CANCER pathophysiology & treatment

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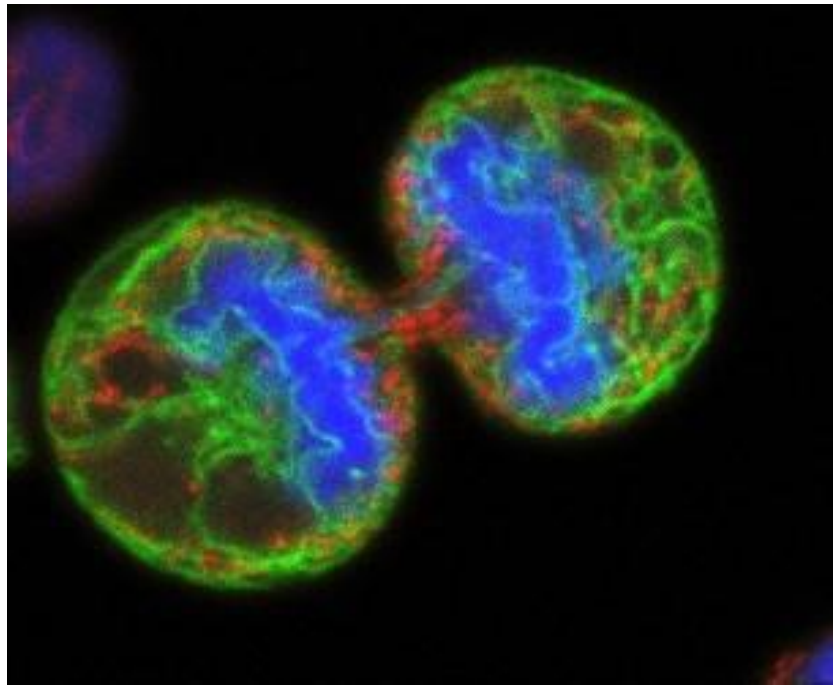
What is cancer?

- All cancers derive from single cells that have acquired the characteristics of continually dividing in an unrestrained manner and invading surrounding tissues.
- Cancer cells behave in this abnormal manner because of changes in the DNA sequence of key genes, which are known as cancer genes. Therefore all cancers are genetic diseases.



Human melanoma cell undergoing cell division
Credit: Paul Smith & Rachel Errington, Wellcome Images

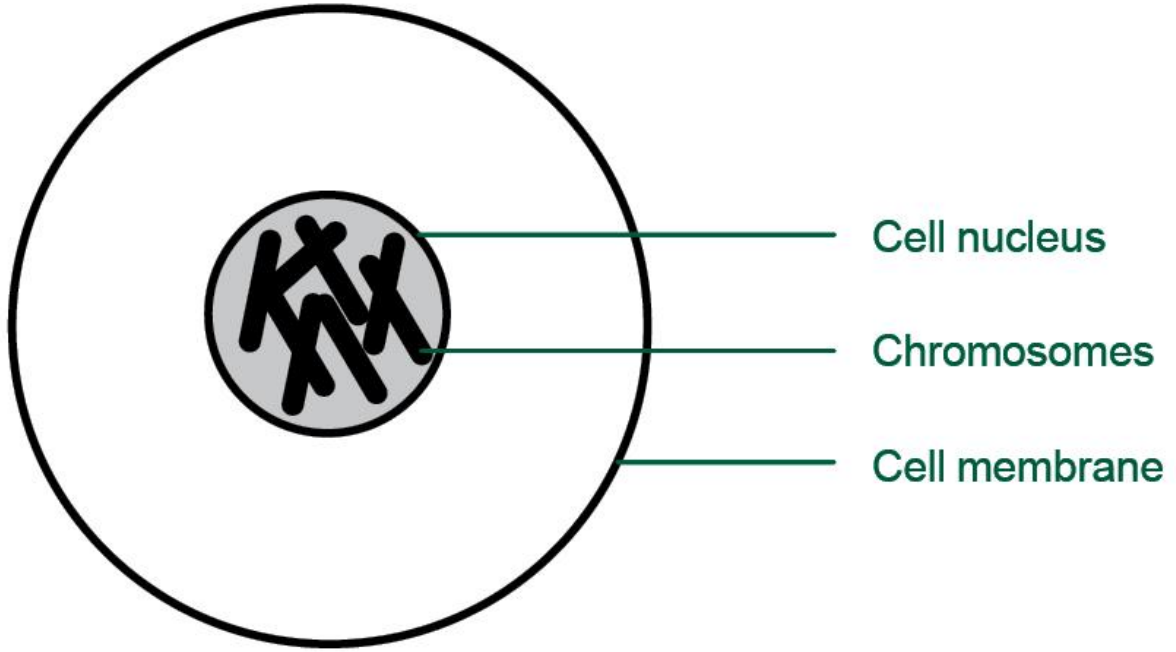
Pathophysiological characteristic of tumor

- Unlimition of growth
- Unregulation of growth
- Anaplasia of tumor cells

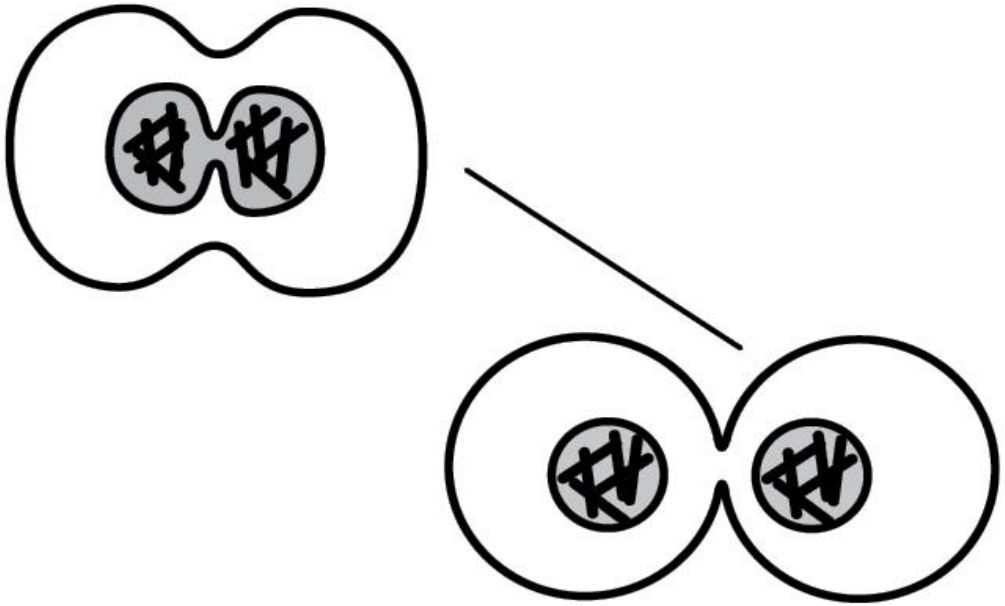
Cellular Kinetics

- Human body contains $5x10^{13}$ cells
- Cells can either be
  - non dividing and terminally differentiated
  - continually proliferating
  - rest but may be recruited into cell cycle
- Tumour becomes clinically detectable when there is a mass of 10^9 cells (1g)

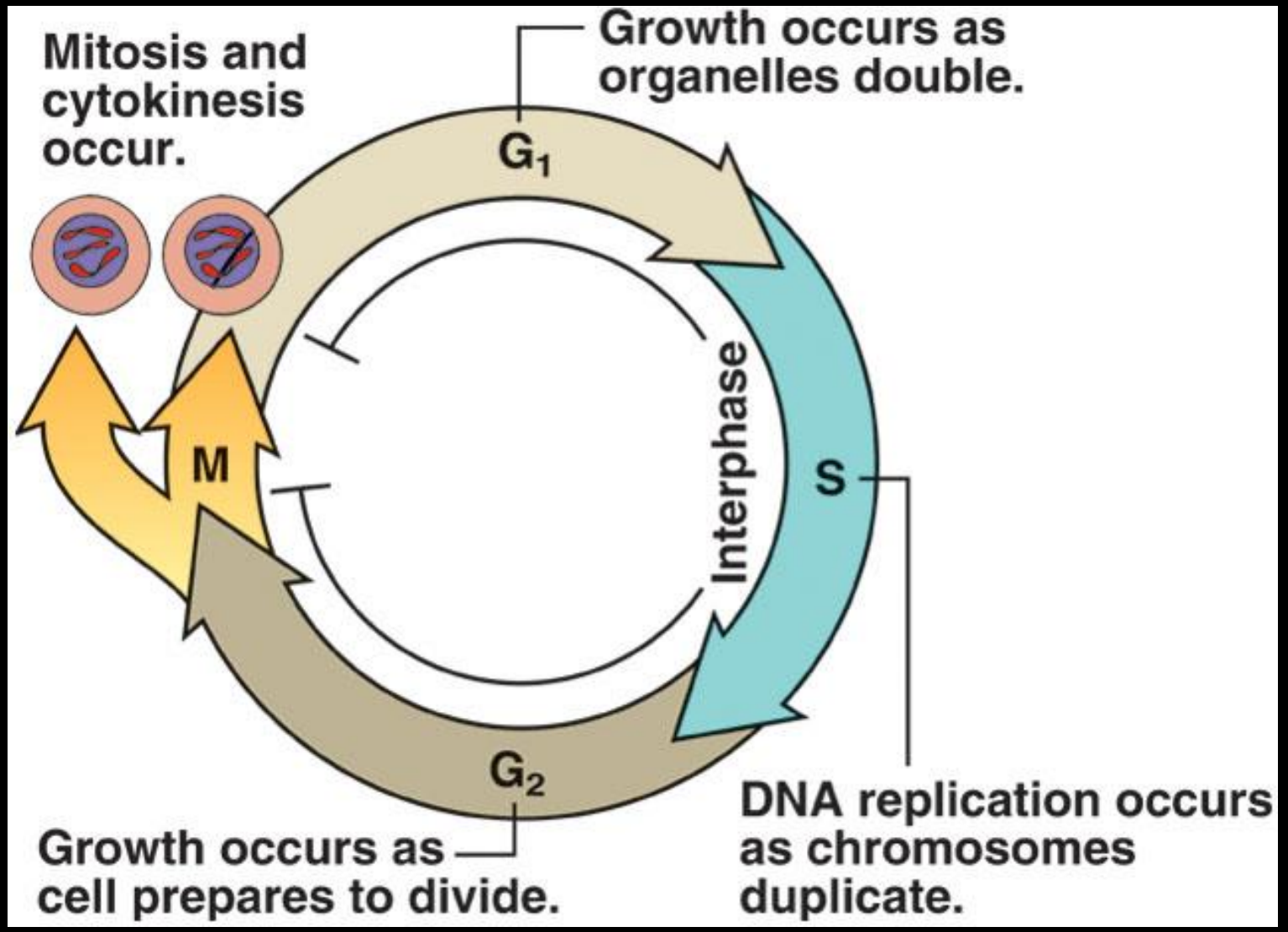
The normal cell



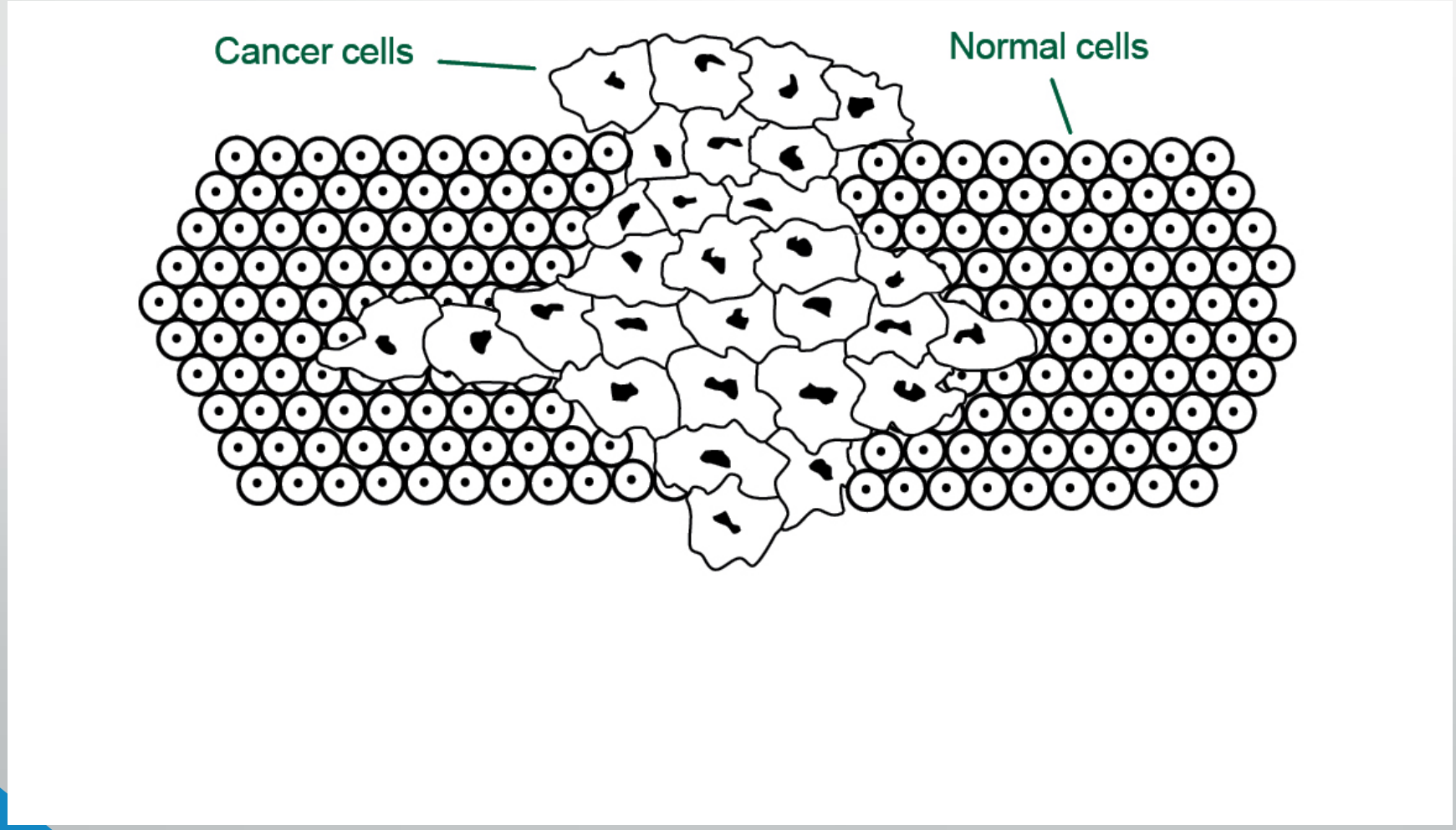
Normal cell dividing



The Cell Cycle



Uncontrolled cell growth



Differences between normal and cancer cells

Normal cells:

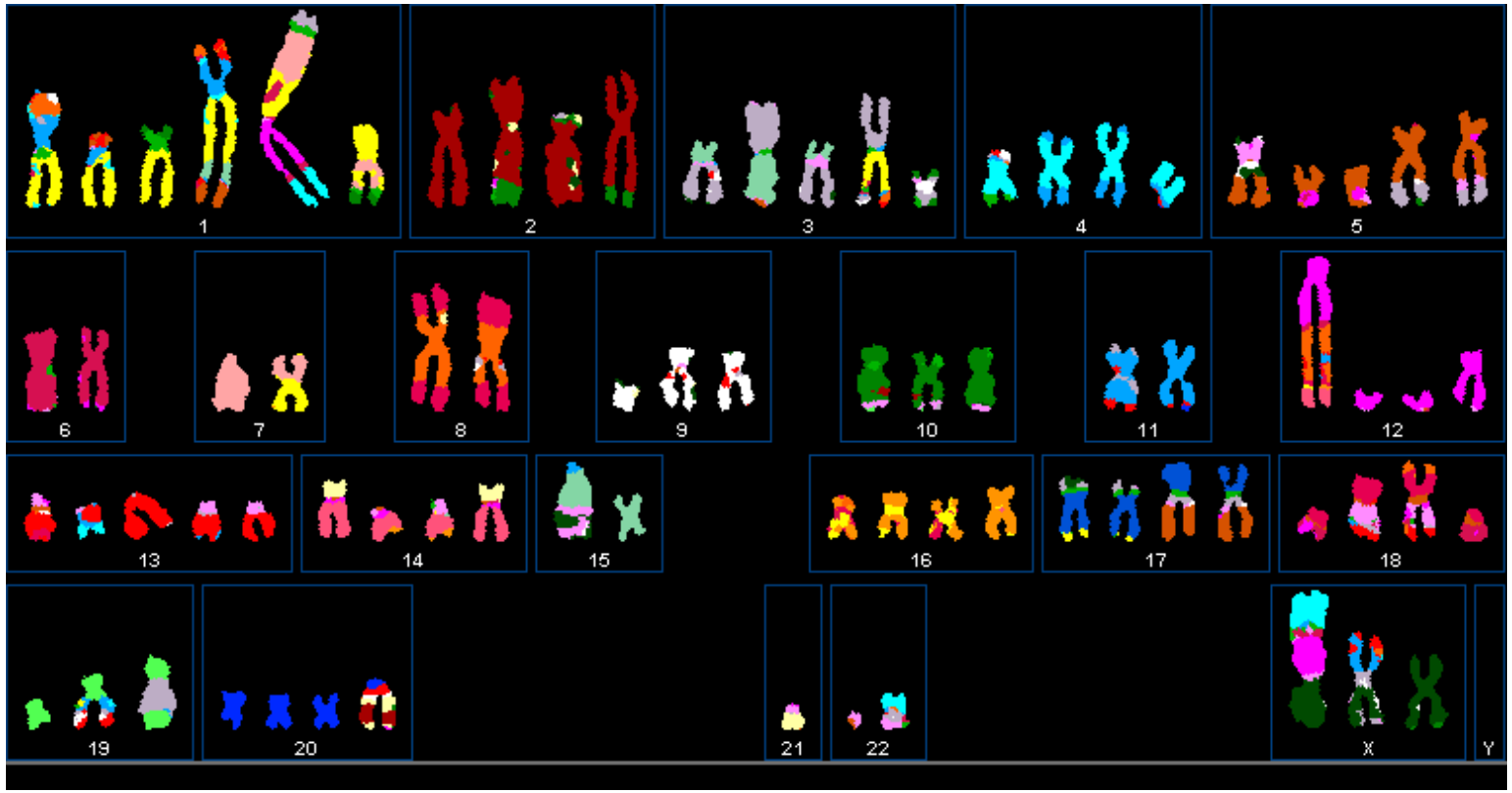
1. Regulated cell division
2. Programmed cell death
3. Respond to external growth and anti-growth signals
4. Balance between blood vessel development and cell need
5. No tissue invasion.

