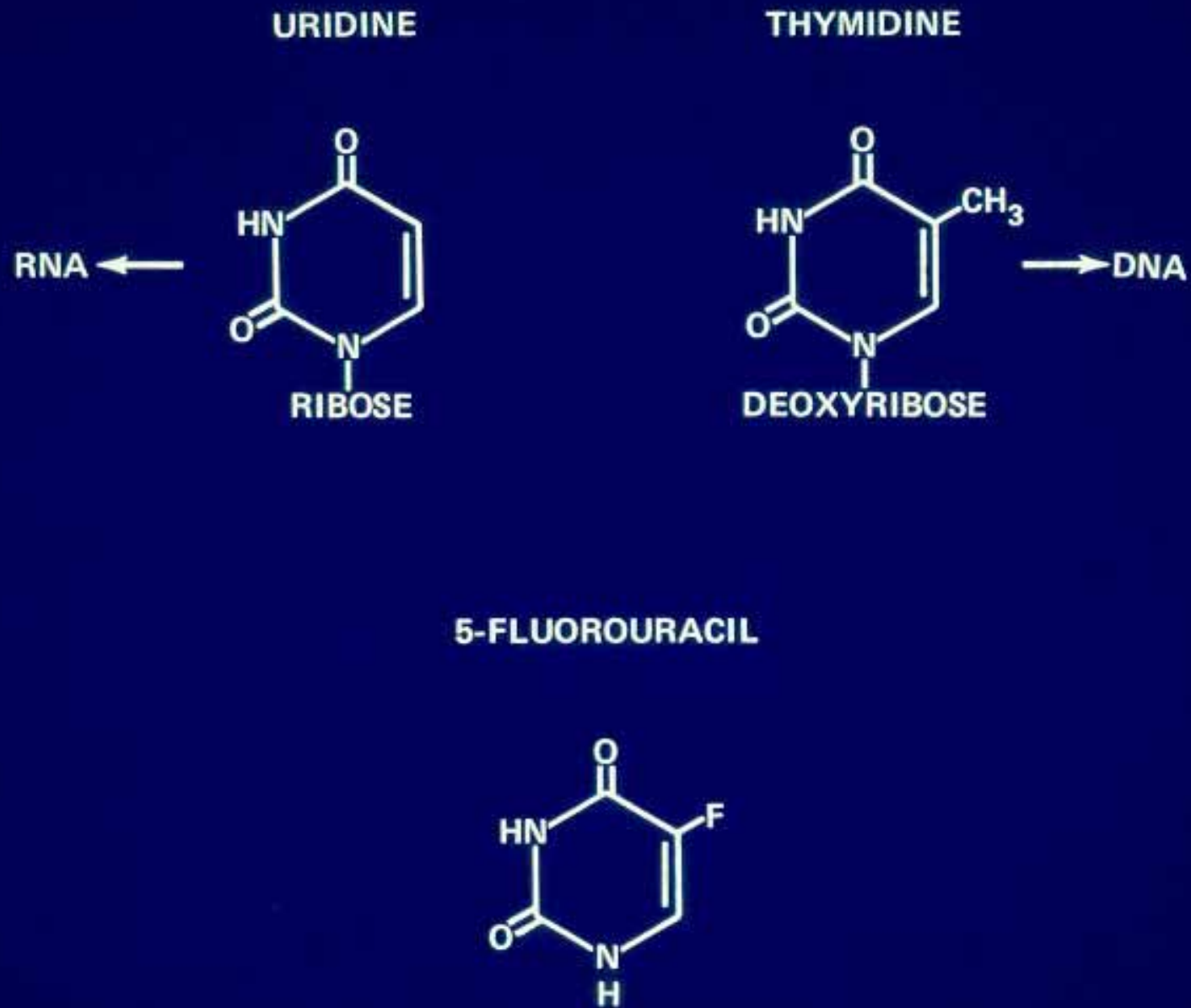


Other alkylating agents with similar mechanism of action

## Structure of folic acid and methotrexate



The first antimetabolite: Designed by Sidney Farber in 1948, following his observation that Vitamin B accelerates leukemia



The second antimetabolite: May interfere with the production of DNA or RNA



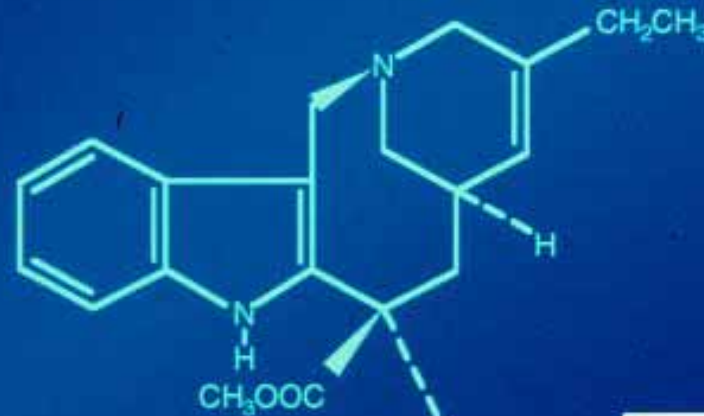
**Vinca Rosea**  
**[plant alkaloids]**



# What is NAVELBINE® (vinorelbine tartrate) Injection?

- ◆ Semisynthetic vinca alkaloid
- ◆ Unique structural change at the catharanthine ring – May account for distinct product characteristics
- ◆ First-line treatment of unresectable, advanced non-small cell lung cancer (NSCLC)