Cancer cells:

1. Unregulated cell division
2. Lack programmed cell death
3. Generate own growth signals and insensitive to antigrowth signals
4. New blood vessel growth
5. Tissue invasion and metastasis.

Cancer cells have altered genomes

Karyotype illustrating structural abnormalities in cancer



Credit : Mira Grigorova and Paul Edwards, Department of Pathology, University of Cambridge, unpublished
Source: www.path.cam.ac.uk/~pawefish/BreastCellLineDescriptions/HCC38.html

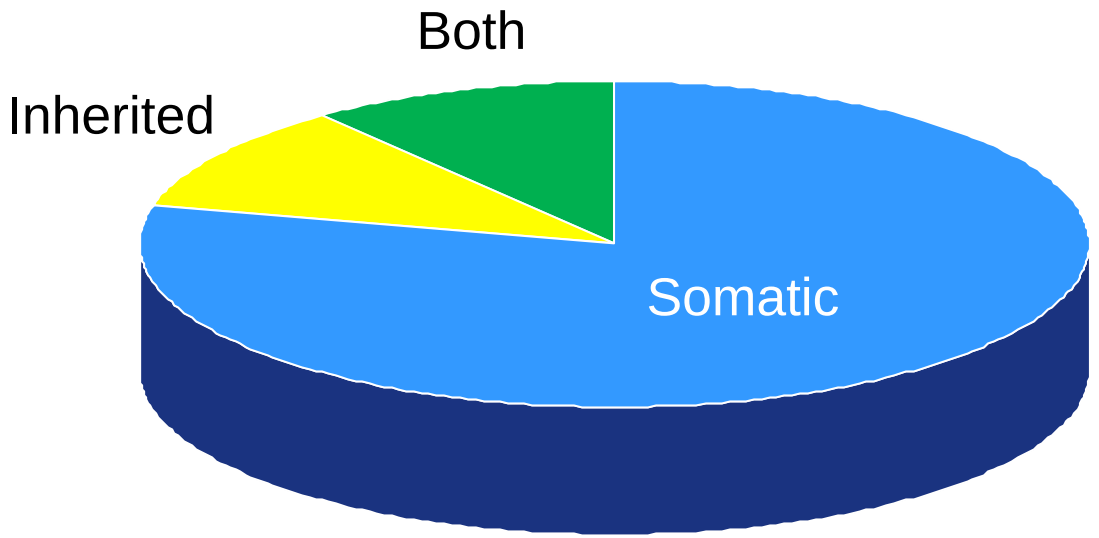
What is a mutation?

- **Germline mutation**
  - A change in the DNA sequence that can be inherited from either parent
- **Somatic mutation**
  - A change in the DNA sequence in cells other than sperm or egg
  - The mutation is present in the cancer cell and its offspring, but not in the patient's healthy cells

Mutations & cancer genes

- Cancer genes are causally implicated in *oncogenesis*
- Mutations in cancer genes can occur somatically or can be inherited.
- Mutations in some cancer genes can be inherited from parents, in which case they are present in every cell of the body. Such people are at a higher risk of developing cancer.
- Somatic mutations can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children.

Importance of somatic DNA changes in human cancer



Only 5 –10% of cancer cases have a clear hereditary component, e.g. *BRCA1* and *BRCA2* in breast cancer

Even in those cases where susceptibility is clearly inherited, somatic changes are required for cancer to develop

The first step in this process is *initiation*, which requires exposure of normal cells to carcinogenic substances.

Substances that may act as carcinogens or initiators include chemical, physical, and biologic agents

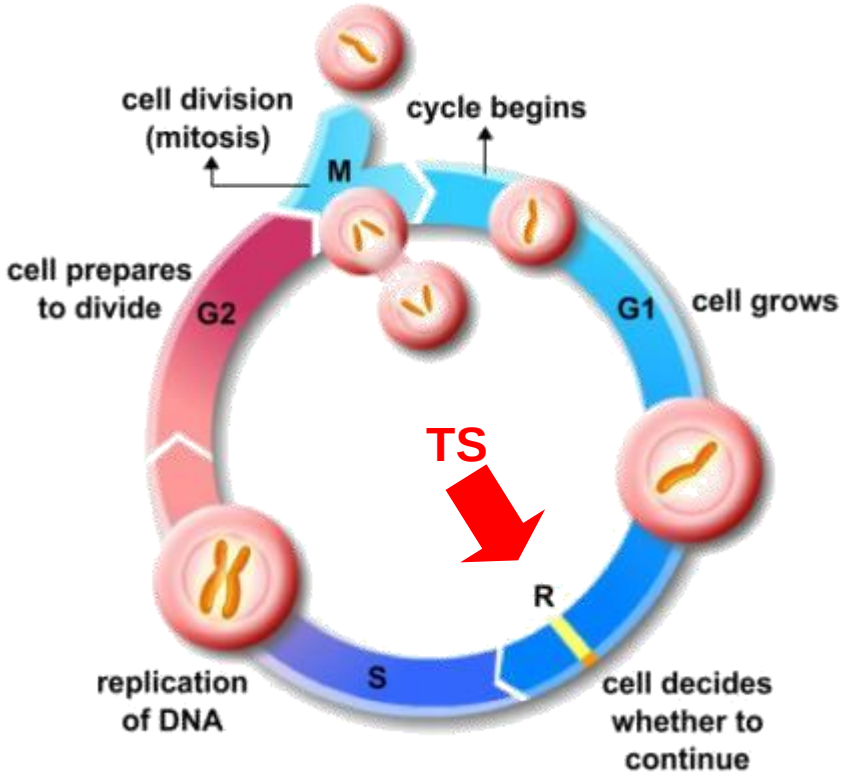
Two major classes of genes are involved in carcinogenesis: oncogenes and tumor suppressor genes

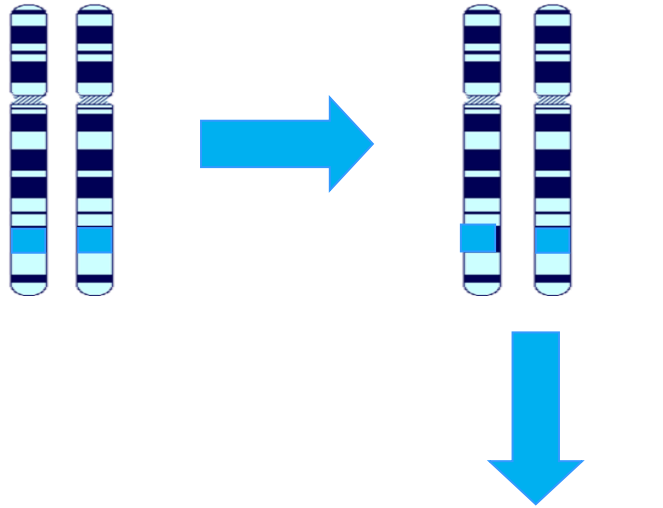
An important development in cancer research over the past decades has been the recognition that genetic changes drive the pathogenesis of tumors of both adulthood and childhood.

these alterations affect 3 principal categories of genes, as follows: proto-oncogenes, tumor suppressor genes, and DNA repair genes

Tumour suppressor gene

These genes normally function to PREVENT cell growth/division





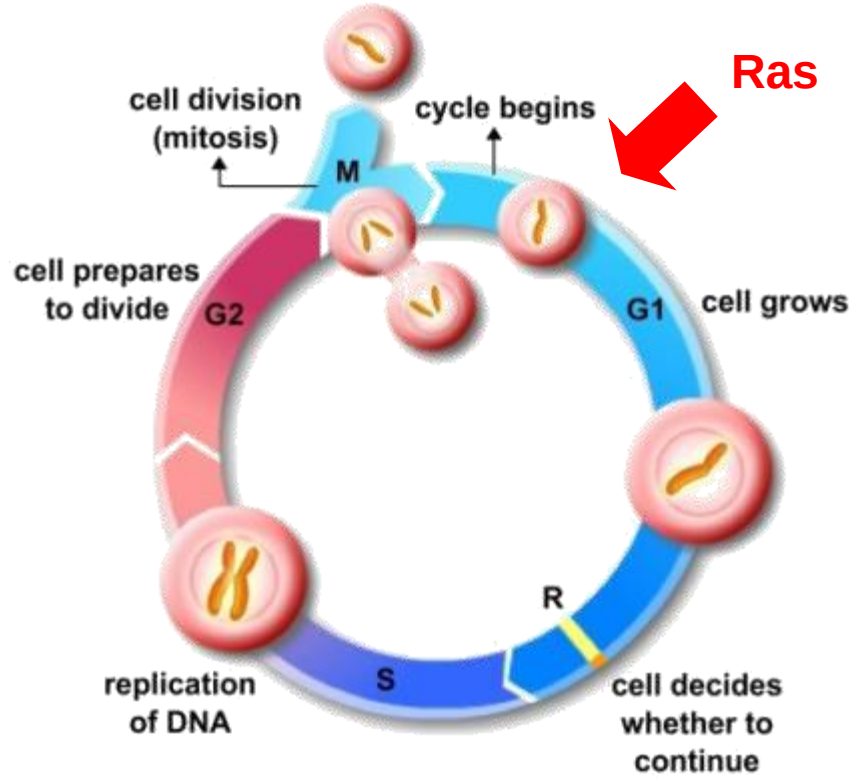
Cancer

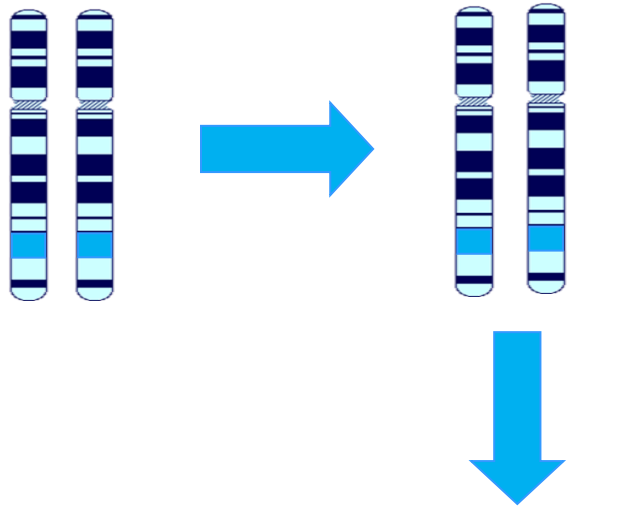
- Tumor suppressor genes (TSG) code for proteins that slow down cell growth. They can halt the cell growth cycle to stop unnecessary division or promote apoptosis (cell death) if the cell's DNA is damaged.

- Different tumor suppressor proteins carry out the following functions:
- Repression of genes which are essential to the cell cycle, therefore inhibiting cell division.
- Linking the cell cycle to DNA damage; if there is damage to the cell it will not allow it to divide.
- Identifying where the DNA damage is irreparable and initiating apoptosis (cell suicide).

Oncogene

Genes which normally function to PROMOTE cell growth/division in a controlled manner





Cancer

Examples of mutations

Sequence 1	Sequence 2	Type
ACTCGTTAGGCA	ACTCCTTAGGCA	Substitution
ACTCGTTAGGCA	ACTCGGCA	Deletion
ACTCGTTAGGCA	ACTCGTTATCAGGCA	Insertion
ACTCGTTAGGCA	ACTTTGCAGGCA	Inversion
ACTCGTTAGGCA	ACTCGTTAGTTAGGCA	Duplication

Activation of proto-oncogenes is a common theme in childhood leukemias and solid tumors.

Transcription factors (proteins that bind to the regulatory sequences of target genes) compose the largest class of oncogenes identified in pediatric tumors.

Bcr/abl & E2A-PBX1 …..

Oncogenes

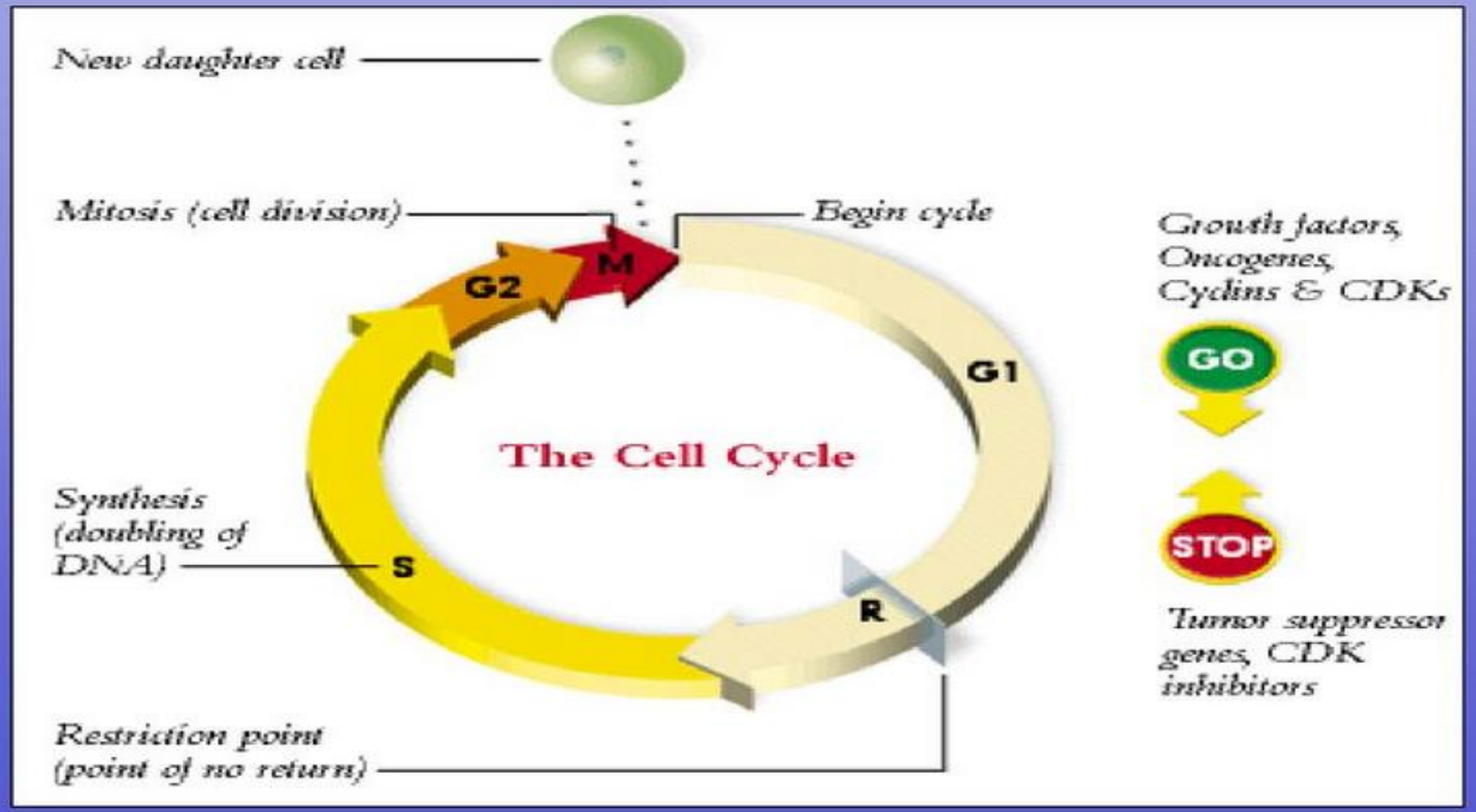
- Genes known as ***proto-oncogenes*** code for proteins that stimulate cell division
- mutated forms, called ***oncogenes,*** cause stimulatory proteins to be overactive, with the result that cells proliferate excessively

- gain of function mutations

Activation of proto-oncogenes

- Viral insertion
- Chromosomal rearrangements
  - Altered regulation
  - Fusion genes
- Gene amplification
- Point mutations
- Loss of degradation signals

Oncogenes and the cell cycle



Inactivation of tumor suppressor genes, whose products normally provide negative control of cell proliferation, contributes to malignant transformation in various cell types.

For example, the TP53 gene, located on chromosome 17, encodes a 53-kd nuclear protein that functions as a cell cycle checkpoint.

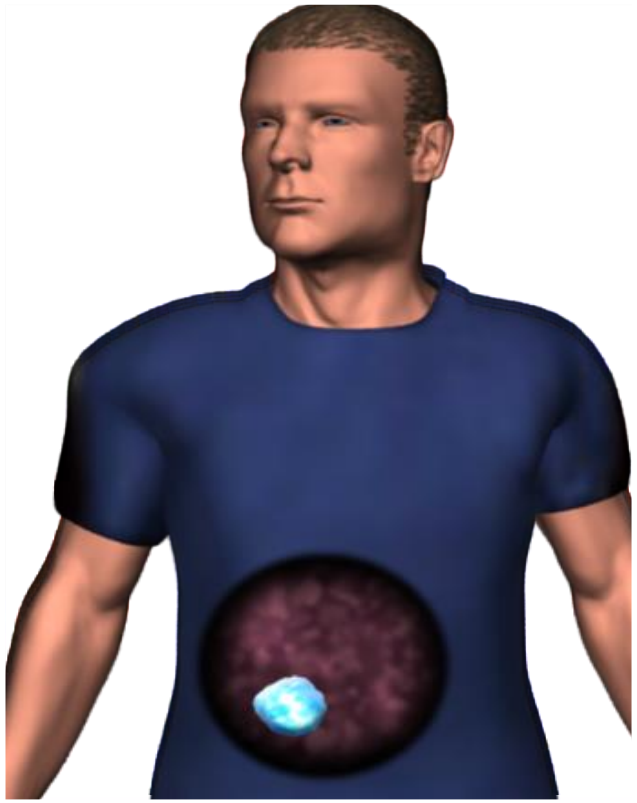
As a transcription factor whose expression is increased by DNA damage, p53 blocks cell division at the G1 phase of the cell cycle to allow DNA repair. The TP53 gene is also capable of stimulating apoptosis of cells containing damaged DNA.

Germline mutation of one TP53 allele is found in patients with Li-Fraumeni syndrome who generally inherit a mutated TP53 gene from an affected parent.

Patients with Li-Fraumeni syndrome are predisposed to sarcomas, breast cancer, brain tumors, adrenocortical cell carcinoma, and acute leukemia; they have a 50% probability of cancer development by age 30 years.

Cancer progression

Mutations in multiple cancer genes are required for the development and progression of a single cancer



Benign Tumour

In situ cancer

Invasive cancer

Metastatic cancer

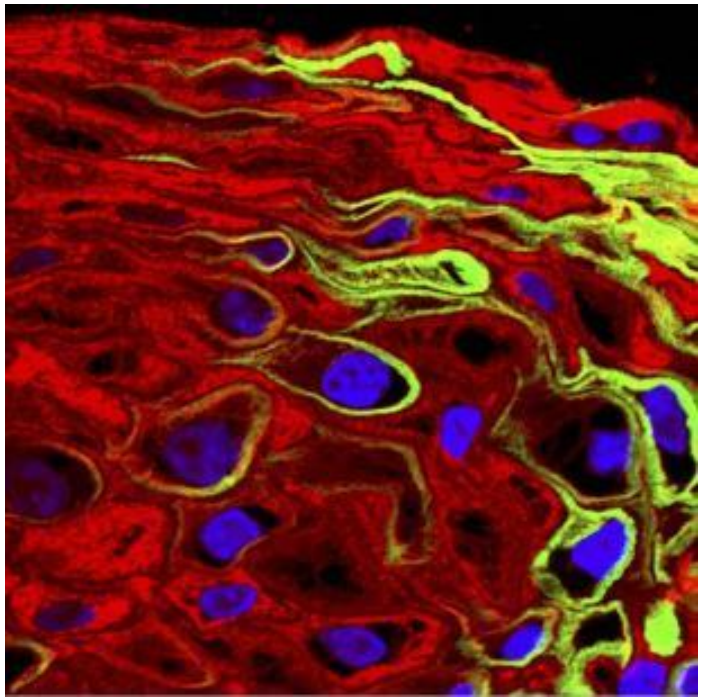
External causes of cancer: ultraviolet radiation

External causes of cancer: tobacco smoke

Lifestyle factor: diet

Biological factor: virus

- HPV is a cause of cervical cancer
- Proteins from the virus activate and deactivate cancer genes
- The role of HPV in cervical cancer has led to the development of vaccines



HPV in cervical epithelium
Credit: MRC NIMR, Wellcome Images

Pathology of cancer

Tumors may arise from any of four basic tissue types

- Epithelial tissue
- Connective tissue (Muscle, bone, and cartilage)
- Lymphoid tissue
- Nerve tissue

Malignant cells are divided into those of epithelial origin or the other tissue types.

- Carcinomas are malignant growths arising from epithelial cells.
- Sarcomas are malignant growths of muscle or connective tissue.
- Adenocarcinoma is a malignant tumor arising from glandular tissue.

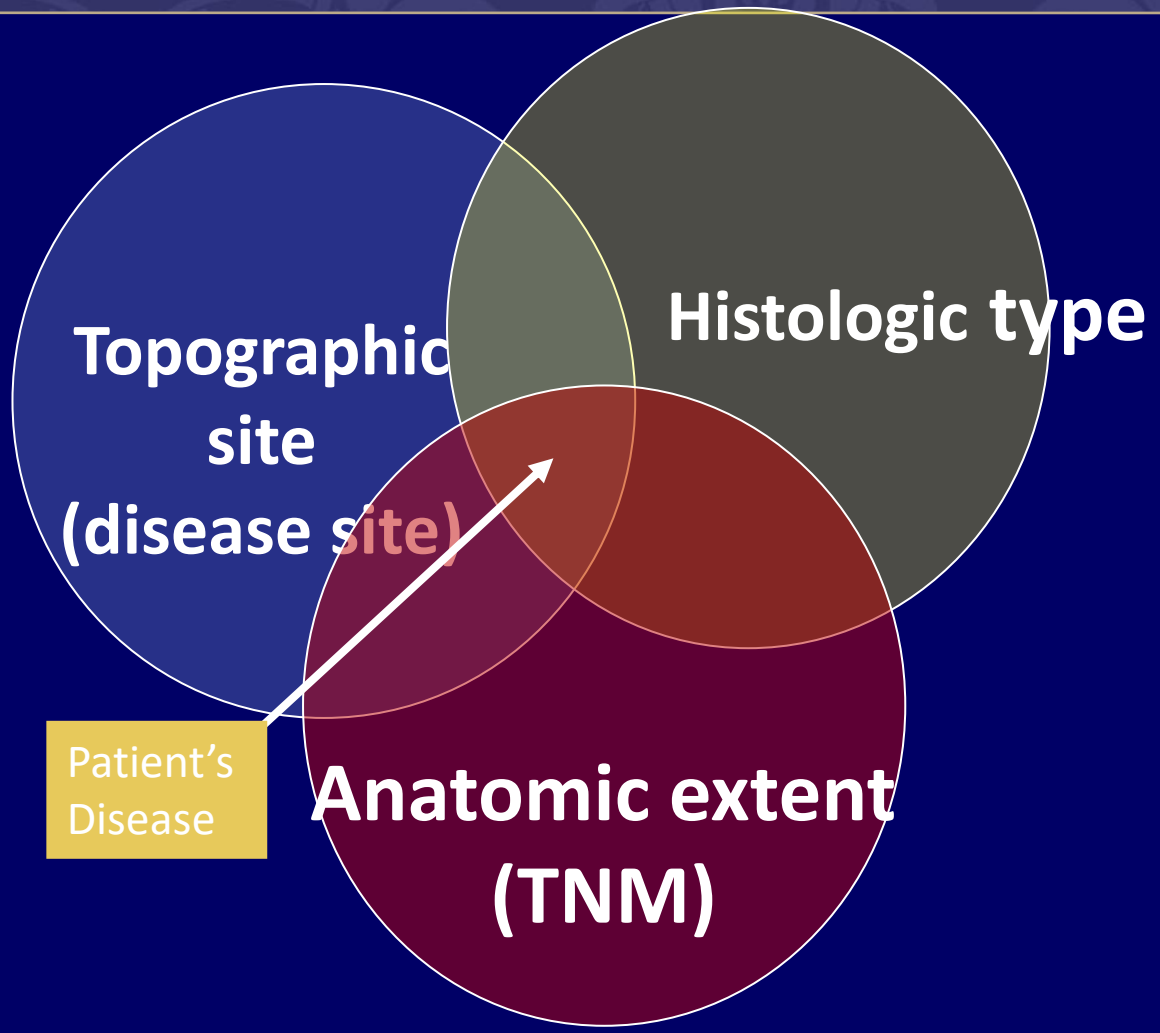
Tumor characteristics

- Invade and destroy the surrounding tissue.
- The cells are genetically unstable
- Loss of normal cell architecture results in cells that are atypical of their origin.
- Lose the ability to perform their usual functions.
- Metastasize, and consequently, recurrences are common after removal or destruction of the primary tumor.

THE THREE AXES OF CANCER CLASSIFICATION

- Topographic site
- Histology
- Anatomic extent

  (Staging)



Staging: Why?

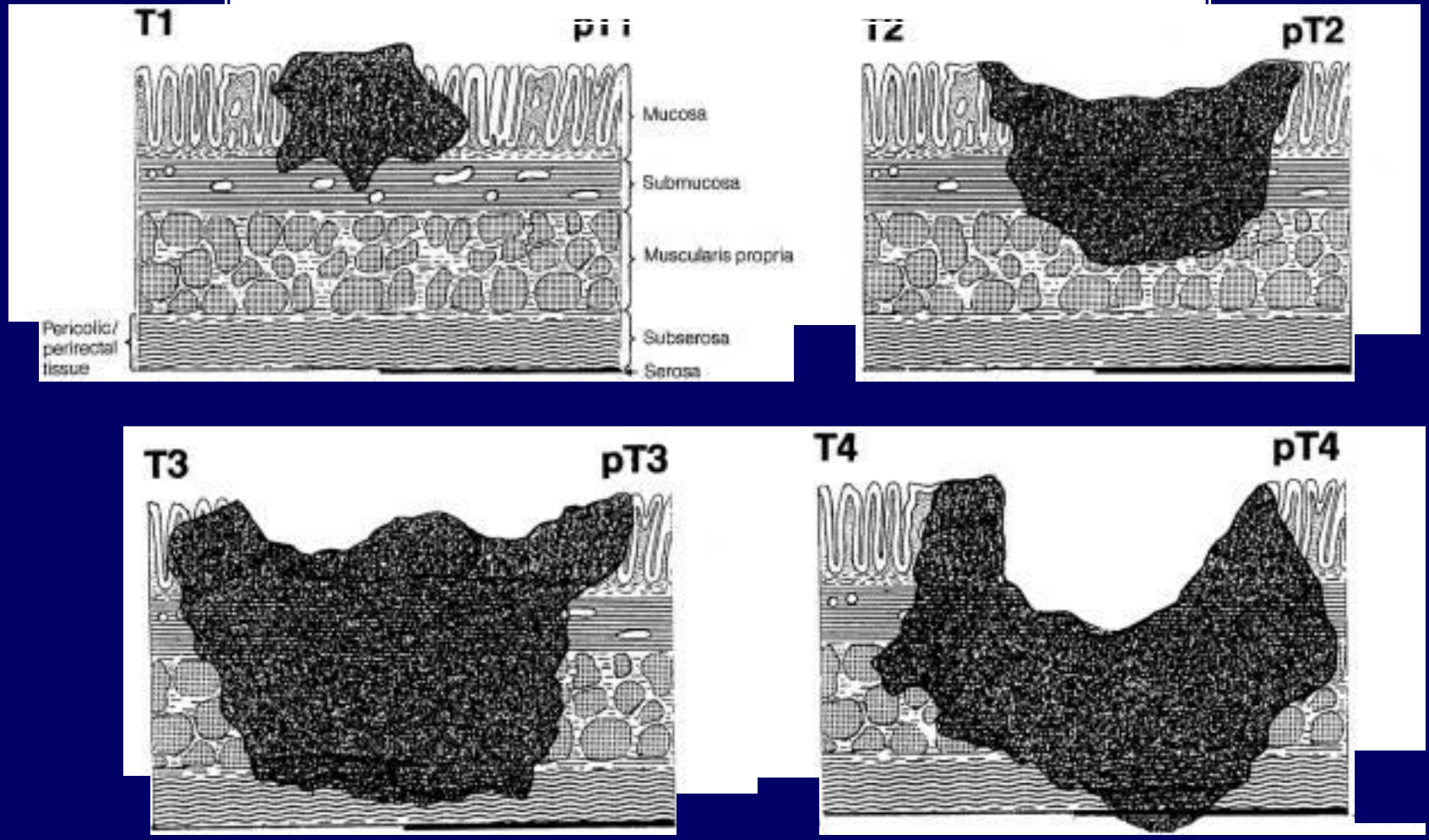
- To aid the clinician in planning treatment
- To give some indication of prognosis
- To assist in evaluating the results of treatment
- To facilitate the exchange of information between treatment centers
- To contribute to continuing investigations of human malignancies

ANATOMIC STAGING

Based on three components

T	**The extent of the primary tumor**
N	**The absence or presence and extent of regional lymph node metastasis**
M	**The absence or presence of distant metastasis**

TUMOR (T): COLORECTAL CANCER



NCCN Guidelines Version 1.2022
Colon Cancer

American Joint Committee on Cancer (AJCC) TNM Staging Classification for Colon Cancer 8th ed., 2017

Table 1. **Definitions for T, N, M**

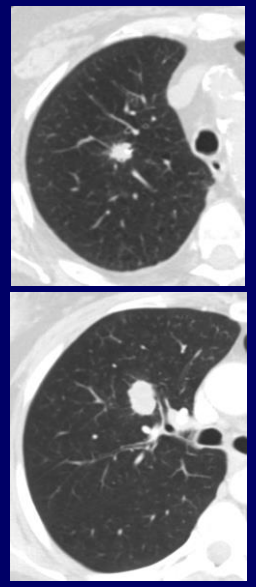
T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*: intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades* the visceral peritoneum or invades or adheres** to adjacent organ or structure
T4a	Tumor invades* through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades* or adheres** to adjacent organs or structures

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues
N2	Four or more regional lymph nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

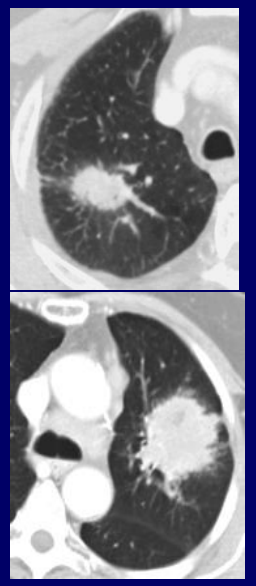
M	**Distant Metastasis**
M0	No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

* Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on

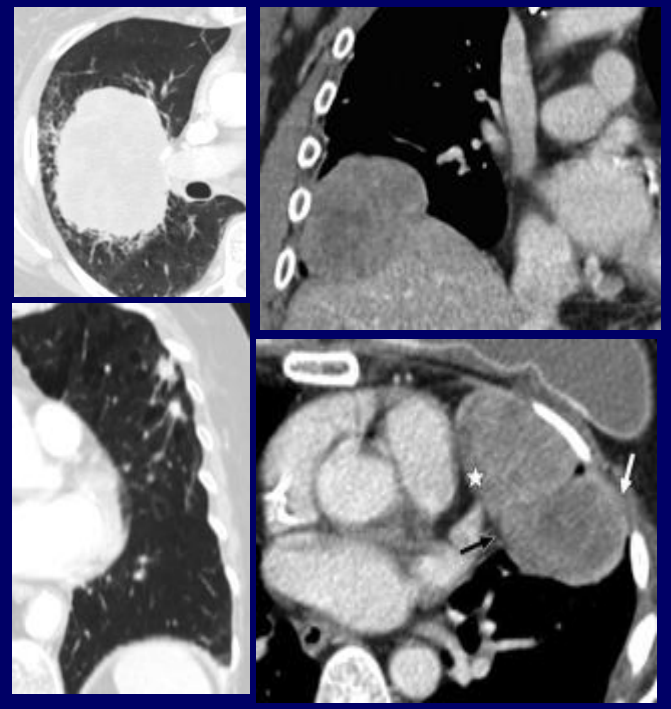
TUMOR (T): LUNG CANCER



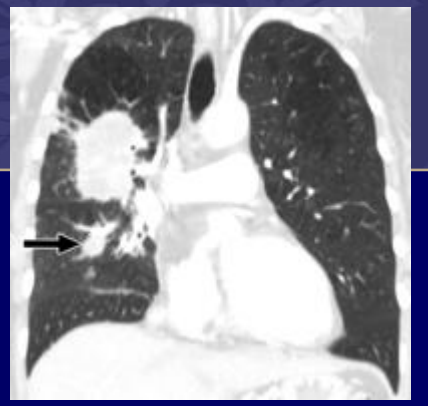
T1

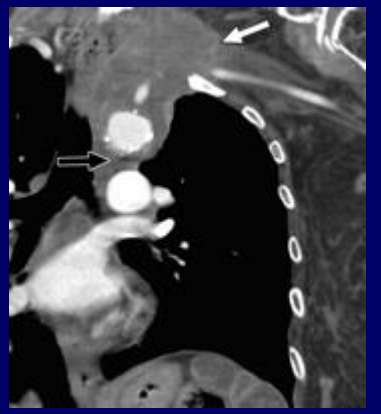


T2



T3





T4

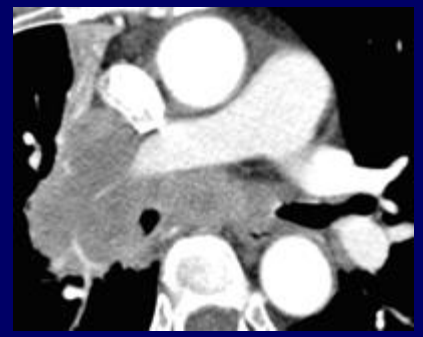


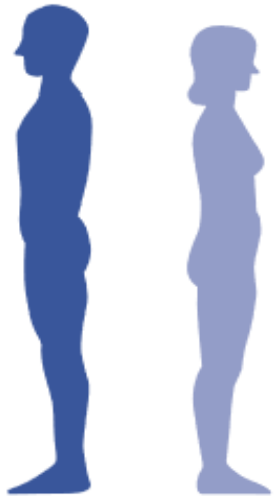
Table 1. **Definitions for T, N, M**

T		Primary Tumor
TX		Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0		No evidence of primary tumor
Tis		Carcinoma *in situ* Squamous cell carcinoma *in situ* (SCIS) Adenocarcinoma *in situ* (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
T1		Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
	T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension
	T1a	Tumor ≤1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.
	T1b	Tumor >1 cm but ≤2 cm in greatest dimension
	T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2		Tumor >3 cm but ≤5 cm or having any of the following features: (1) Involves the main bronchus, regardless of distance to the carina, but without involvement of the carina; (2) Invades visceral pleura (PL1 or PL2); (3) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
	T2a	Tumor >3 cm but ≤4 cm in greatest dimension
	T2b	Tumor >4 cm but ≤5 cm in greatest dimension
T3		Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
T4		Tumor >7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2022 Estimates

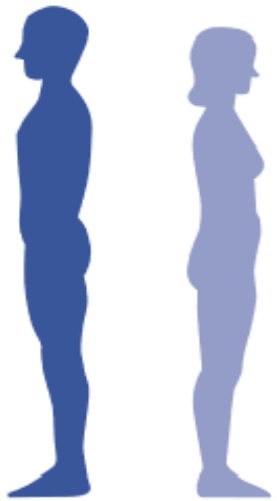
Estimated New Cases

Male			Female		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All sites	**983,160**		**All sites**	**934,870**	