Catharanthine Ring



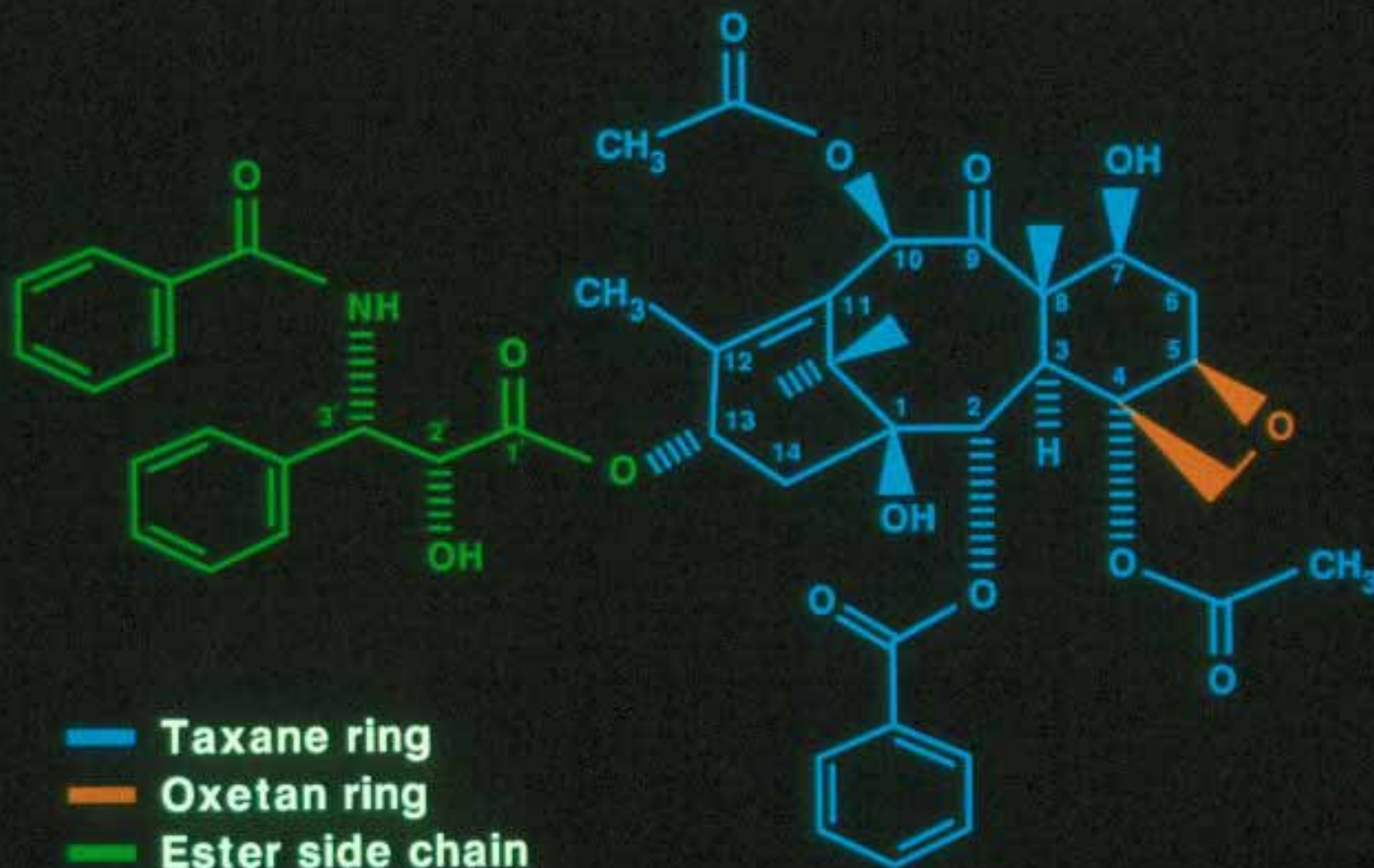
Vindoline Ring



A vinca alkaloid; others are vincristine, vinblastine



# PACLITAXEL: CHEMICAL STRUCTURE



Another plant alkaloid

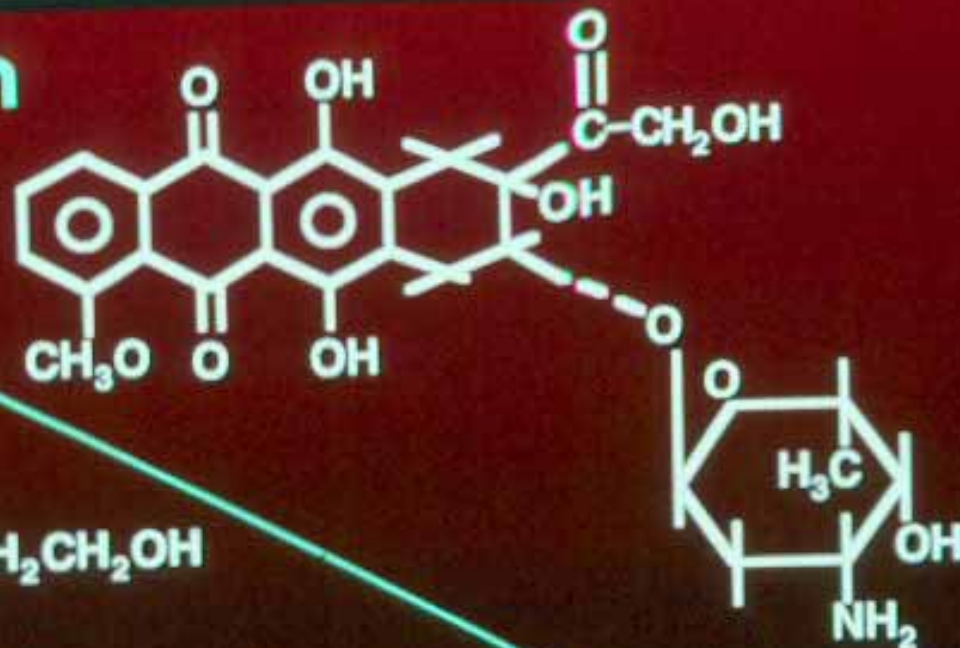






# Chemical structures of adriamycin and mitoxantrone.

**Adriamycin**

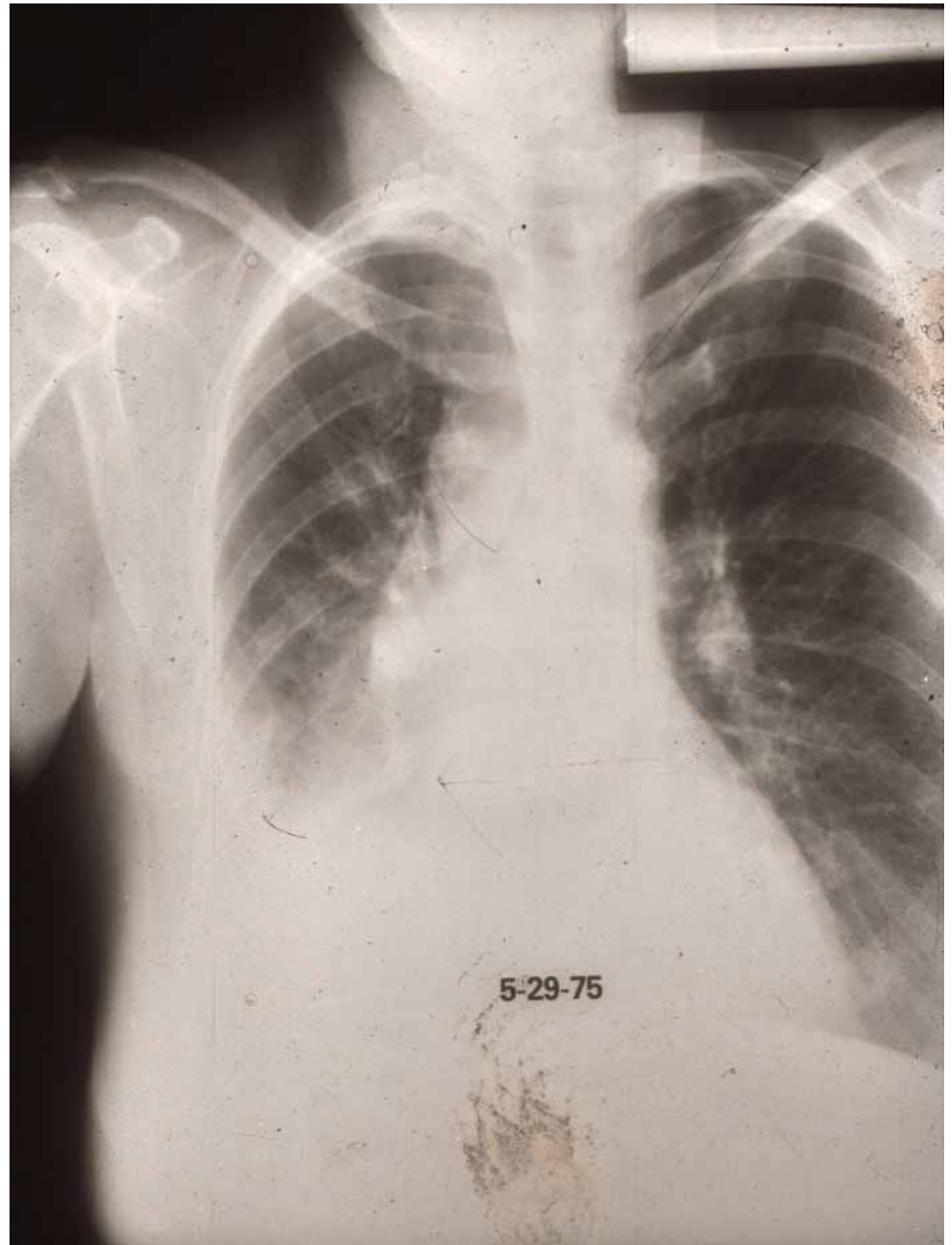


**Mitoxantrone**

Anthracyclines; adriamycin is an antibiotic!

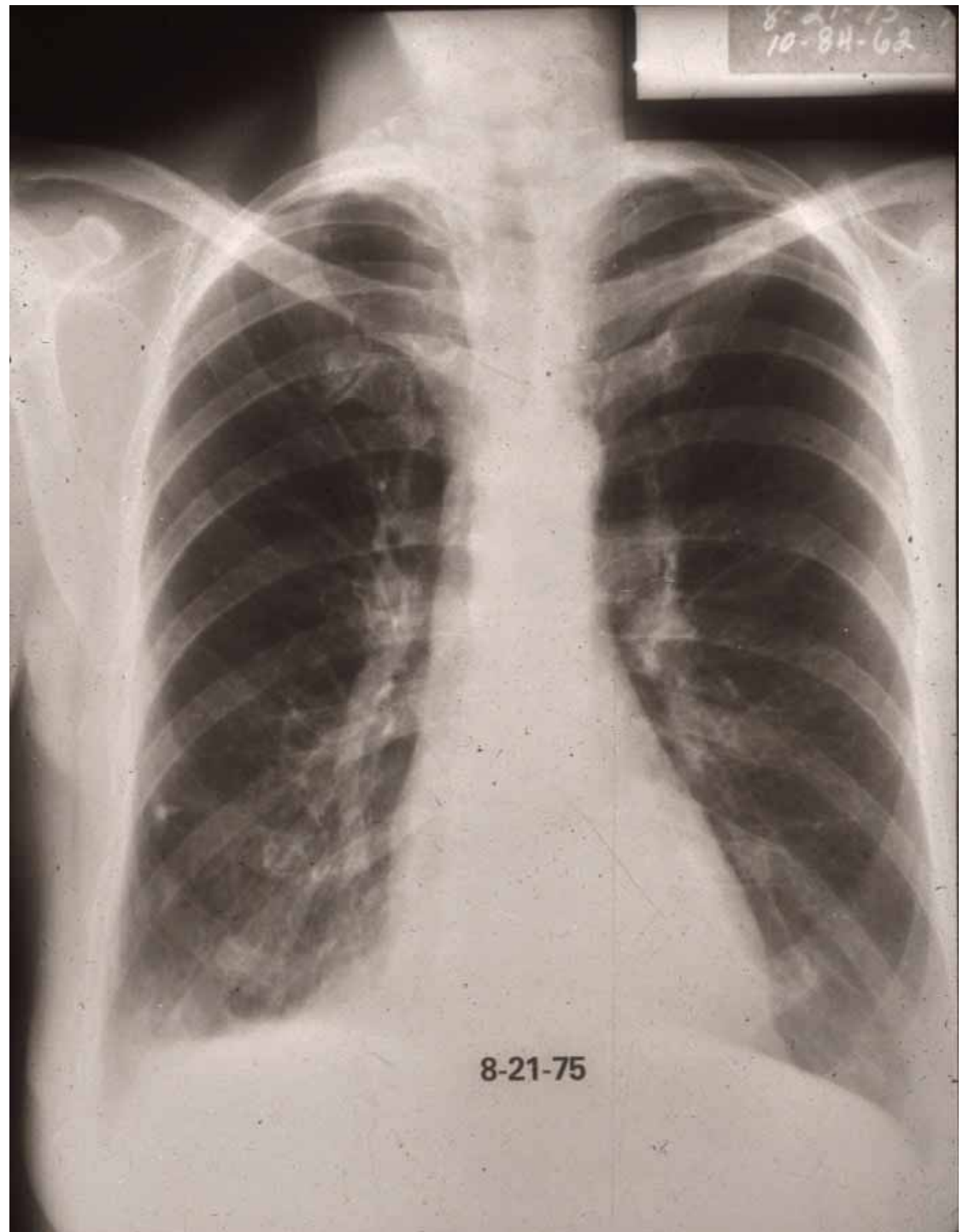


**A patient with advanced  
lung cancer and pleural  
effusion**

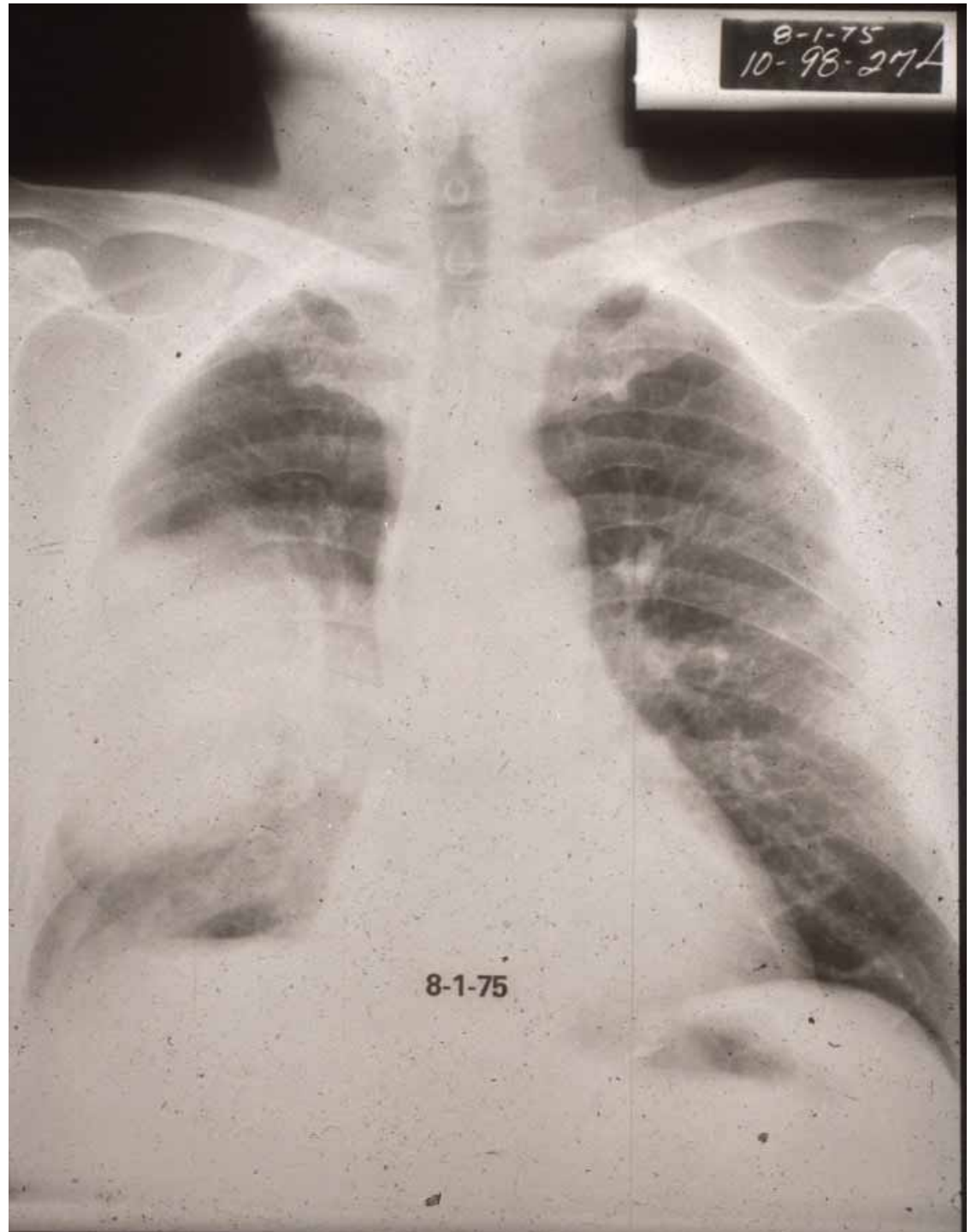




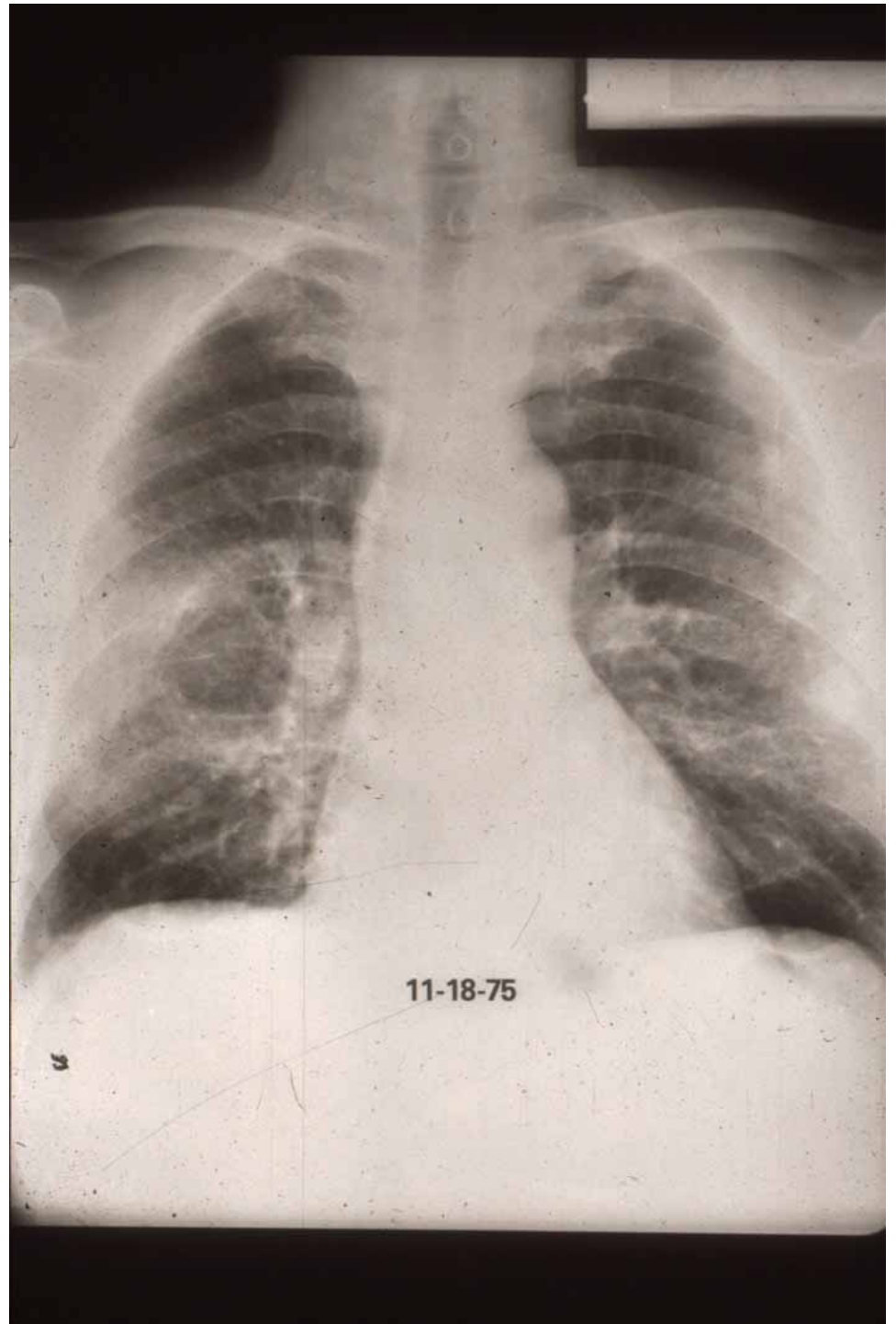
**Same patient 3 months after  
initiating cytotoxic chemotherapy**