Estimated Deaths

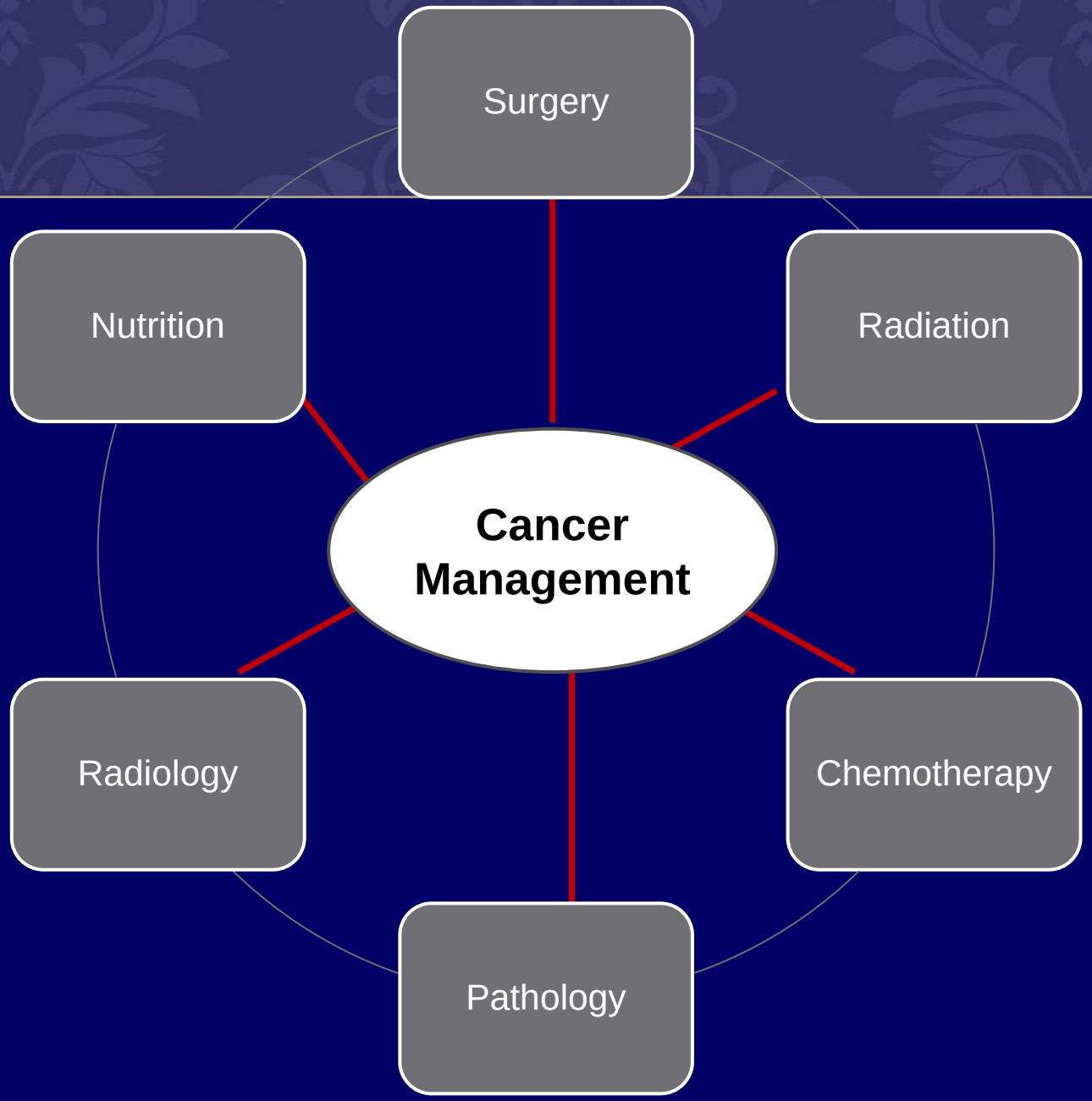
Male			Female		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All sites	**322,090**		**All sites**	**287,270**	



Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

MANAGEMENT

- Prevention
- Screening
- Diagnosis
- Treatment
- Rehabilitation
- Follow-up care
- Palliative care
- Terminal Care


Surgery
Nutrition
Radiation
Cancer Management
Radiology
Chemotherapy
Pathology

Goals of cancer treatment

1- Primary goal

Cure the patient

Render him clinically and pathologically free of disease and return their life expectancy to that of healthy individuals of the same age and sex.

Goals of cancer treatment

2- The best alternative goal

To prolong survival while maintaining the patient's functional status and quality of life.

3- The 3rd goal

Relieve symptoms such as pain for patients in whom the likelihood of cure or prolonged survival is very low

SURGERY

Long considered the most important aspect of cancer treatment for solid tumours

Controls the disease locally

May be curative for many tumours especially if caught early

RADIATION THERAPY

- Local therapy
- Causes DNA damage to cancer cells and leads to their death
- May be curative on its own

CHEMOTHERAPY

- Multitude of drugs developed to kill cancer cells
- DNA damage, RNA damage, inhibit cell growth and division, antimetabolites
- Can be used as sole modality for cure (hematologic malignancies) or as adjunct to either surgery or radiation to cure
- May also be given to incurable individuals to palliate

NEW PARADIGM OF TREATMENT

- Target unique proteins/genes/structures in cancer cells with novel agents
- Differential toxicity between the tumour cell and normal tissues
- More specificity for tumours makes cancer kill greater
- Combine newer treatments with traditional strategies
- Molecular profiling
    - Oncogenes, protooncogenes, apoptotic markers, cytogenetics

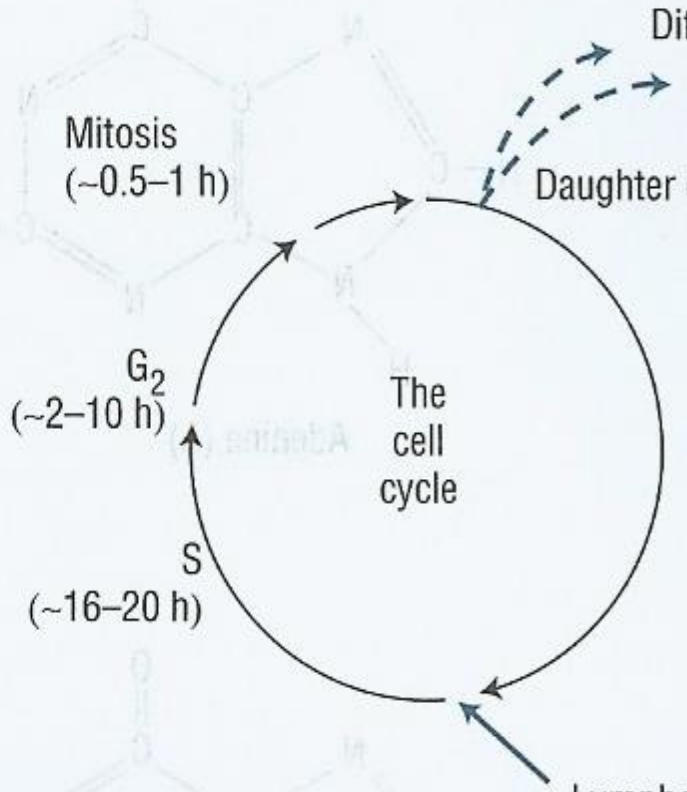
What is Chemotherapy?

- Medication given to treat cancer
- Systemic treatment
- Interfere with cancer cells' growth and replication
- Destroys the cancer cells

TYPES of CHEMOTHERAPY

- One or more drugs
- Intravenously or orally
- Determined by your cancer type
- Length of treatment may vary from minutes to hours; and can repeat daily, weekly, every 2-3 weeks or even monthly

1. Vinca alkaloids
   - Vincristine, vinblastine, vinorelbine
2. Taxanes
   - Paclitaxel, docetaxel



1. Bleomycin
2. Podophyllotoxins
   - Etoposide (VP-16)
   - Teniposide (VM-26)

Nitrosoureas
- Carmustine (BCNU)
- Lomustine (CCNU)

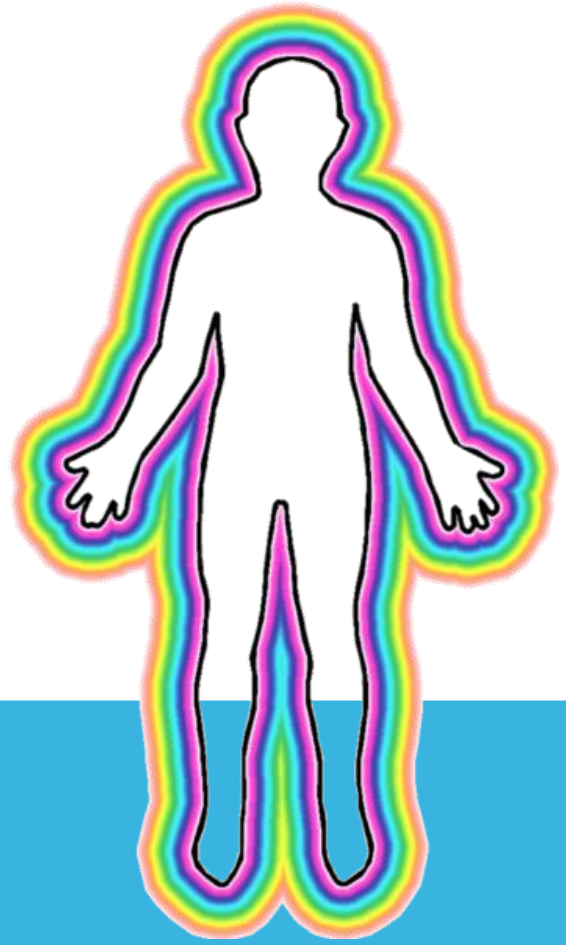
1. Steroids?
2. Asparaginase

Antimetabolites
1. Antifolates (methotrexate)
2. Antipyrimidines (cytarabine, fluorouracil, gemcitabine, capecitabine)
3. Antipurines (mercaptopurine, thioguanine, fludarabine, chlorodeoxyadenosine)
4. Miscellaneous (hydroxyurea, procarbazine)
5. Steroids? (also G_1)

Cell cycle (phase)–nonspecific agents
1. Classic alkylating agents (mechlorethamine, melphalan, busulfan, chlorambucil, cyclophosphamide, ifosfamide)
2. Anthracycline antibiotics (doxorubicin, daunorubicin, idarubicin)
3. Miscellaneous (dacarbazine, cisplatin, carboplatin)
4. Nitrosoureas (also G_0)
5. Mitomycin C
6. Dactinomycin

POSSIBLE SIDE EFFECTS

- Nausea
- Vomiting
- Diarrhea
- Constipation
- Mouth Sores
- Neuropathy
- Blood Clots
- Hair Loss



- Reduced Blood Cell Levels (Red Blood Cells, White Blood Cells, Platelets)
- Fatigue
- Fever
- Chemo “brain”/fog

REMEMBER…

- Response is individual
- Side effects vary from person to person
- Side effects vary with different drugs
- The chemotherapy is working even if you have no ill effects
- Do not compare yourself to others

NAUSEA

- ✓ Use anti-nausea medication as prescribed
- ✓ Sit upright after eating
- ✓ Eat small amounts more often
- ✓ Salty foods, crackers and dry toast may help
- ✓ Fresh air & exercise
- ✓ Avoid high acid and spicy foods

VOMITING

- ✓ It is safe to repeat your anti-nausea medication if you throw up within 1 hour of taking it
- ✓ If it’s more than 1 hour, wait until the next dose is due before taking more
- ✓ Call the Cancer Clinic if vomiting lasts longer than 24 hours

MOUTH SORES

- ✓ Can occur in the mouth and on lips
- ✓ Can be very painful
- ✓ Makes eating and drinking difficult
- ✓ “Thrush” can also occur
- ✓ Call Cancer Clinic right away

PREVENTING MOUTH SORES

- ✓ Frequent rinsing
- ✓ Rinse mouth with baking soda and water or salt and water 3 – 4 times/day
- ✓ Remove dentures
- ✓ Avoid alcohol-containing commercial mouthwashes
- ✓ Drink lots of fluids
- ✓ Avoid spicy and acidic foods

TREATING MOUTH SORES

- ✓ Soft foods, high in calories and protein
- ✓ Yogurt, pudding, milkshakes, custard, watermelon
- ✓ Medication can be prescribed

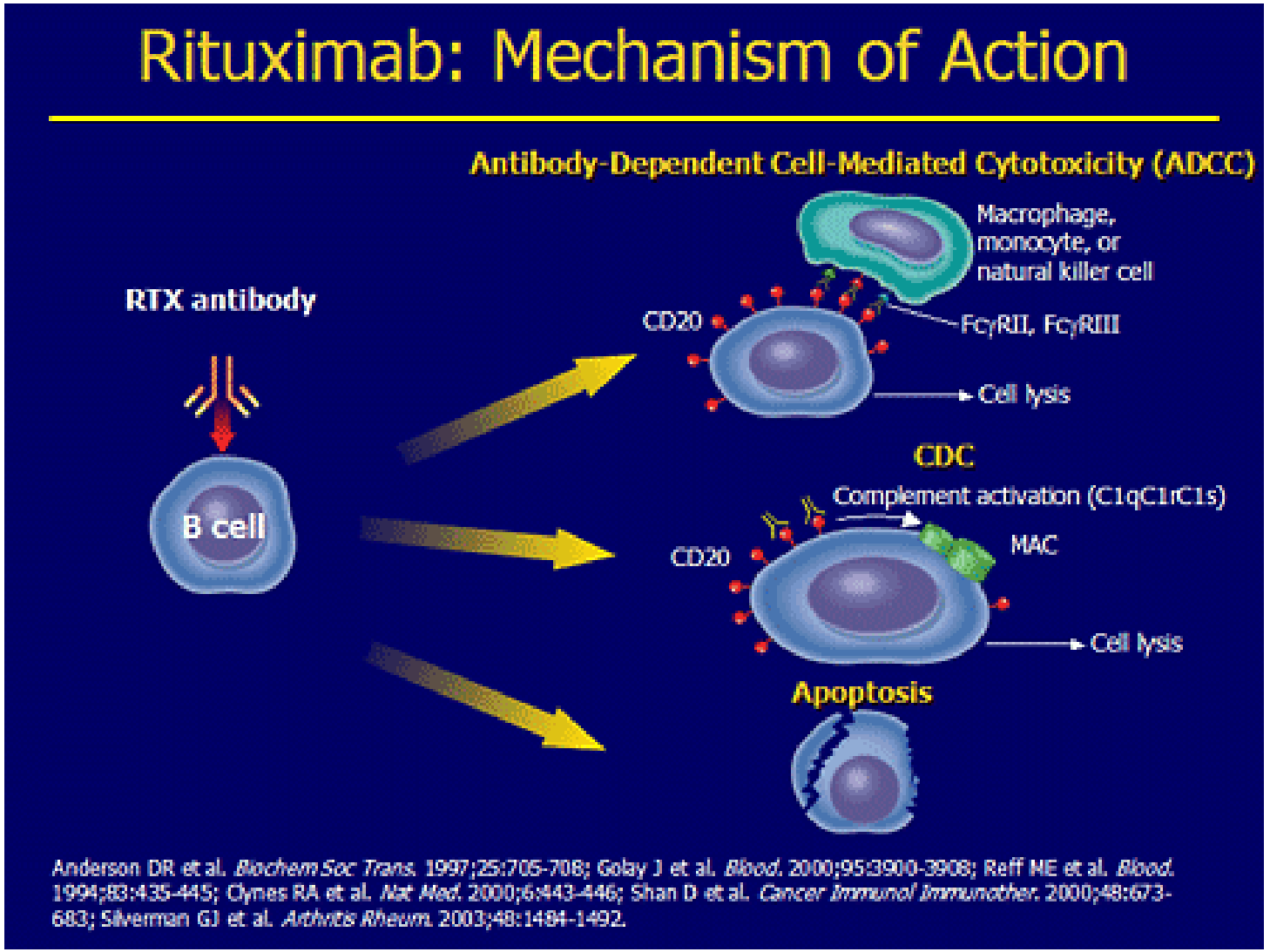
Targeted Therapies!