**Another patient with  
advanced lung cancer**



**Three months after chemotherapy**



**A patient with locally advanced  
recurrent breast cancer**





**Two months after starting chemotherapy  
with paclitaxel**

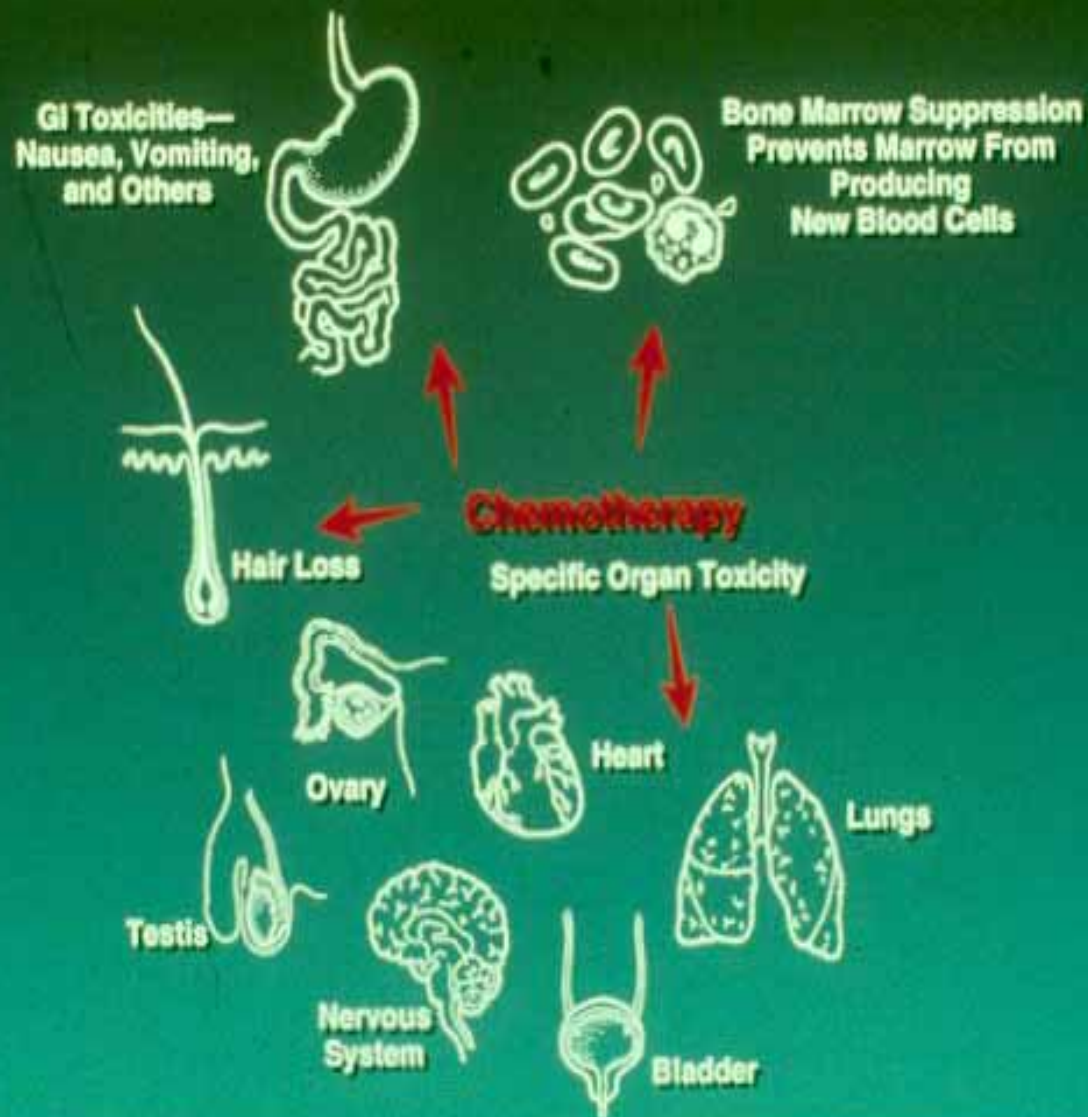




**Six months on paclitaxel chemotherapy**



# Common Toxic Effects of Chemotherapy



# Conventional [old fashioned] chemotherapy

- Severe, occasionally life threatening, toxic side effects.
- Frequently cumulative toxicity, hence no prolonged treatments.
- Usually administered intravenously.
- Efficacy assessed by measurement of tumor shrinkage.

# Targeted Therapy

Treatment that targets the tumor, with minimal effect on normal tissue.

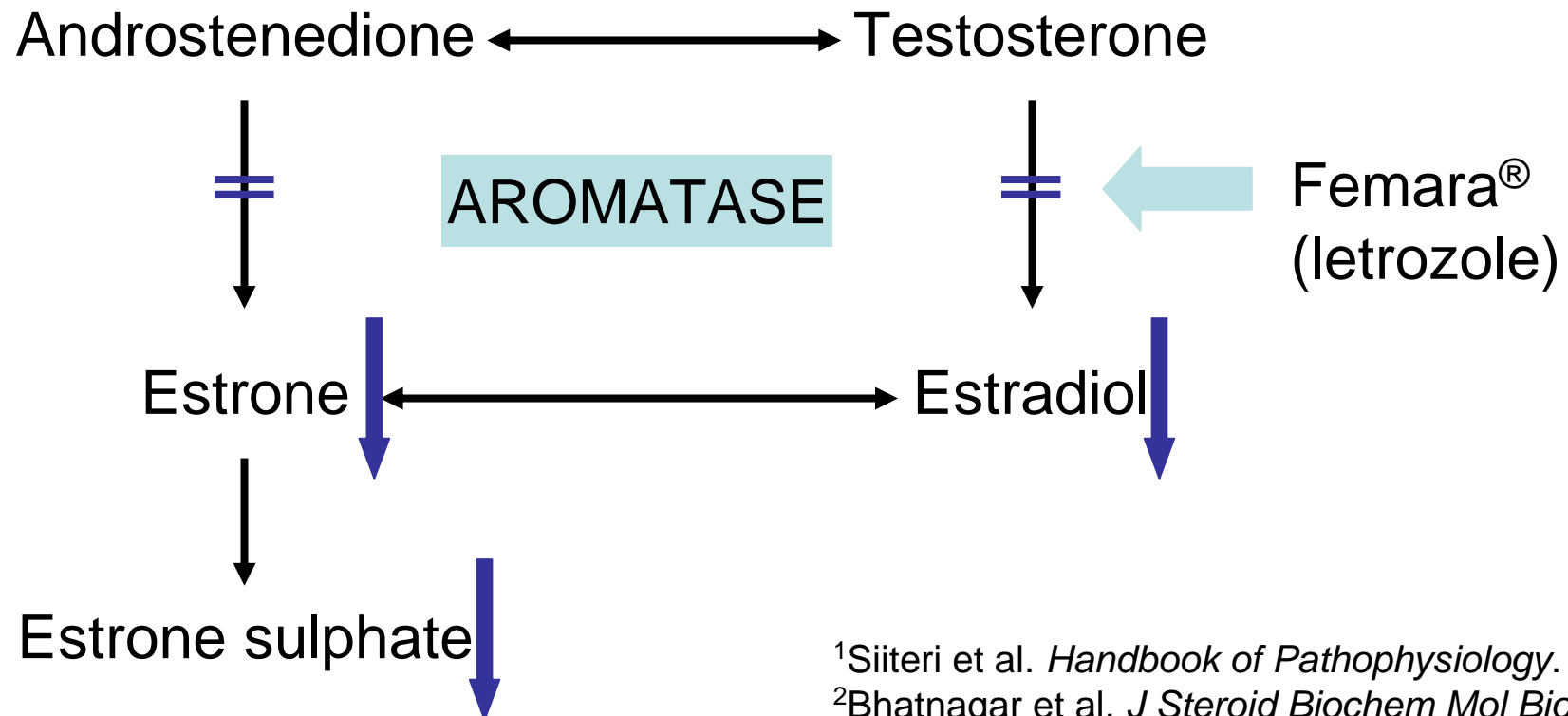
# Targeted Therapy

- Traditional: **Hormonal treatment**
- The most common cancers [breast in women and prostate in men] are frequently dependent on hormonal factors and changing the hormonal status may shrink the tumor.
- For example: Aromatase inhibitors are very effective in hormone-dependent breast cancer



# Aromatase and Estrogen Synthesis

- Aromatase catalyses the last step of estrogen biosynthesis
- Femara<sup>®</sup> (letrozole) inhibits aromatase and blocks estrogen synthesis



<sup>1</sup>Siiteri et al. *Handbook of Pathophysiology*. 1973;

<sup>2</sup>Bhatnagar et al. *J Steroid Biochem Mol Biol*. 2001

Another example of Targeted  
Therapy

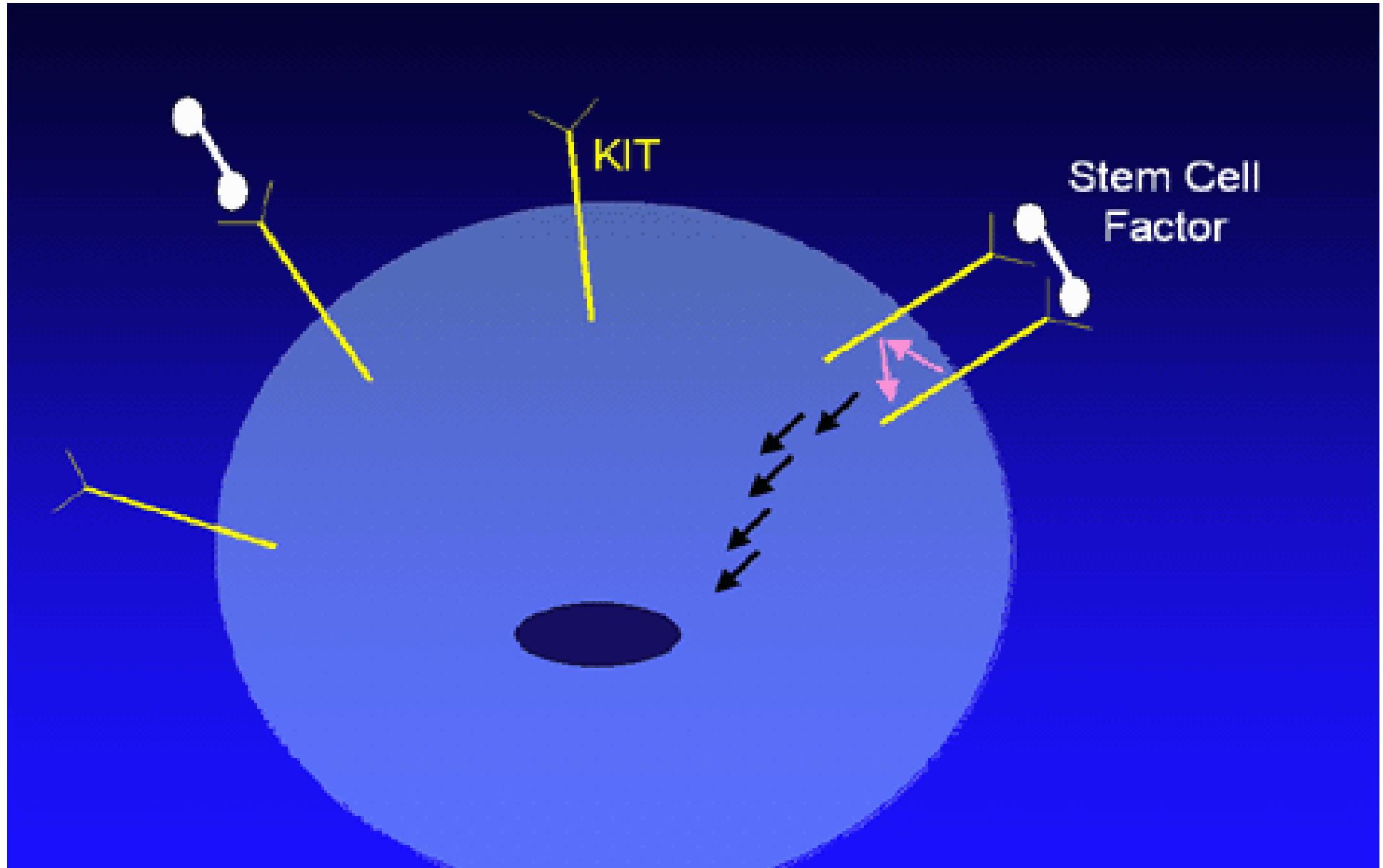
**Imatinib [Glivec, STI]**

**targets c-KIT**

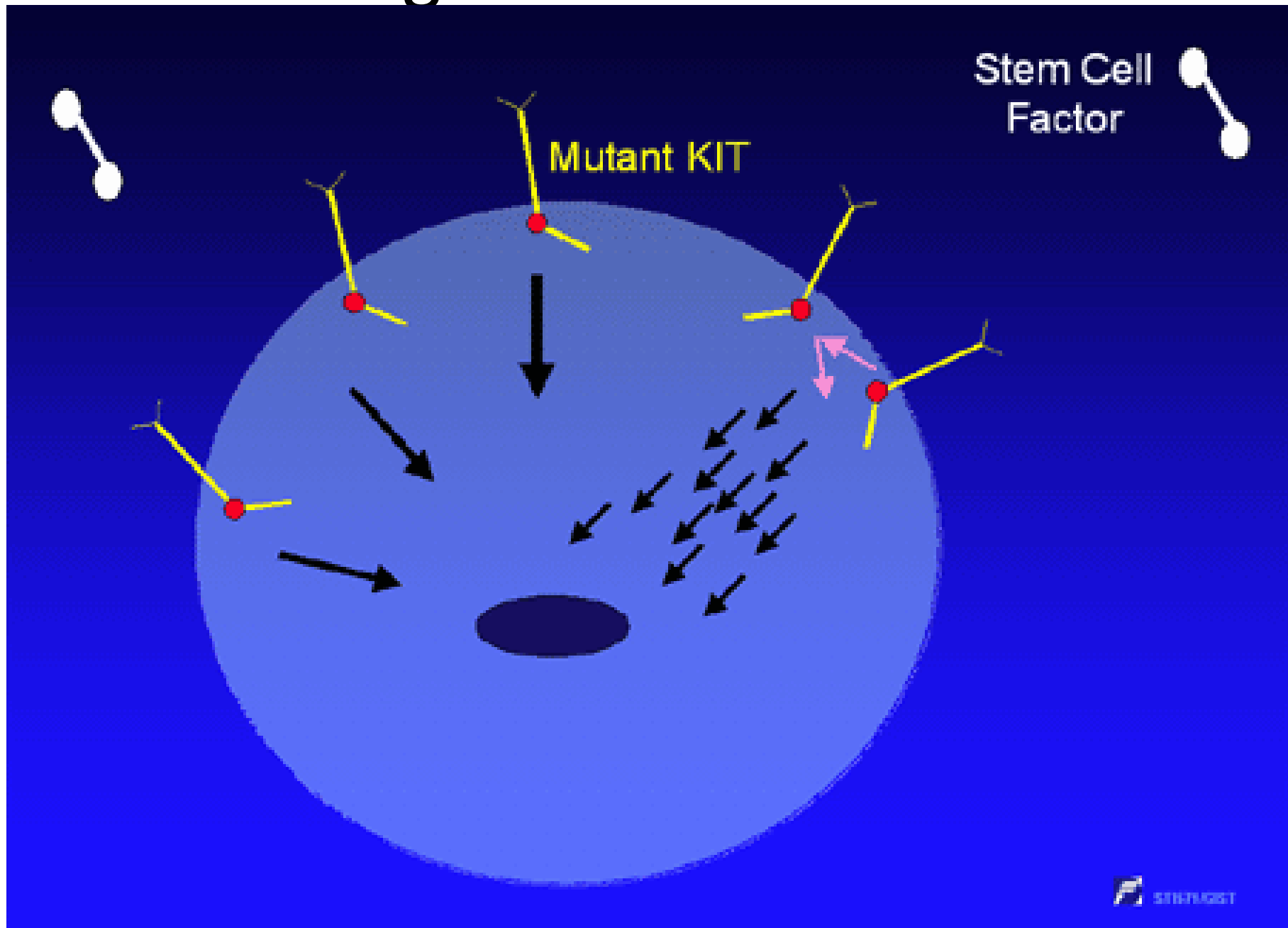
**and controls GIST**

**[Gastro Intestinal Stromal Tumor]**

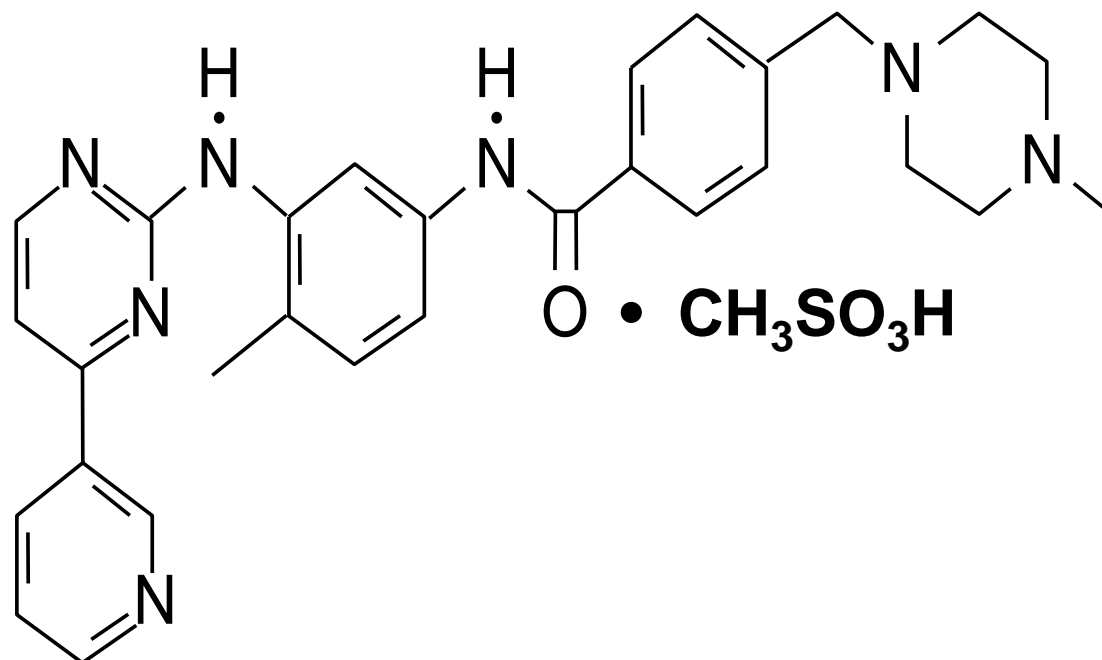
# Normal Stromal Cell



# Malignant Stromal Cell



# Structure of Imatinib

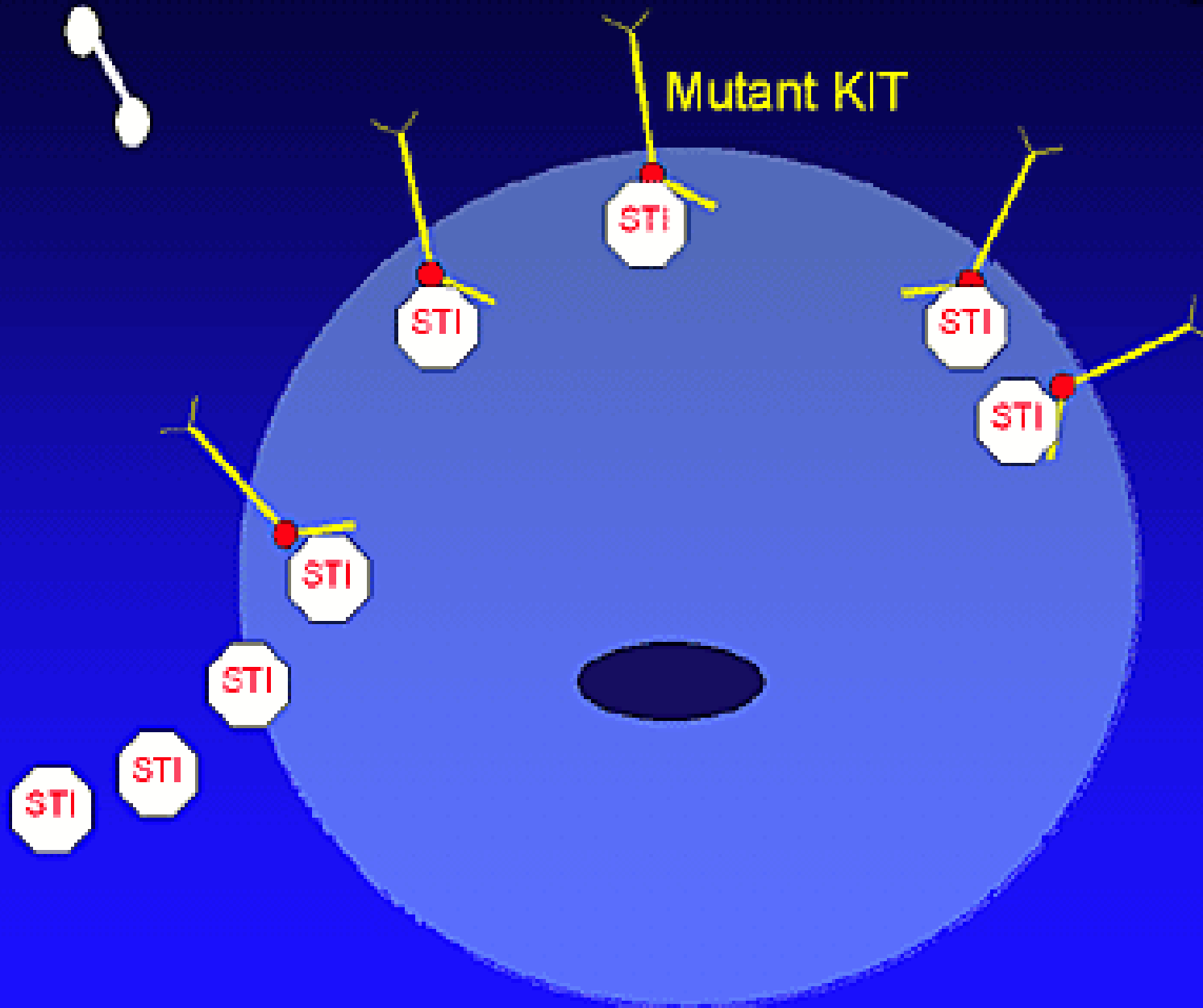