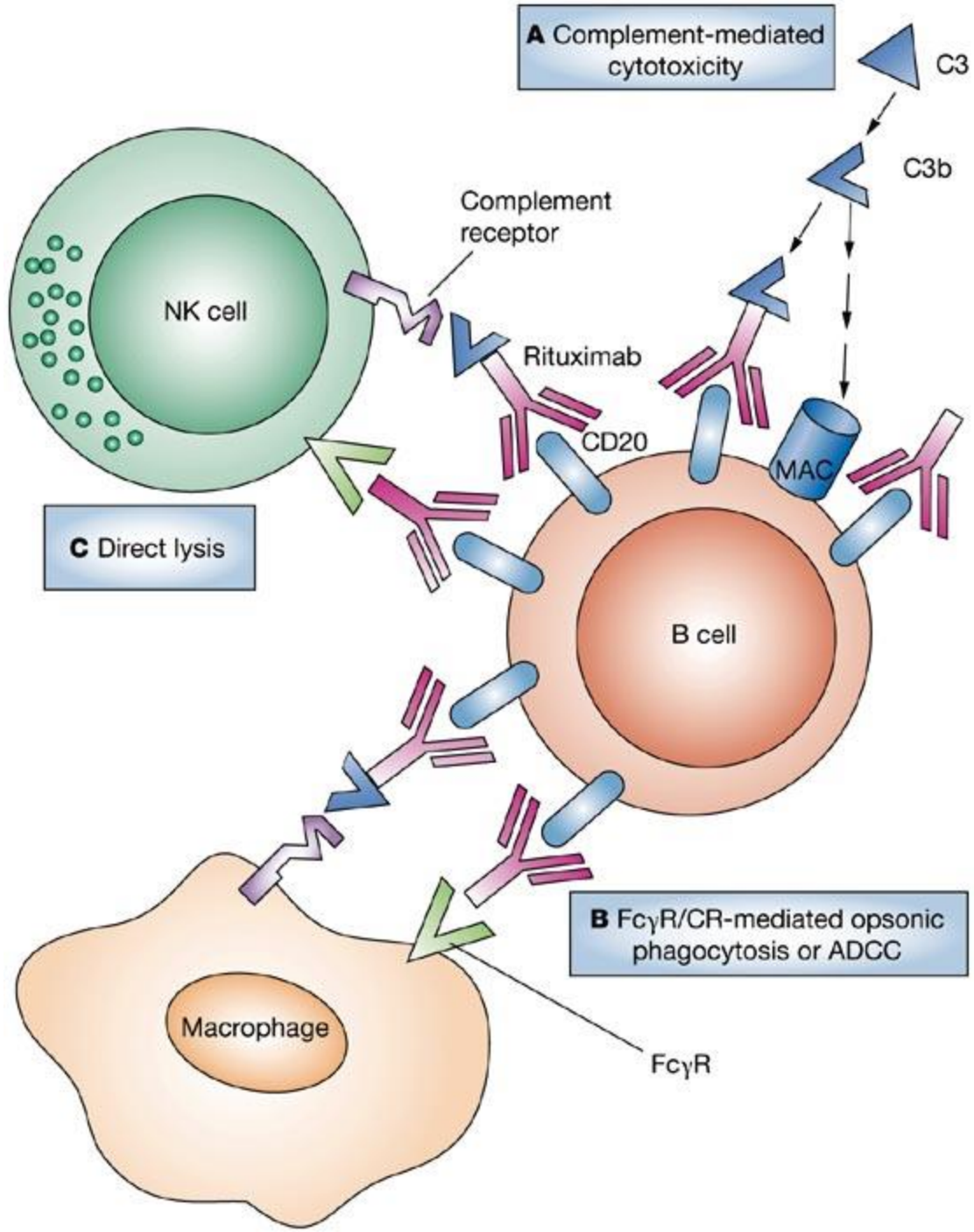
Monoclonal antibodies

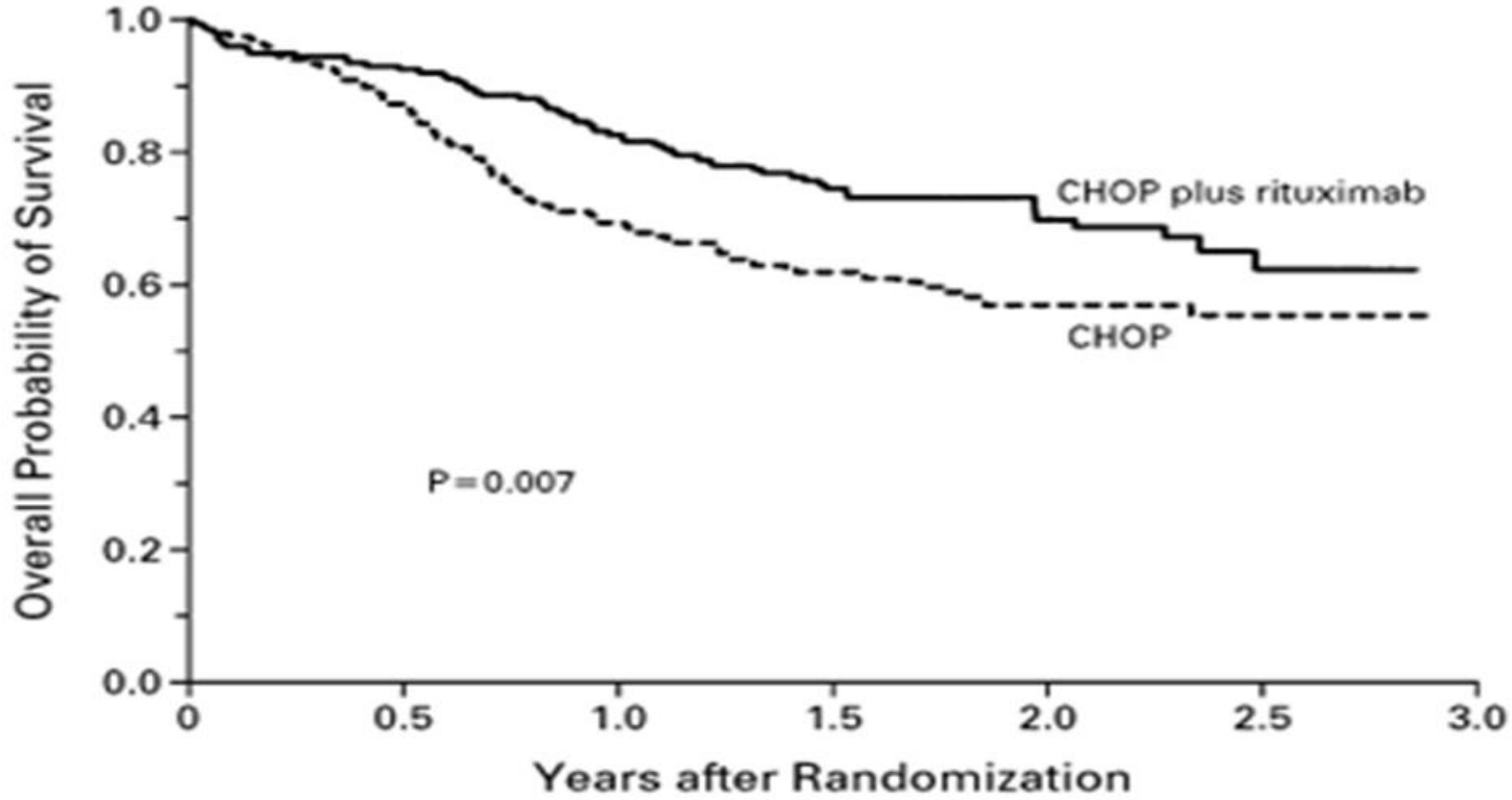
Targeted therapies

Immunotherapies

Monoclonal antibodies

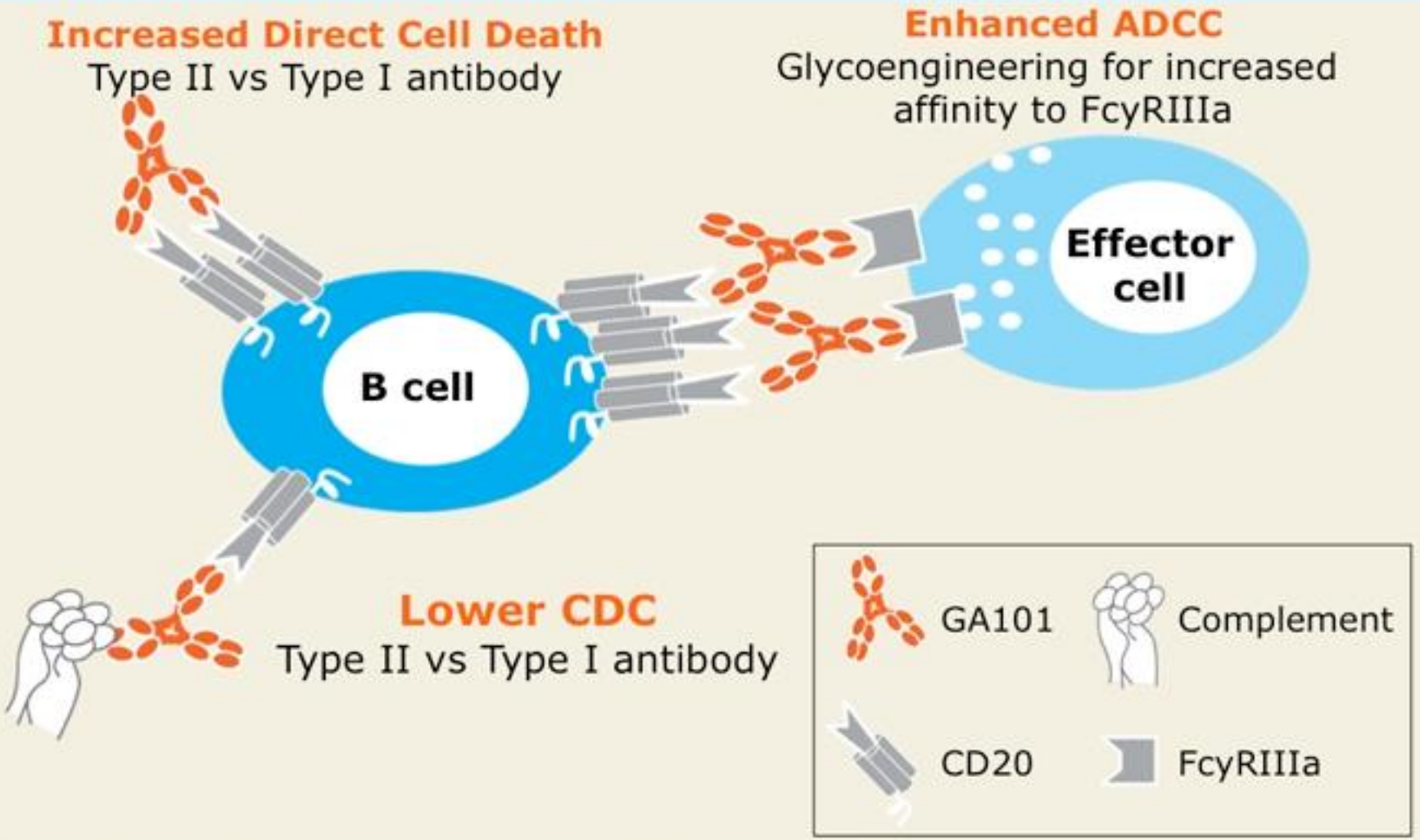



A Complement-mediated cytotoxicity
C3
C3b
Complement receptor
NK cell
Rituximab
CD20
MAC
C Direct lysis
B cell
B FcγR/CR-mediated opsonic phagocytosis or ADCC
Macrophage
FcγR



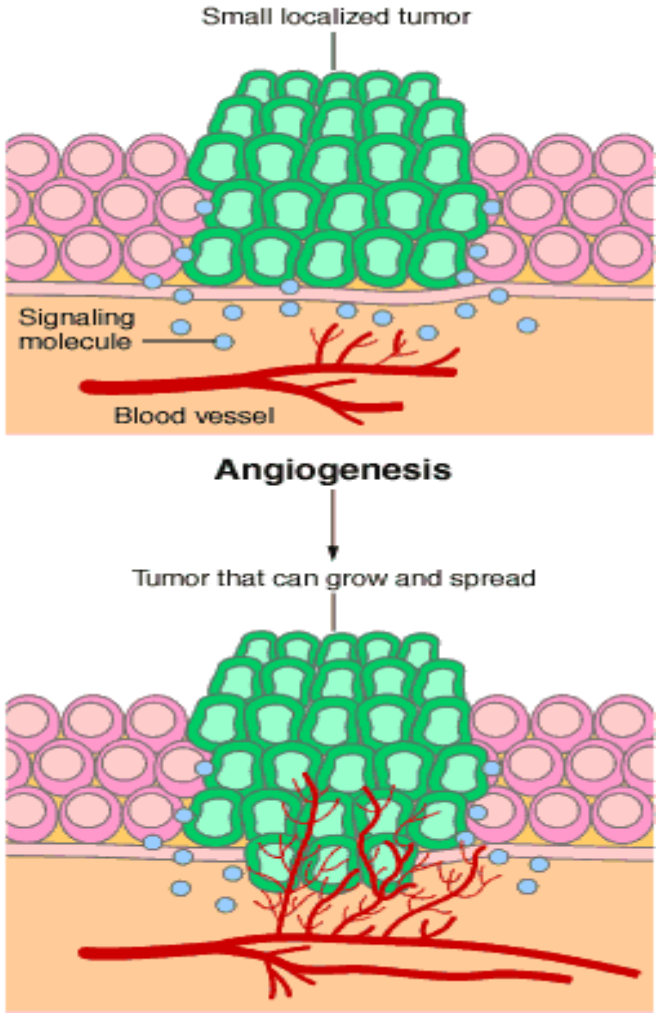
No. at Risk						
CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

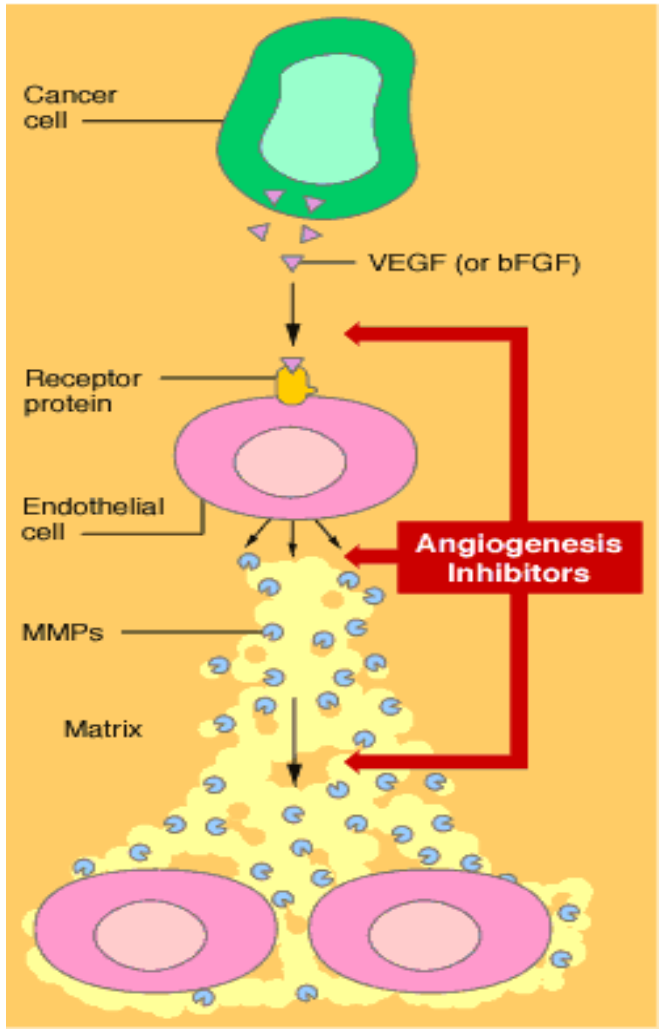
Mechanism of Action of Obinutuzumab



With permission from Goede V et al. *Proc ASH* 2013;Abstract 6.

Angiogenesis in tumors

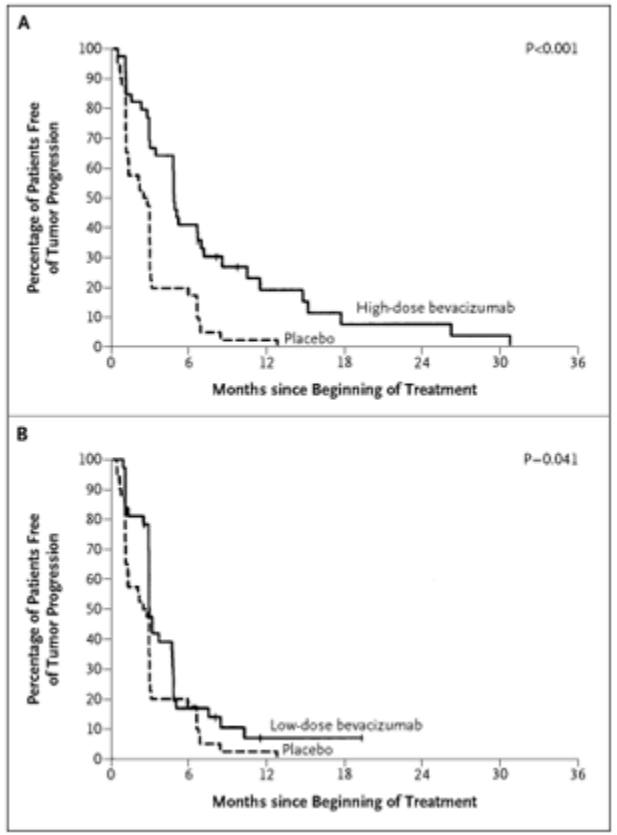




Bevacizumab

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

Bevacizumab in Renal Cancer

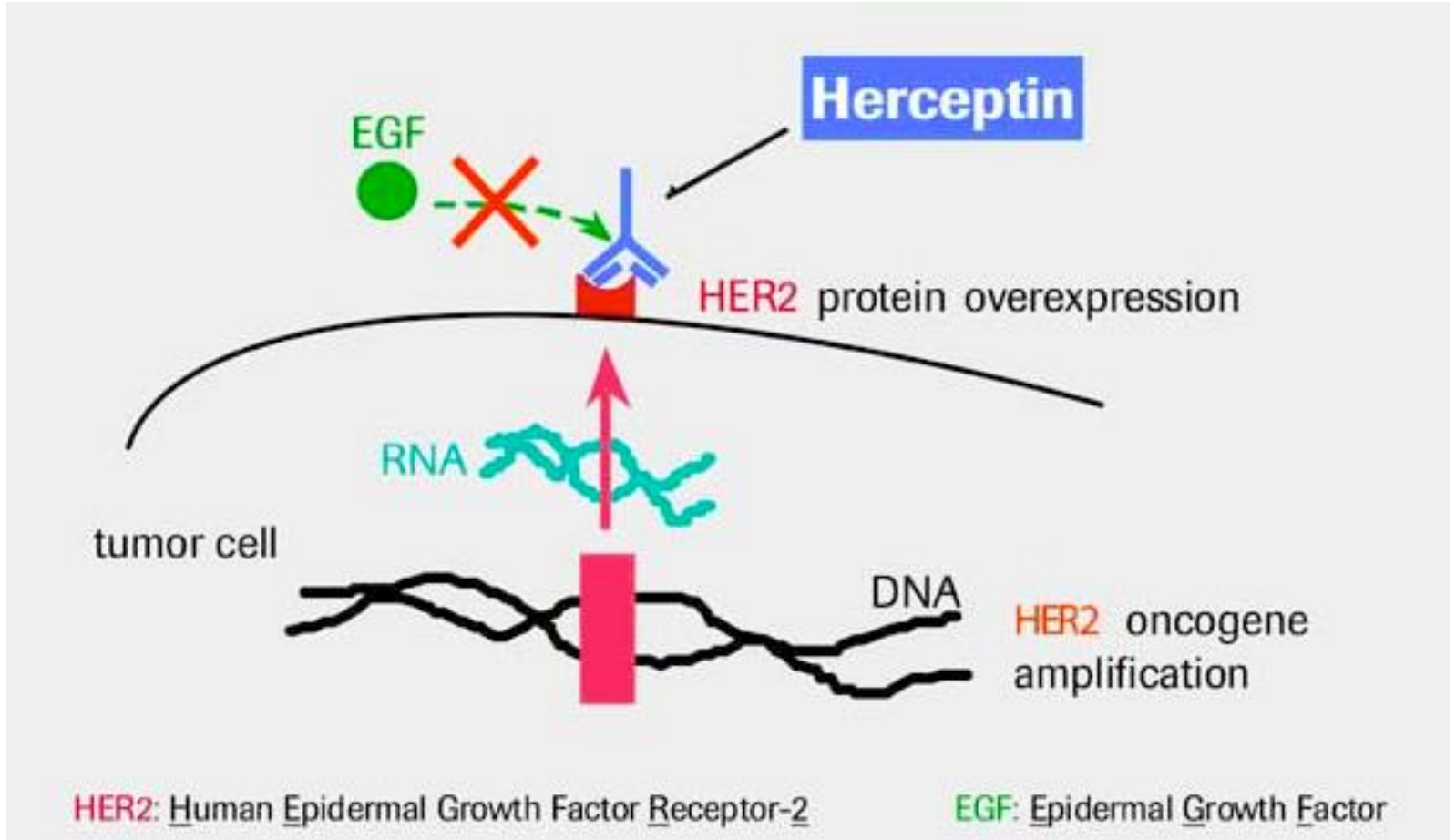


- Bevacizumab, a neutralizing antibody against vascular endothelial growth factor
- A randomized, double-blind, phase 2 trial was conducted comparing placebo with bevacizumab at doses of 3 and 10 mg/ kg, given q2 weeks
- After 116 patients randomly assigned to treatment groups, the trial was stopped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