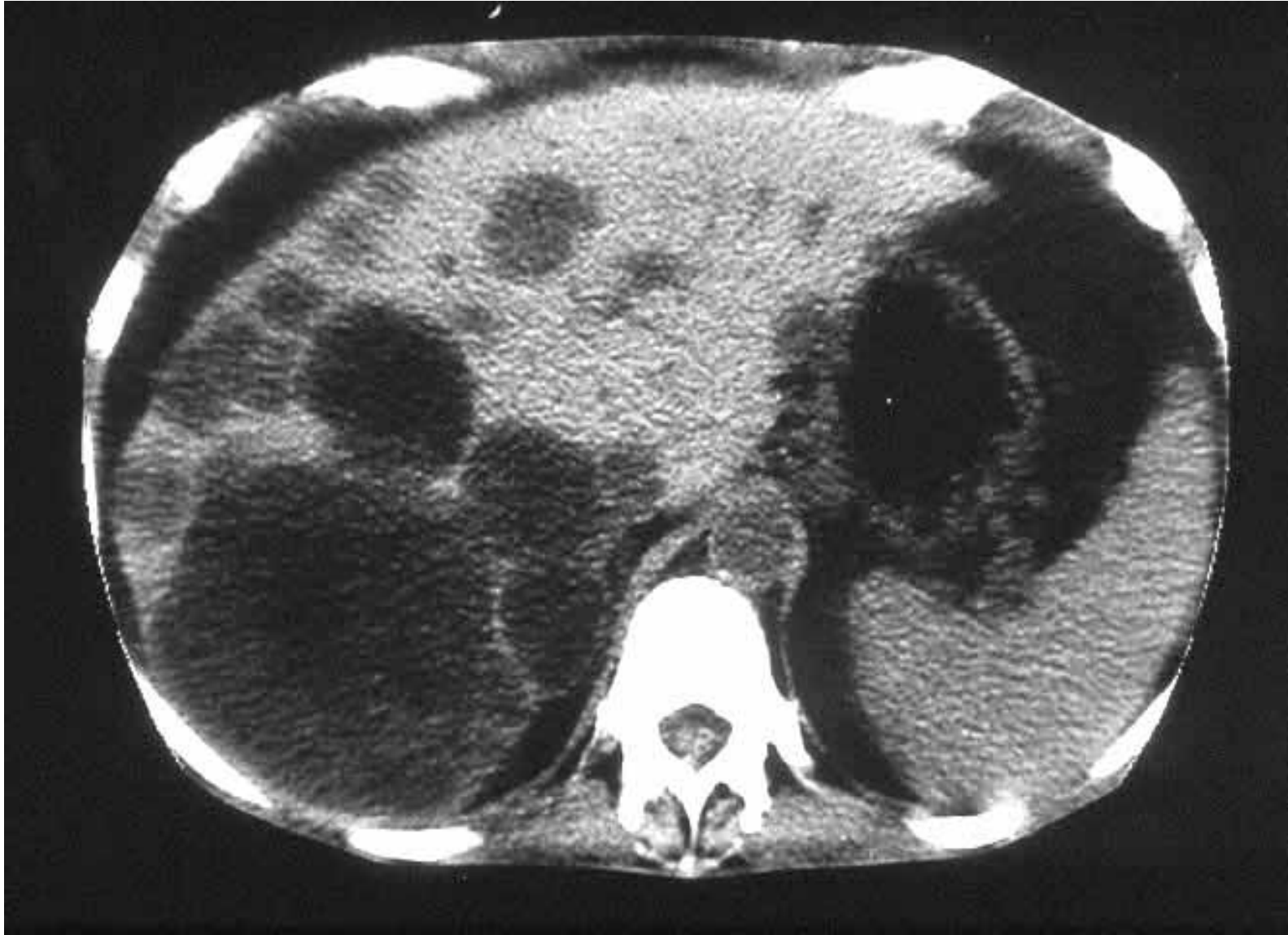
**Other names: STI, Glivec, Gleevec**



Stem Cell  
Factor

Mutant KIT



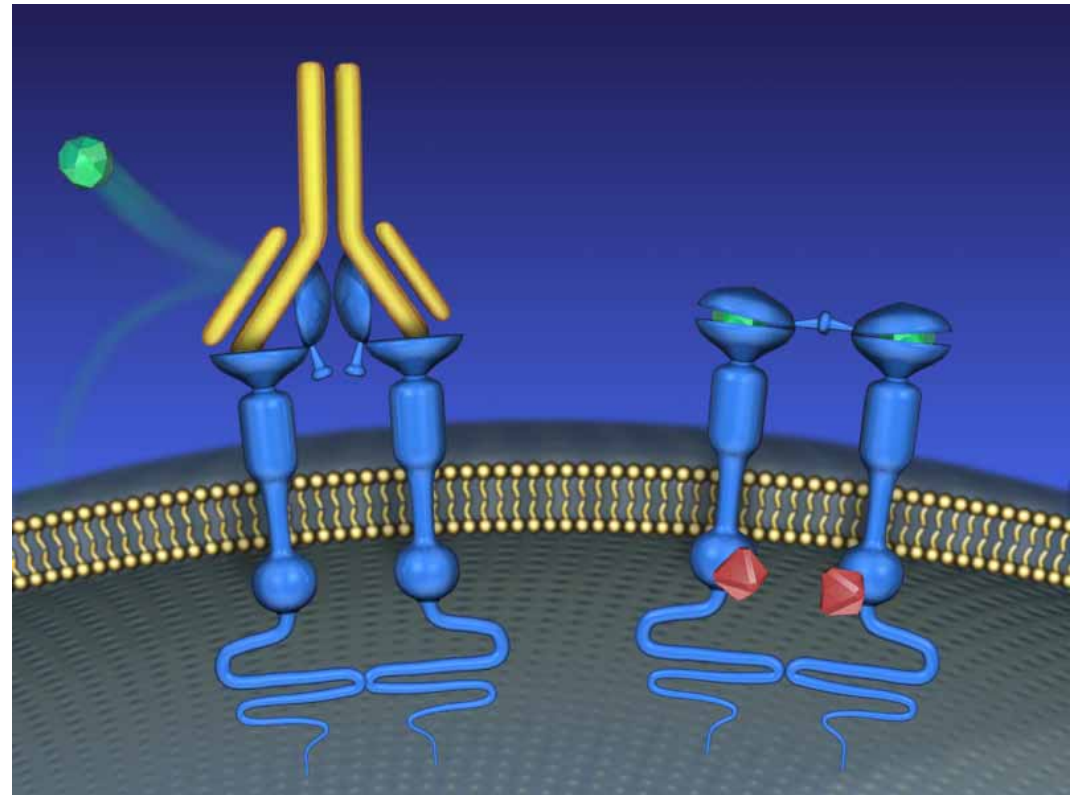




# Strategies for Oncogenic Receptor Inhibition

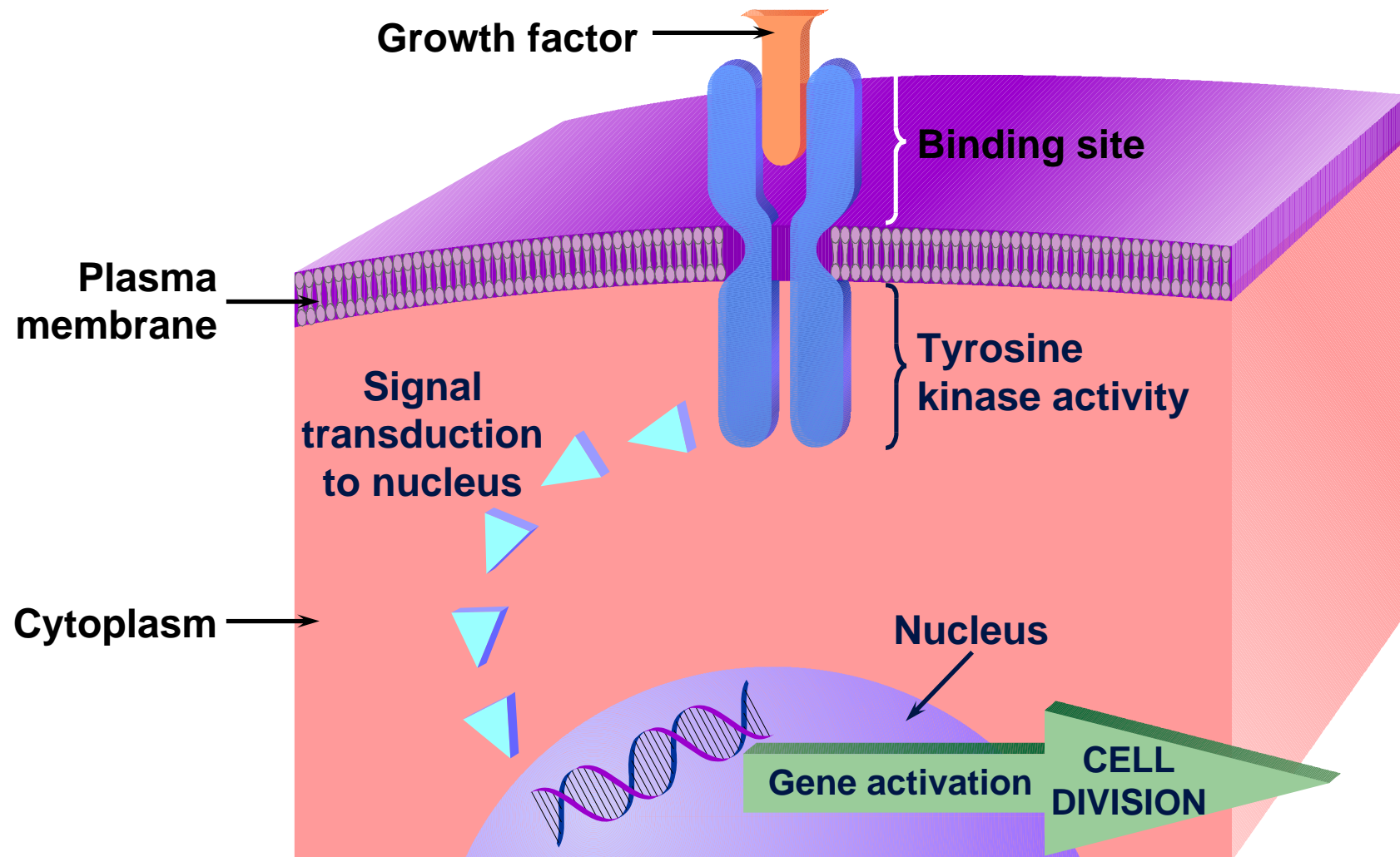
Monoclonal •  
antibodies (MAbs)  
against the  
receptors

Small-molecule •  
tyrosine kinase  
inhibitors  
(SMTKIs)

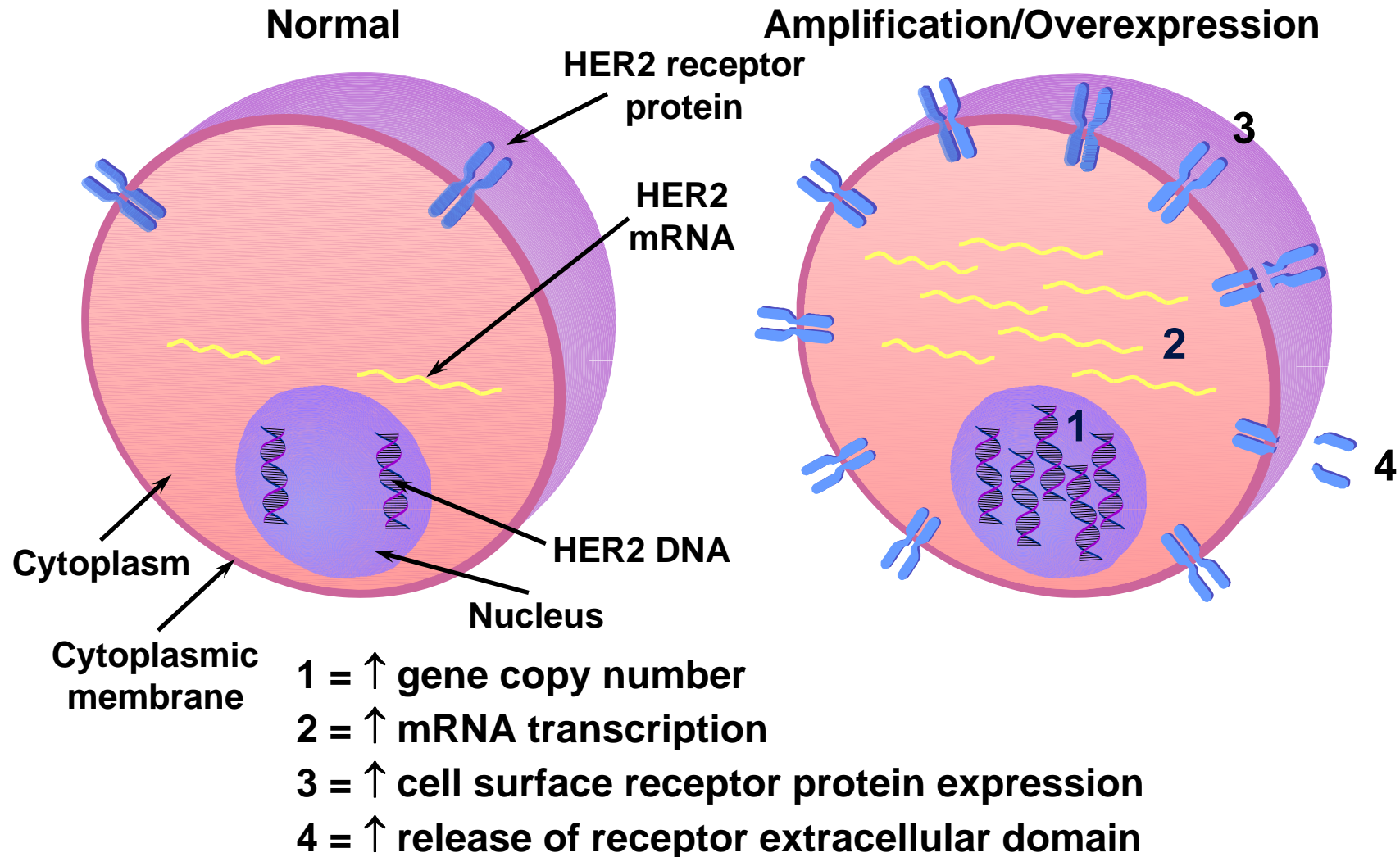




# HER2 receptor dimer transmembrane signal transduction pathway

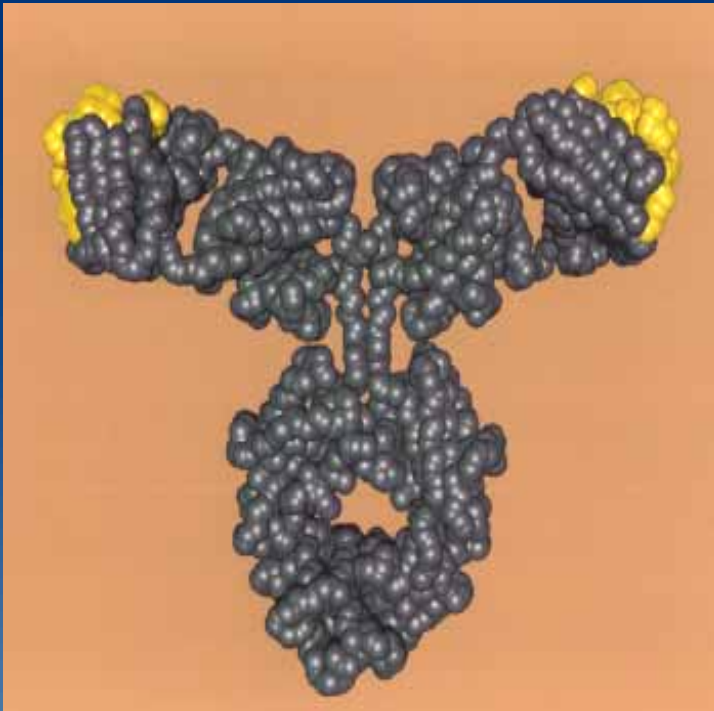


# Indicators of increased HER2 production



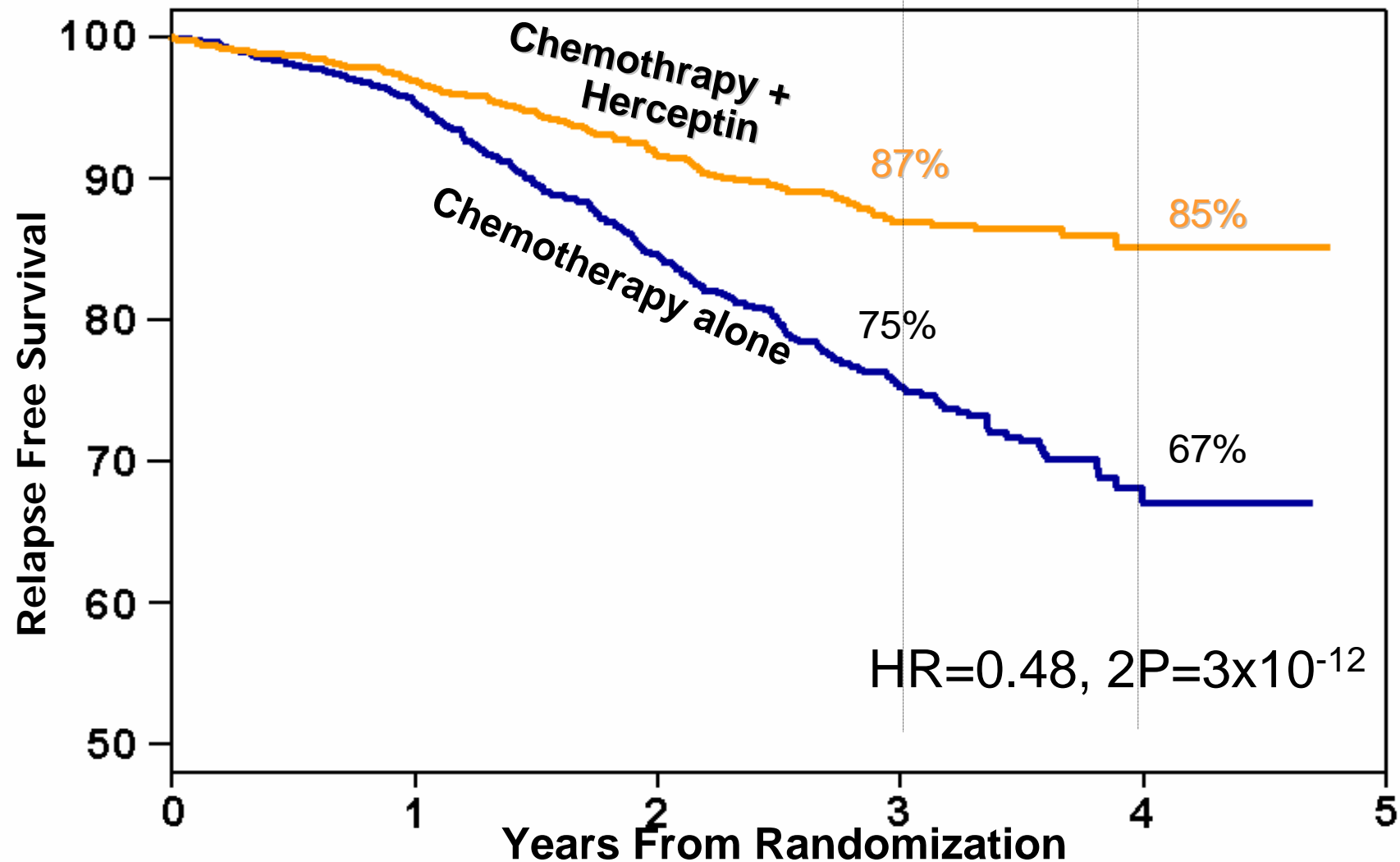
# Herceptin (trastuzumab) – humanised anti-HER2 monoclonal antibody

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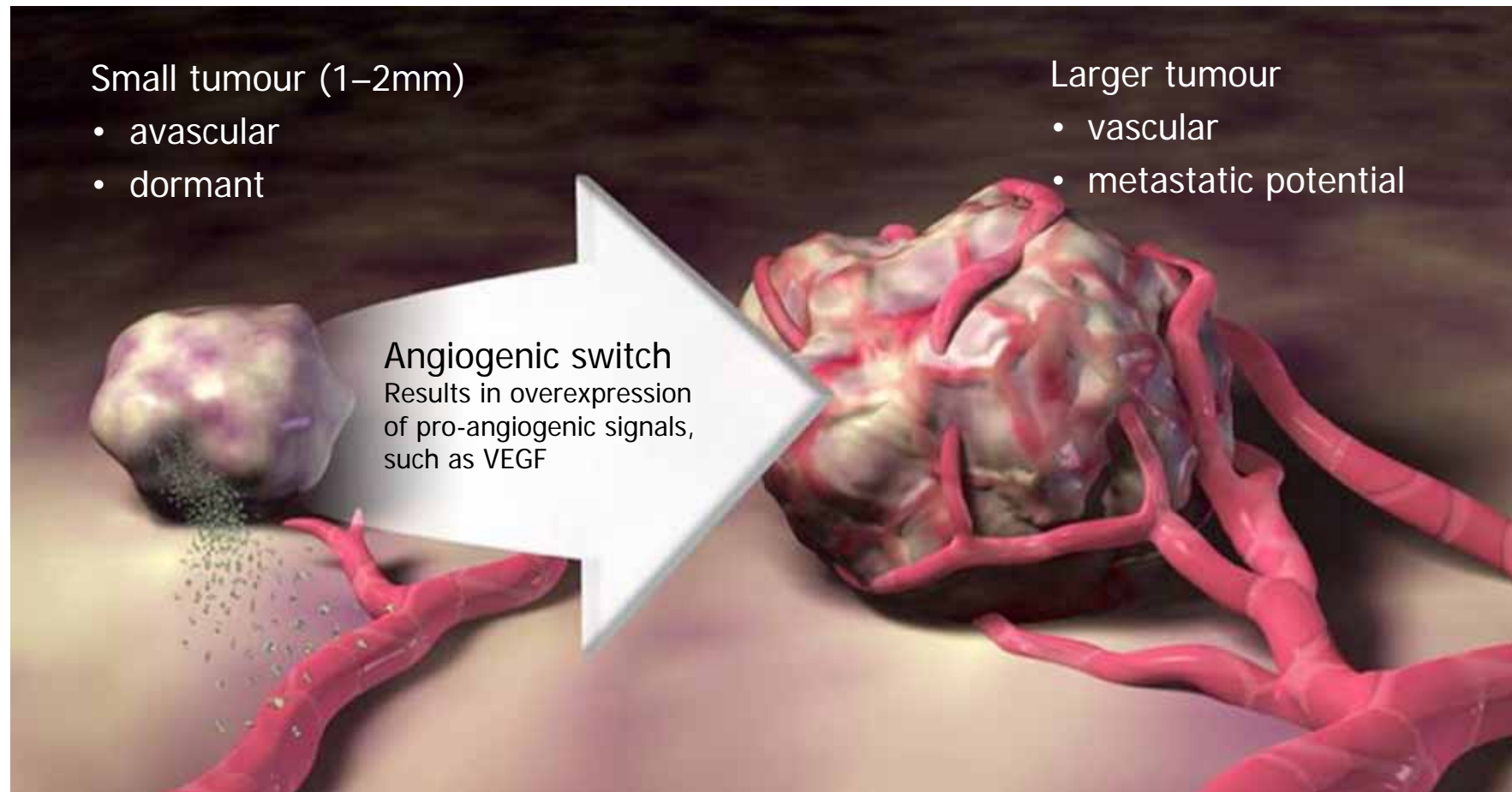
- High affinity ( $K_d=0.1\text{nM}$ ) and specificity
- 95% human, 5% murine --> decreased potential for immunogenicity

# Herceptin as Adjuvant Therapy



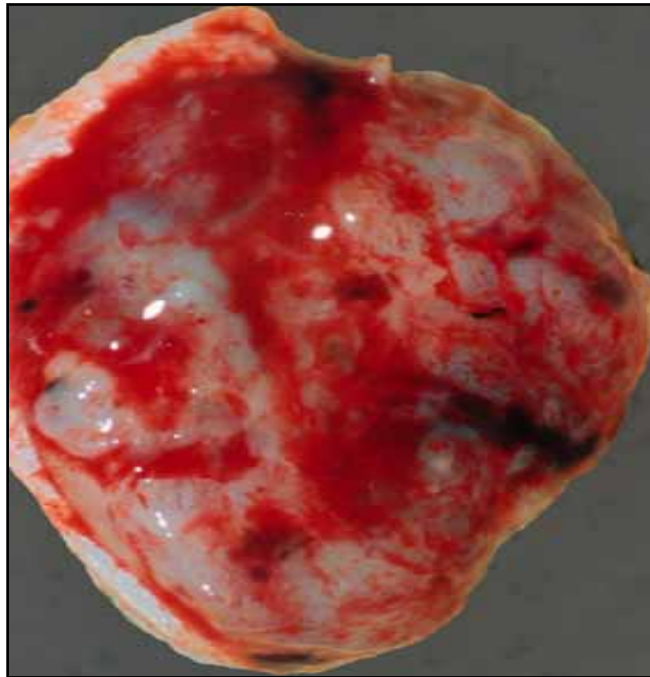


# The angiogenic switch in tumour development

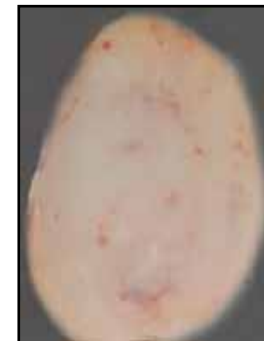


Adapted from Bergers G, et al. Nat Rev Cancer 2002;3:401–10

Anti-VEGF antibody prevents the growth of new tumour blood vessels



Control



Avastin

Presta LG, et al. Cancer Res 1997;57:4593-9

# New targeted antitumor therapy

- By definition, less toxic side effects.
- Commonly observed untoward effects: allergic reactions, edema, diarrhea, skin rash, hypertension.
- Can be administered for prolonged periods.
- Frequently available orally.
- Rarely cause significant tumor shrinkage.

# Evolution of Cancer Therapy

## Conventional chemotherapy

- Toxic
- Acute therapy
- Shrinkage of tumors

### Efficacy measured by:

Partial Response

Complete Response

Tumor markers

## Targeted Treatment

- Non-toxic
- Chronic treatment
- Tumor stabilization

### Efficacy measured by:

Disease free survival

Relapse free survival

Quality of Life

instruments