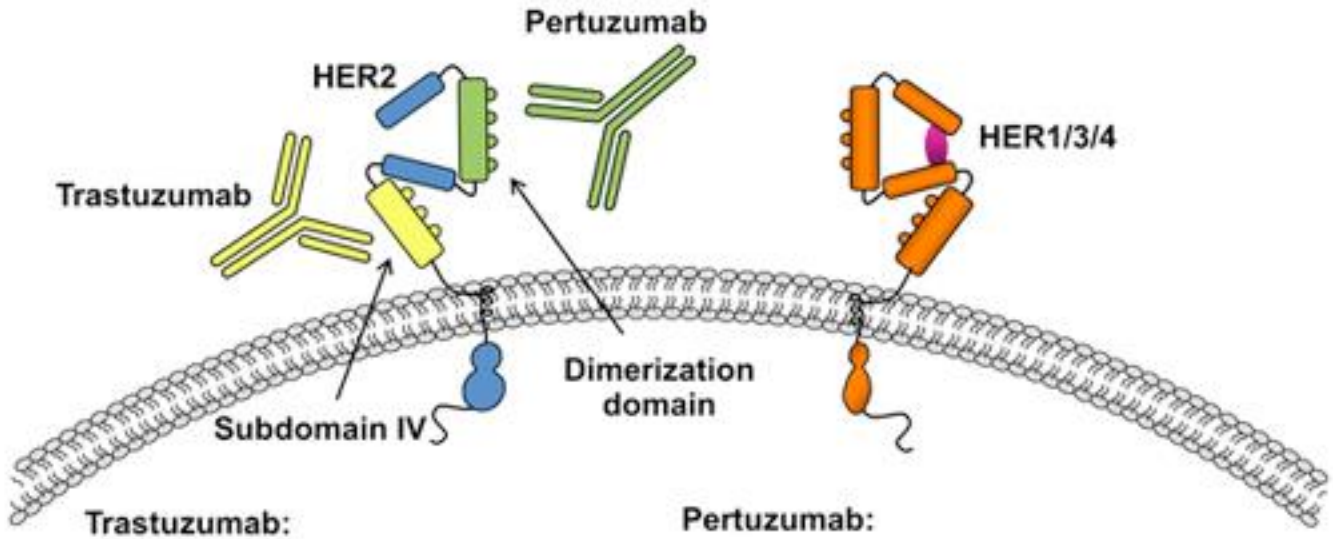
Yang et al, NEJM 2003

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


Herceptin
EGF
HER2 protein overexpression
RNA
tumor cell
DNA
HER2 oncogene amplification
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

Baselga J, et al.[5]

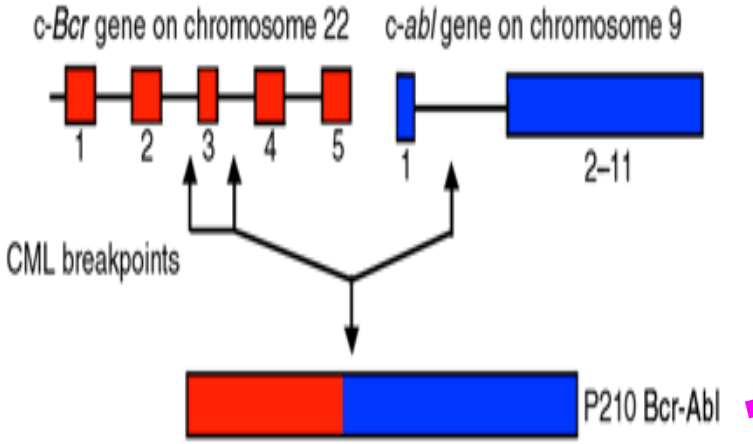
FDA-approved monoclonal antibodies for cancer treatment

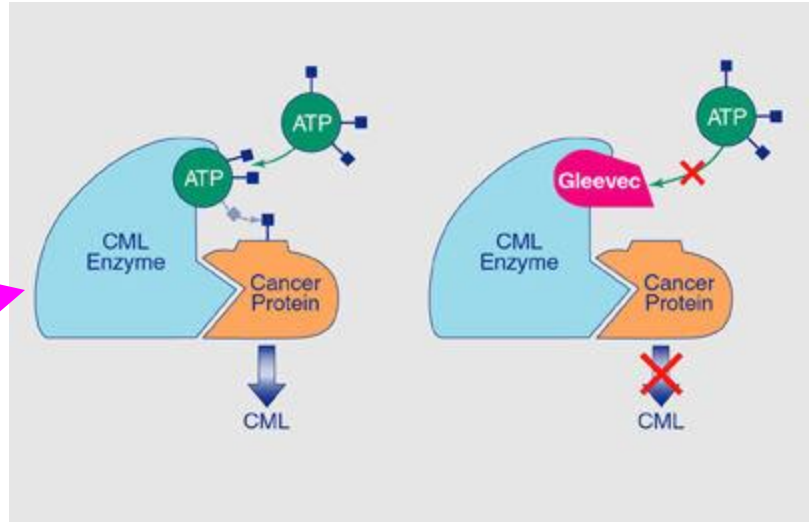
Name of drug	Type of cancer it treats
Alemtuzumab (Campath)	Chronic lymphocytic leukemia
Bevacizumab (Avastin)	Brain cancer Colon cancer Kidney cancer Lung cancer
Cetuximab (Erbitux)	Colon cancer Head and neck cancers
Ibritumomab (Zevalin)	Non-Hodgkin's lymphoma
Ofatumumab (Arzerra)	Chronic lymphocytic 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

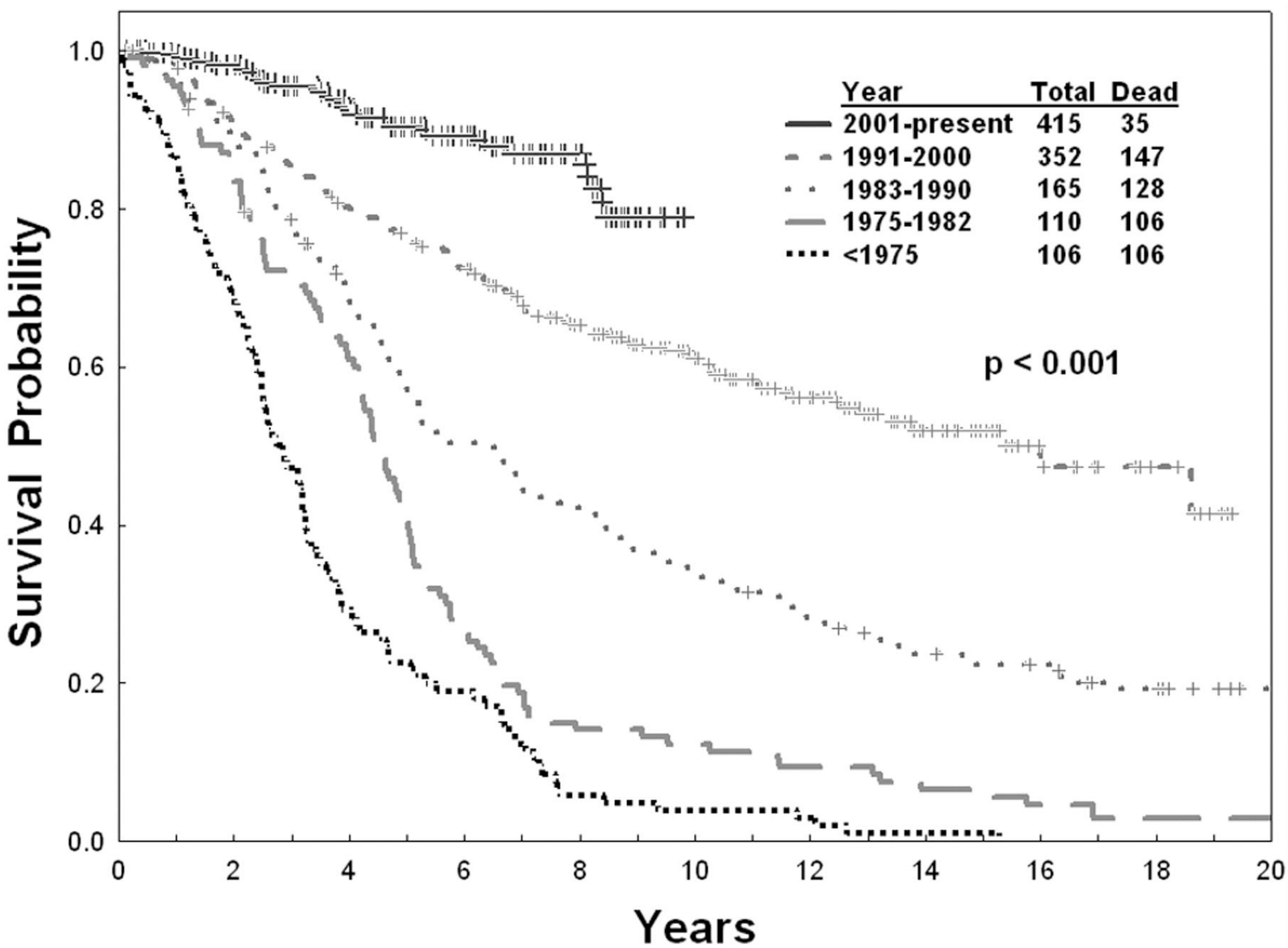
Source: Food and Drug Administration (FDA), Center for Drug Evaluation and Research

Targeted therapy

(Imatinib)






Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
14
16
18
20
Years
Year Total Dead
2001-present 415 35
1991-2000 352 147
1983-1990 165 128
1975-1982 110 106
<1975 106 106
p < 0.001

Targeted therapy in Lung cancer

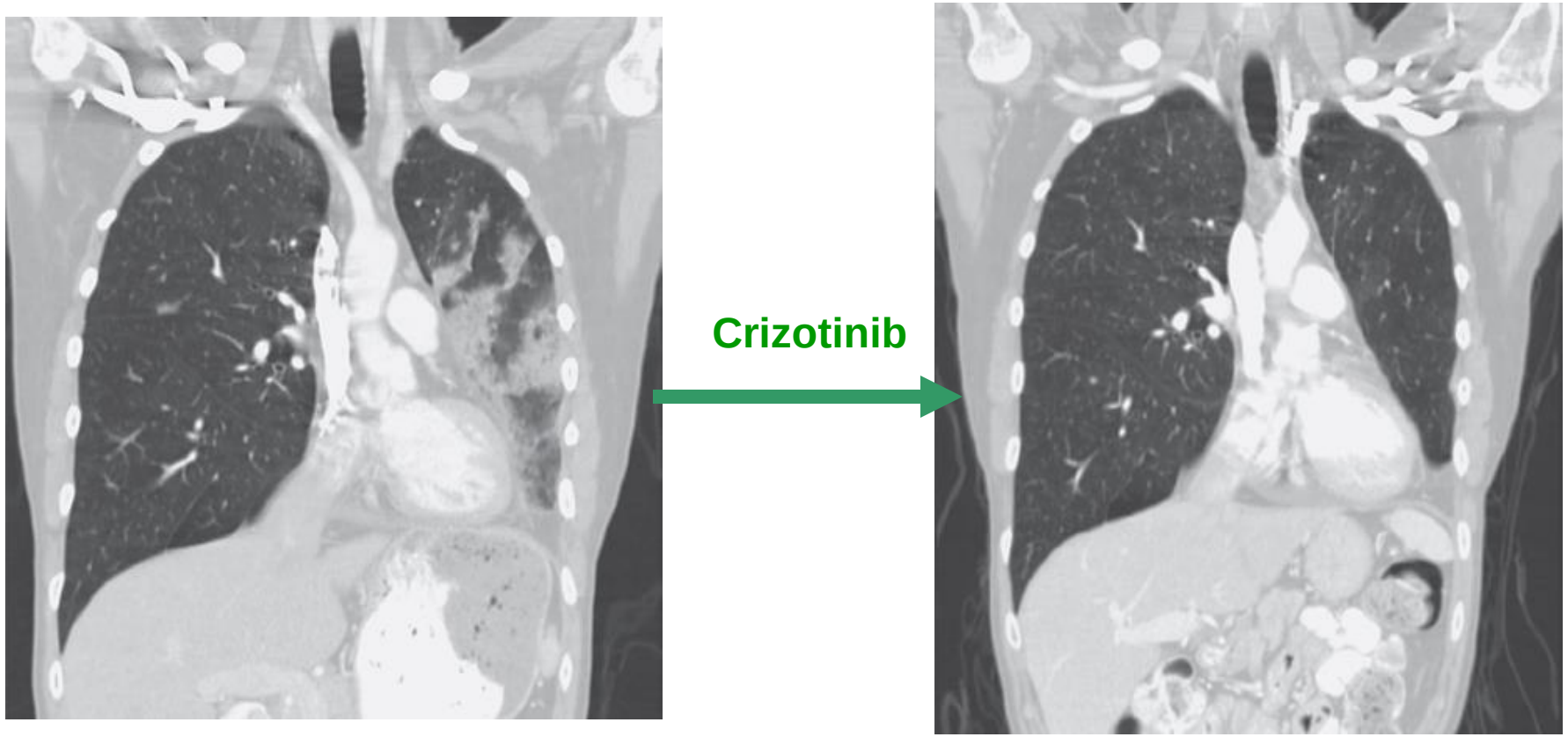
10% of patients

- 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

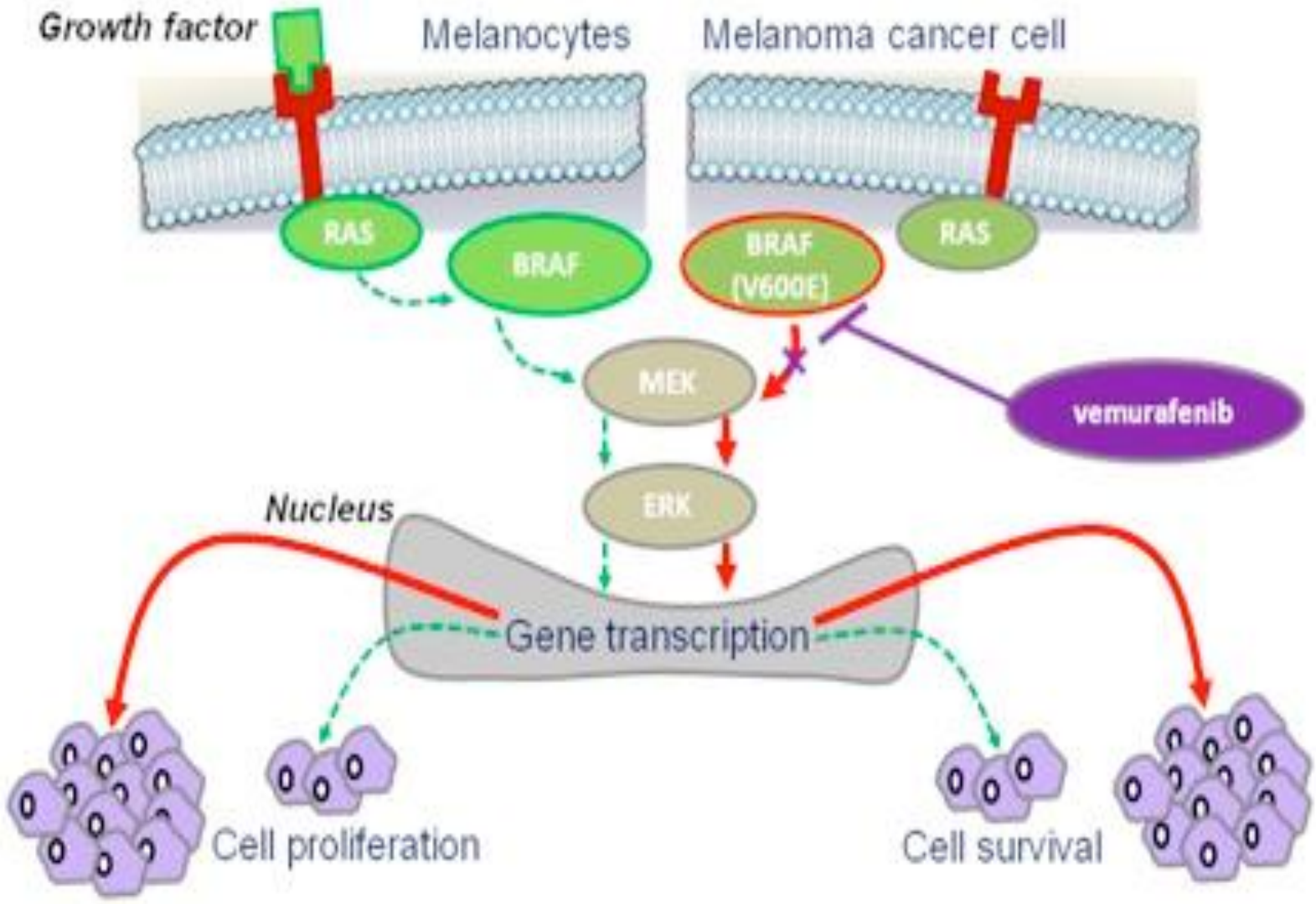
- A small group of patients with NSCLC have genetic lesions that activate anaplastic lymphoma kinase (ALK).
- Crizotinib, an oral ALK kinase inhibitor, produced a 57% response rate in this subgroup, (NEJM Oct 2010)

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



Vemurafinib

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


Growth factor
Melanocytes
Melanoma cancer cell
RAS
BRAF
BRAF (V600E)
RAS
MEK
vemurafenib
ERK
Nucleus
Gene transcription
Cell proliferation
Cell survival

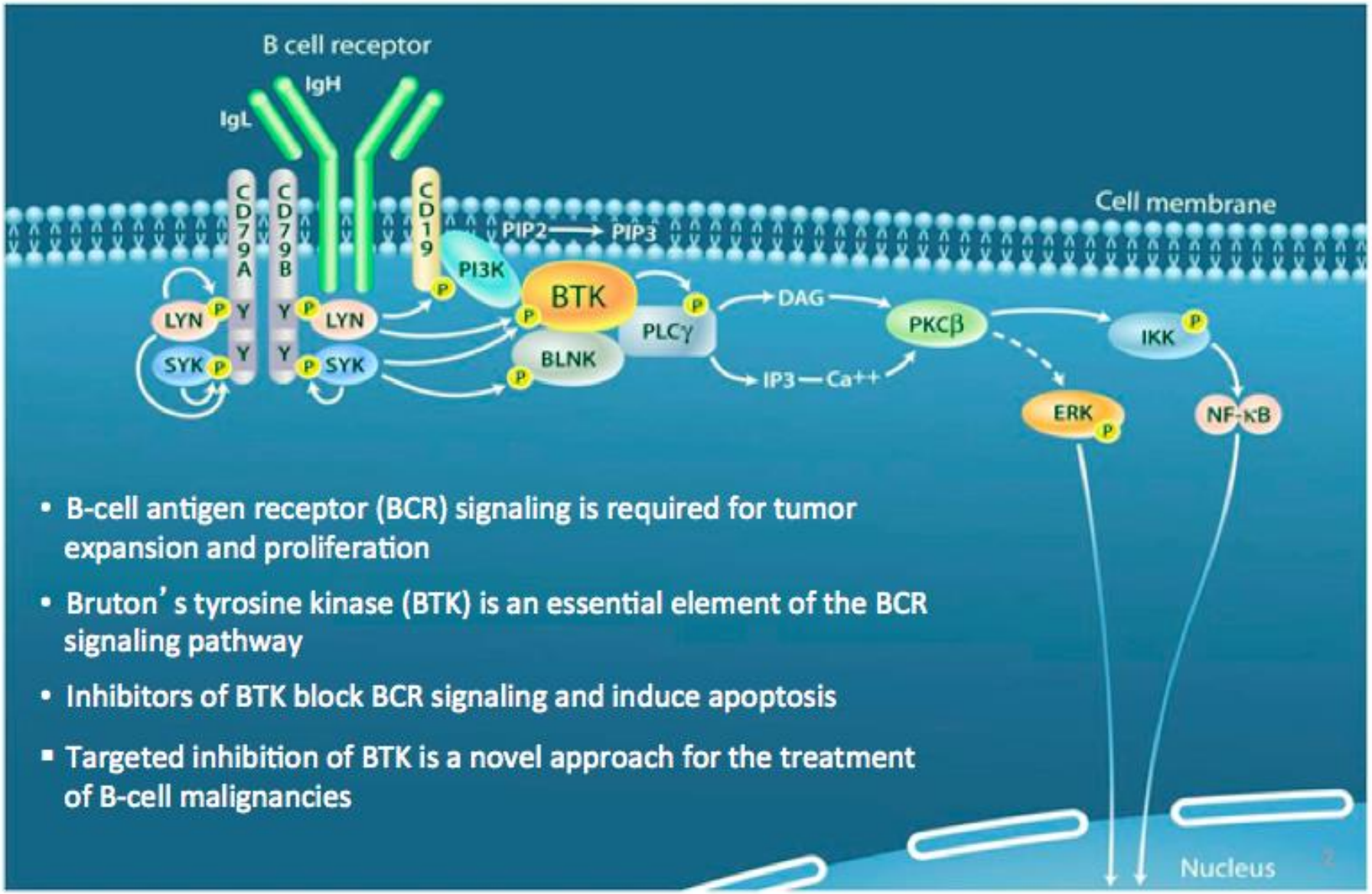
Ibrutinib (Ibruvica)

- Newly approved last year for use in relapsed/refractory CLL and mantle cell lymphoma

- Novel Bruton’s tyrosine kinase inhibitor

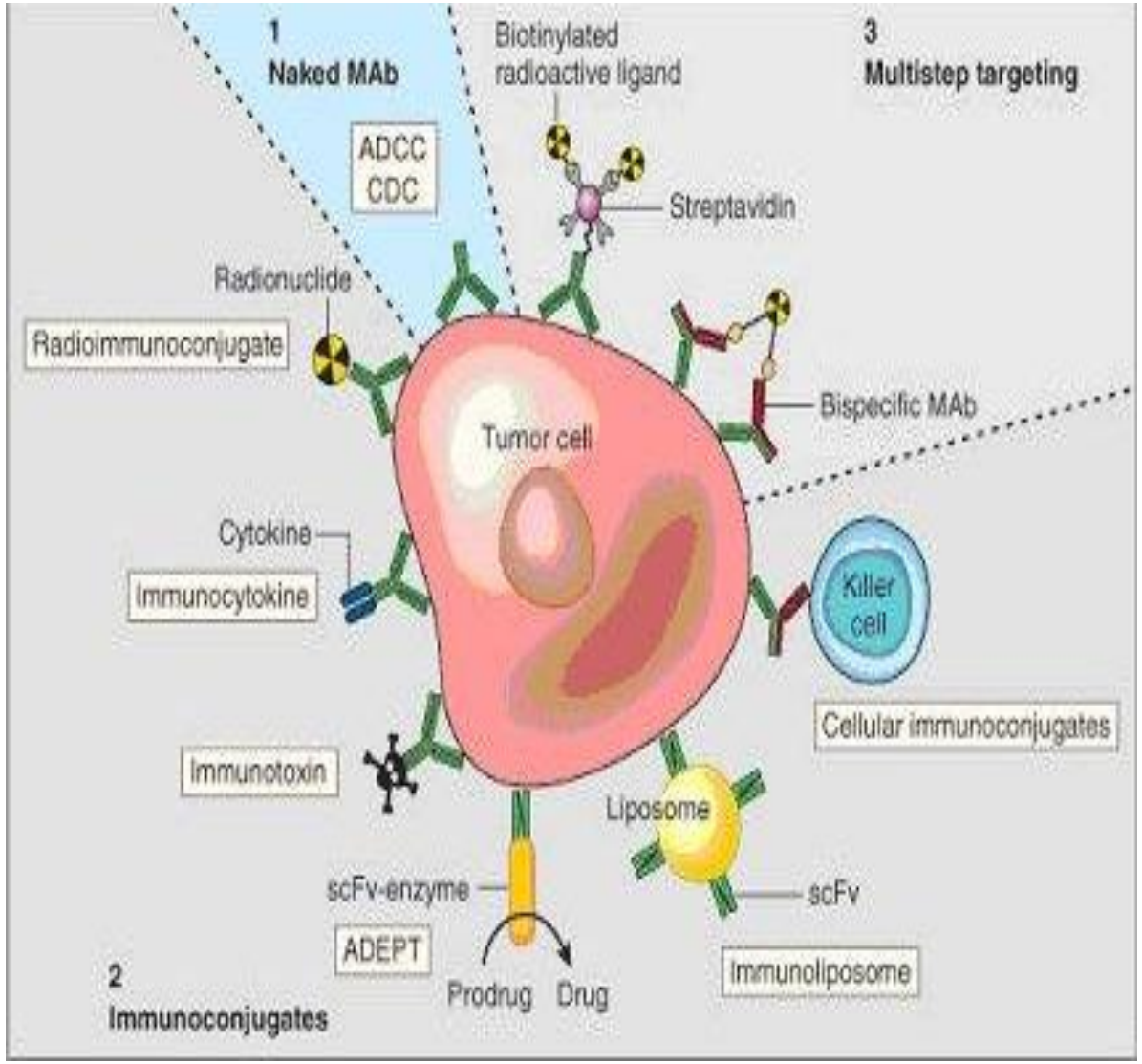
Bruton's Tyrosine Kinase (BTK)

A critical kinase for lymphoma cell survival and proliferation



- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation
- Bruton's tyrosine kinase (BTK) is an essential element of the BCR signaling pathway
- Inhibitors of BTK block BCR signaling and induce apoptosis
- Targeted inhibition of BTK is a novel approach for the treatment of B-cell malignancies

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

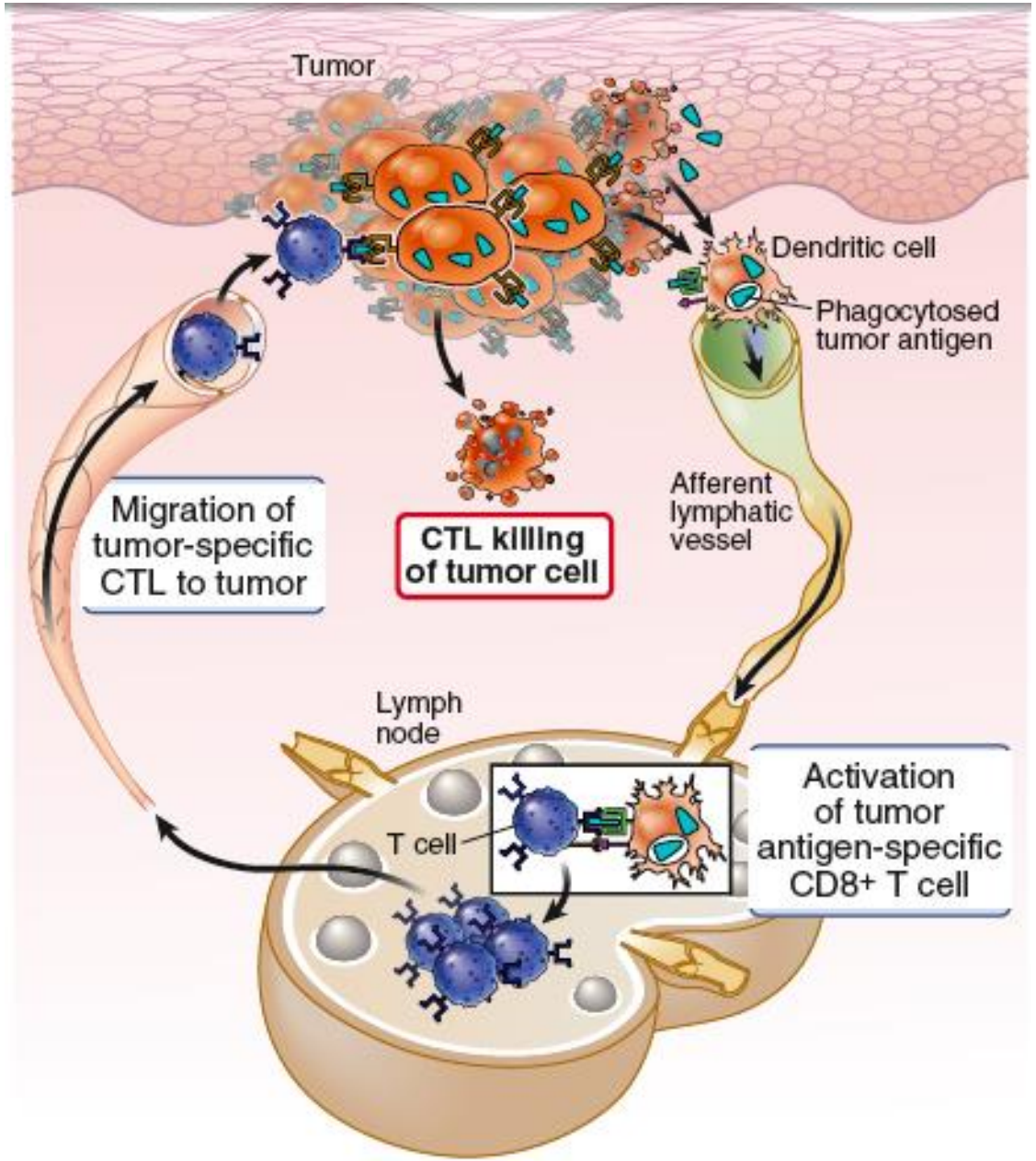
Immunotherapy

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

General principles

- The immune system recognizes and reacts against cancers
- The immune response against tumors is often dominated by regulation or tolerance
  - Evasion of host immunity is one of the hallmarks of cancer
- Some immune responses promote cancer growth
- Defining the immune response against cancers will help in developing new immunotherapies

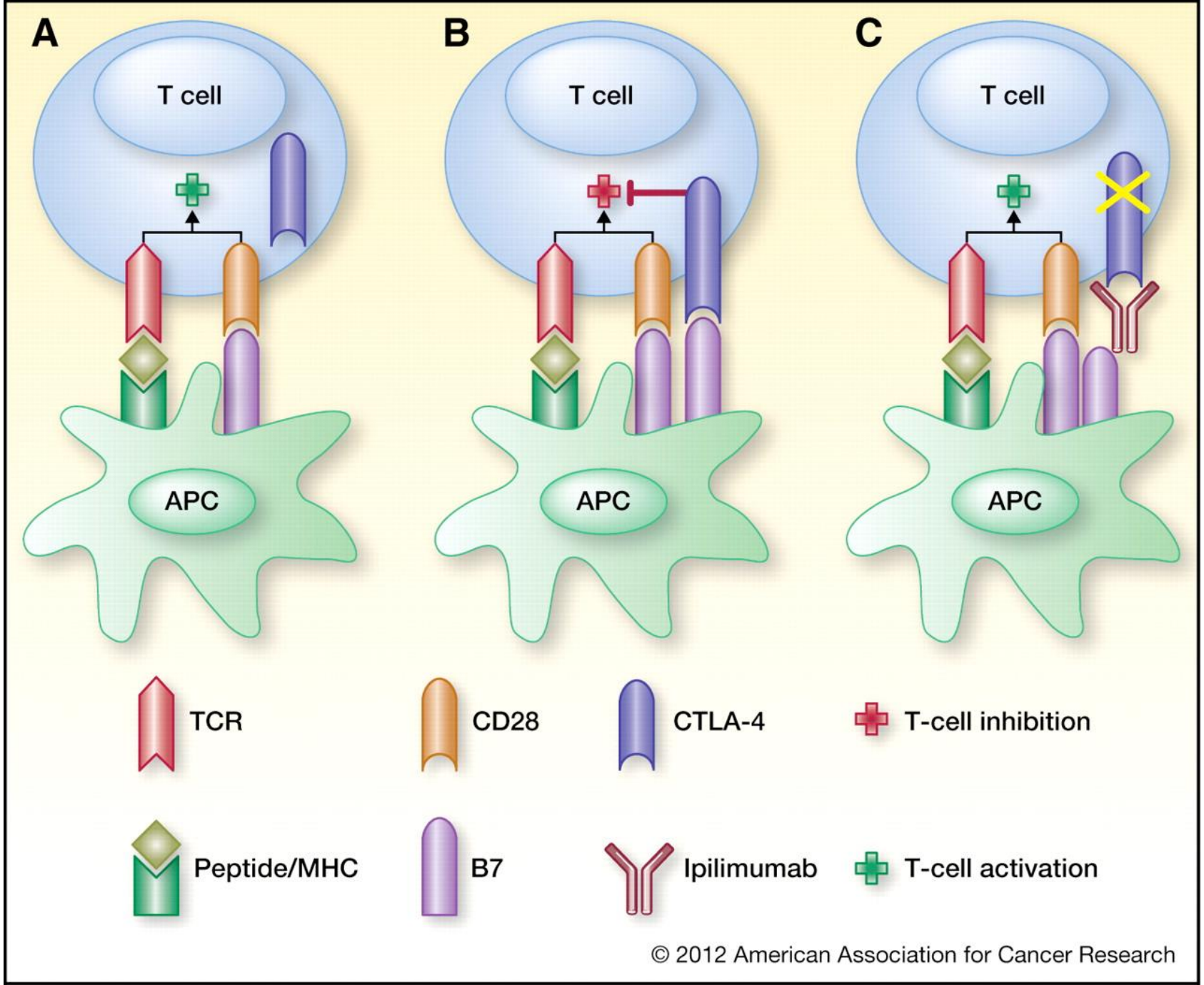
T cell responses to tumors



Ipilimumab (Yervoy)

- For use in metastatic melanoma

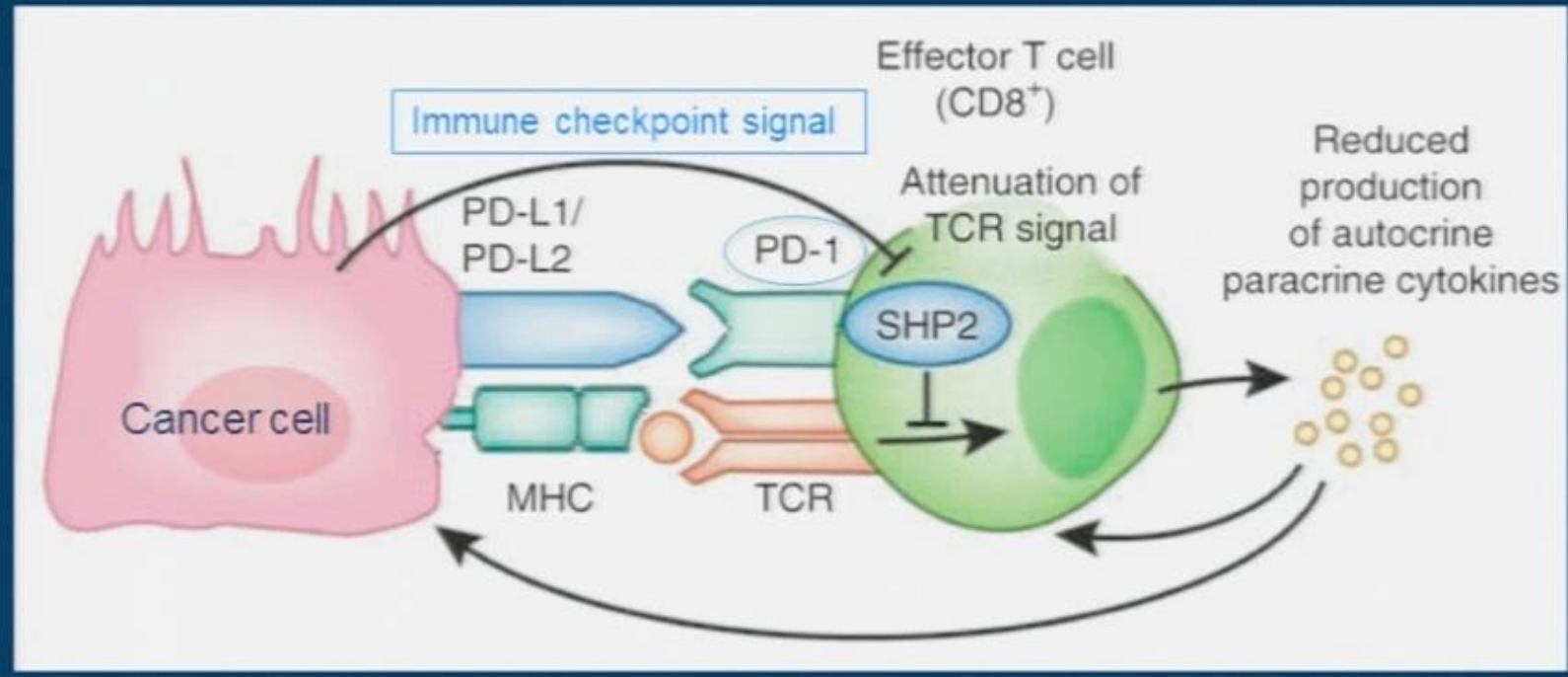
- Interrupts inhibitory mechanism that prevents cytotoxic T lymphocytes from killing cancer cells



Programmed Cell Death Protein 1 (PD-1)

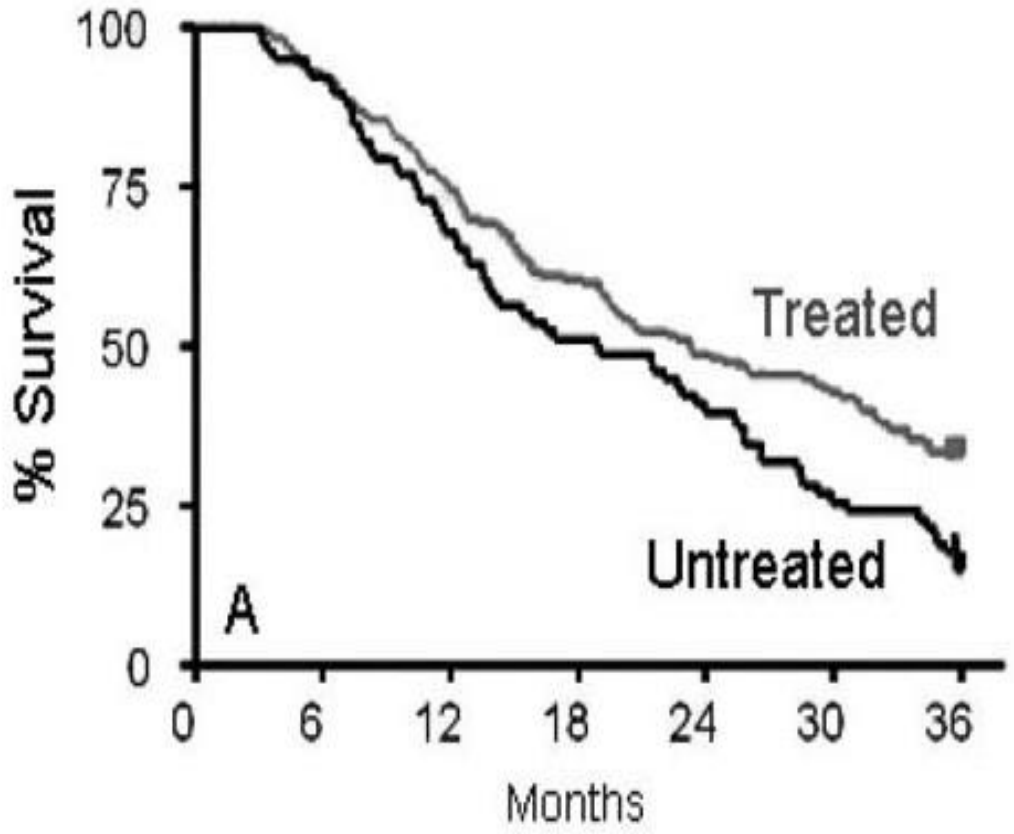
- New class of drug are inhibitors that activate immune system to attack tumors
- Pembrolizumab FDA approved Sept 2014 for metastatic melanoma
- Nivolumab FDA approved Dec 2014 for metastatic melanoma

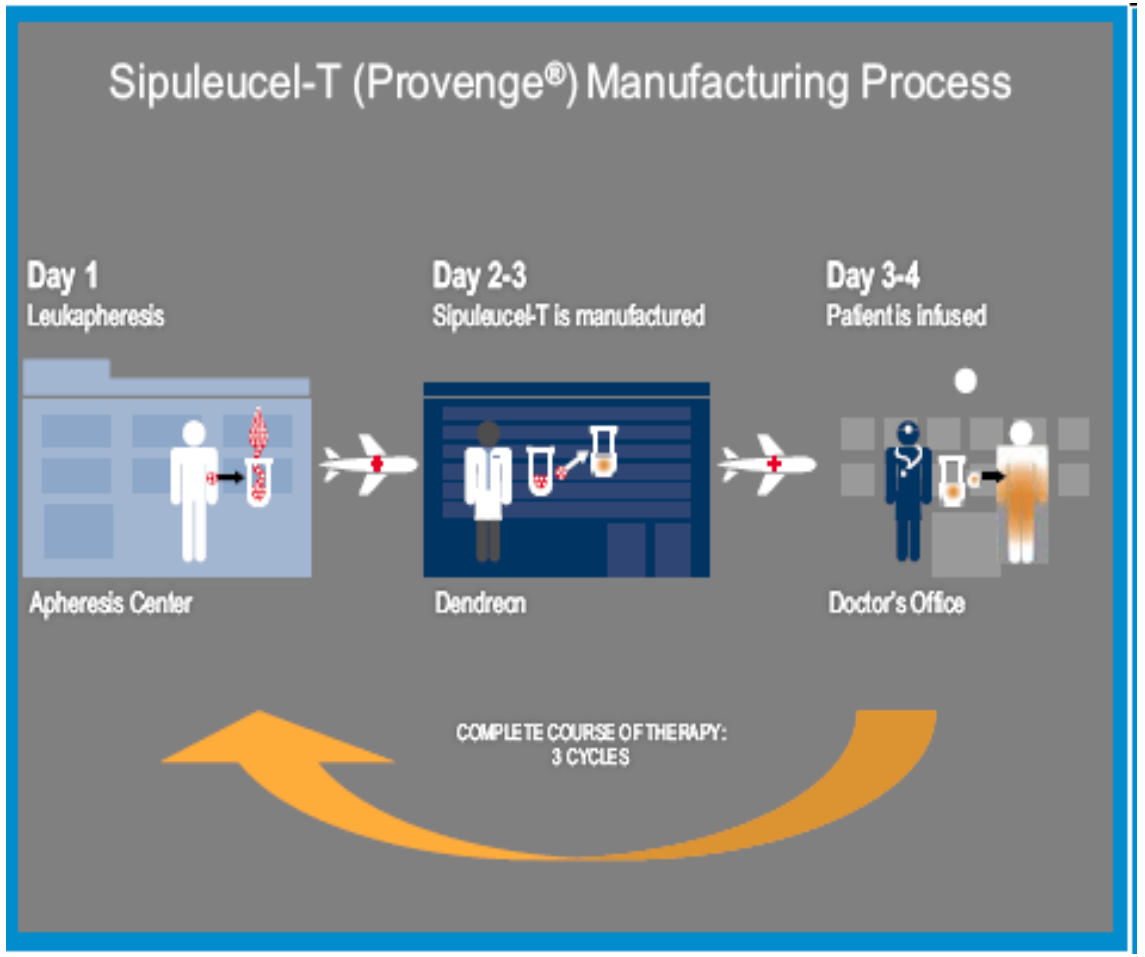
PD-1/ PD-L1 pathway in suppressing anti-tumor immunity



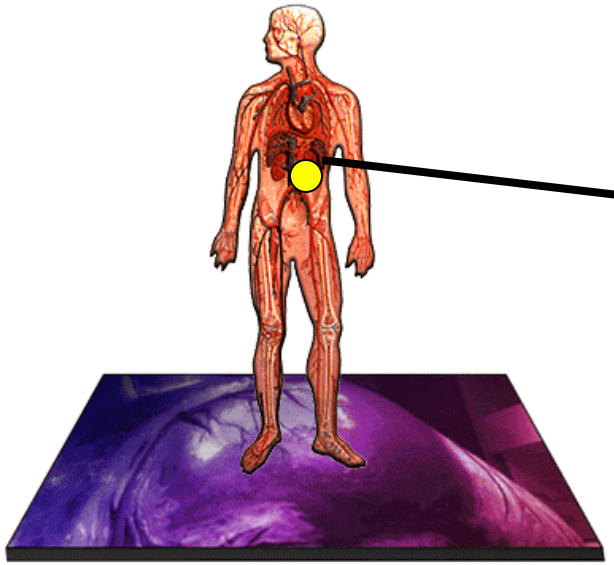
(Okazaki, Honjo et al. Nat Rev Immunol 2013, modified)

Vaccine as therapy: Provenge

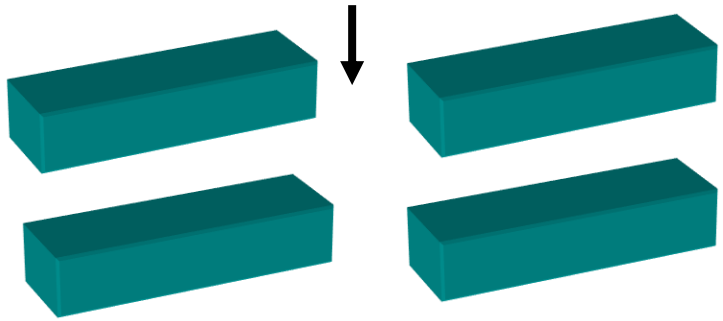




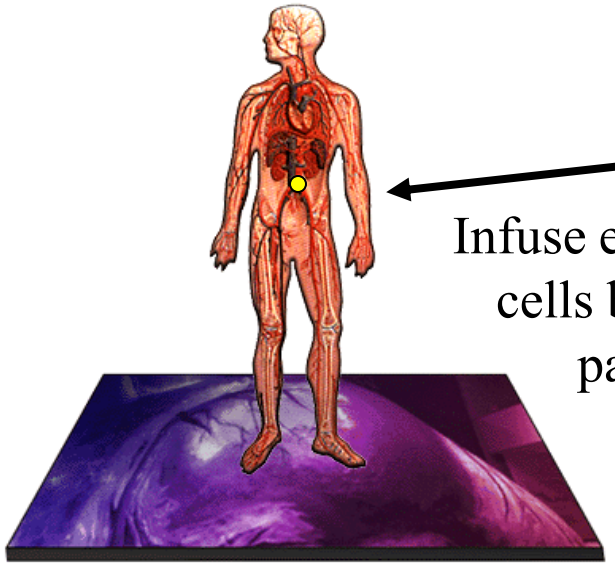
Adoptive Transfer



Isolate T cells from blood or from tumor tissue



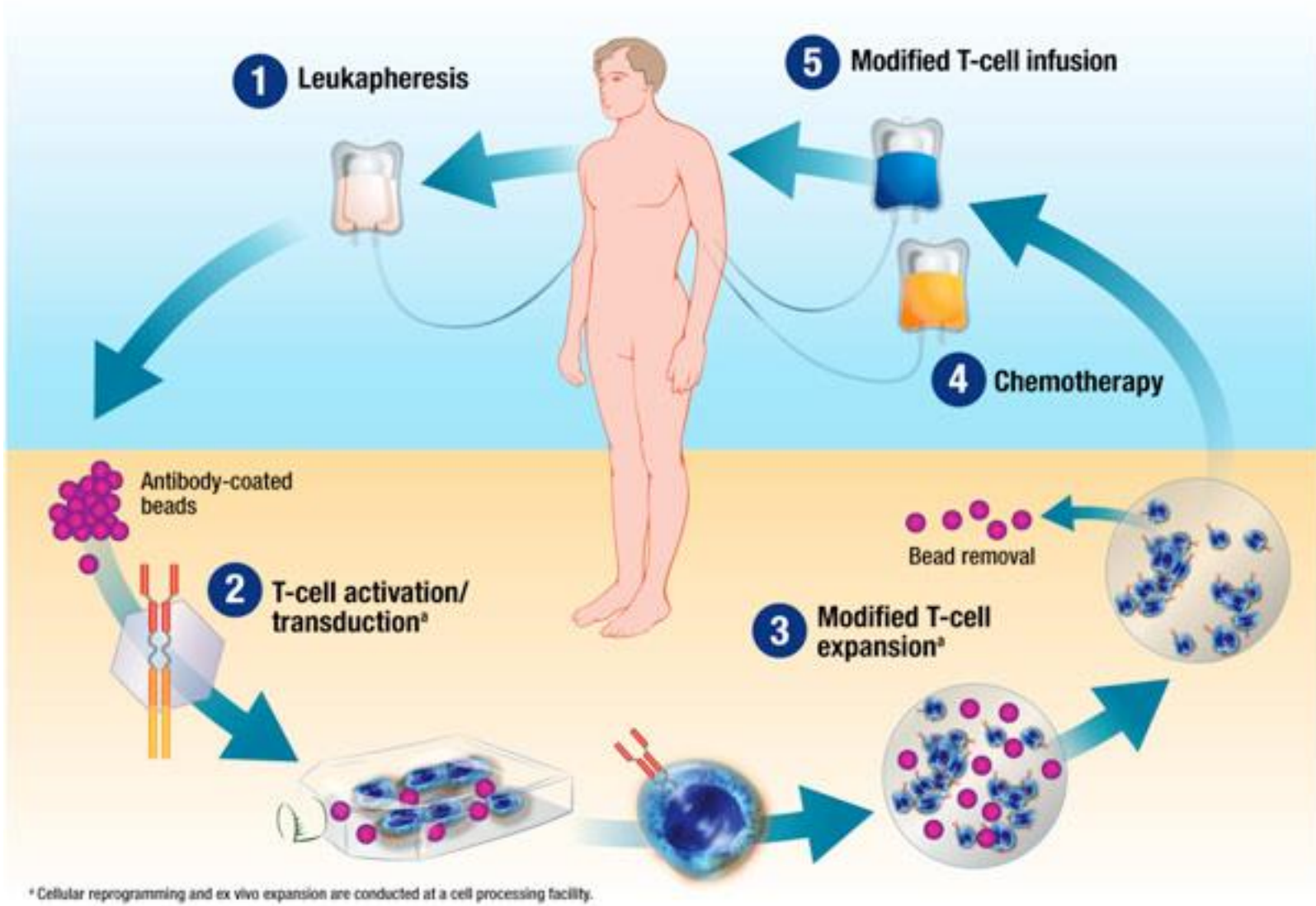
Amplify tumor specific T cells by culturing *in vitro* with IL-2



Infuse expanded T cells back into patient

CAR-T Therapy

- Chimeric Antigen Receptor T-Cell Immunotherapy


1 Leukapheresis
5 Modified T-cell infusion
4 Chemotherapy
Antibody-coated beads
2 T-cell activation/ transduction[a]
Bead removal
3 Modified T-cell expansion[a]
[a] Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

cancer-related anorexia/cachexia syndrome

- The cancer-related anorexia/cachexia syndrome (CACS) is characterized by anorexia and a loss of body weight associated with reduced muscle mass and adipose tissue.

- In addition to a variable contribution from decreased energy intake, resting energy expenditure can be elevated in CACS in association with increases in both muscle protein breakdown and lipolysis, changes that appear to be due in part to an inflammatory response with the elaboration of cytokines, including tumor necrosis factor-alpha, interleukin (IL) 6, and IL-1 beta.

- The most commonly used objective measures of nutritional status are serial measurement of body weight and assessment of dietary intake, while subjective information on nutritional status can be provided by malnutritional assessment tools.
- Laboratory measures of nutritional status (eg, albumin, transferrin) are rarely needed for assessment of nutritional status, although some screening tools (eg, the Nutrition Risk Index) do include a measurement of serum albumin.

approach to management of CACS follows published guidance from the American Society of Clinical Oncology (ASCO)

- Communication regarding cachexia management and issues around feeding, particularly in the setting of advanced cancer or end of life care, should involve caregivers as well as patients.

- Optimizing management of major contributors to anorexia, such as chronic nausea, constipation, taste alterations, dyspnea, and depression (nutrition impact symptoms) may improve appetite.

- The goals include practical and safe advice for feeding; education regarding high-protein, high-calorie, nutrient-dense food; and advice against fad diets and other unproven or extreme diets.

- For most patients with advanced cancer and CACS, we suggest not routinely using enteral tube feeding or parenteral nutrition to manage cachexia.

- A short-term trial of parenteral nutrition may be offered to a very select group of patients, such as those who have a reversible bowel obstruction, short-bowel syndrome, or other issues contributing to malabsorption, but are otherwise reasonably fit.

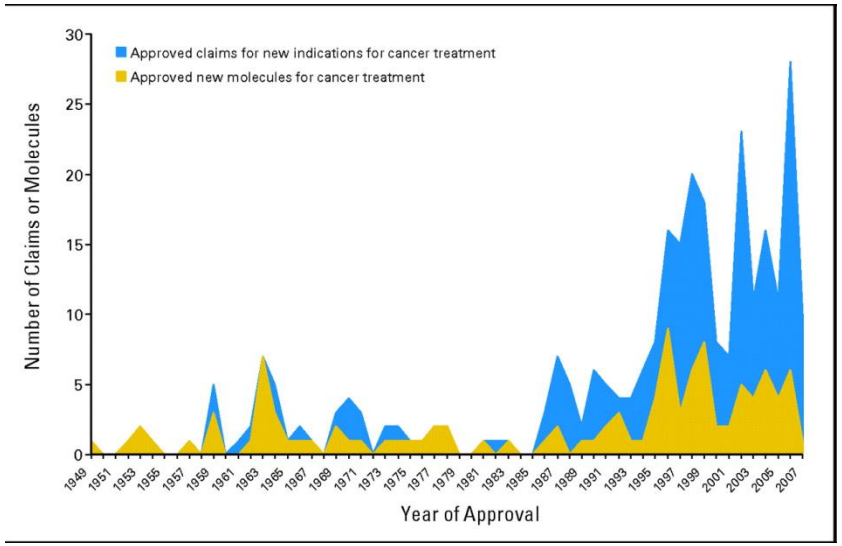
- The decision to use pharmacologic agents for appetite stimulation is highly dependent on the values and preferences of individual patients and other considerations such as degree of anorexia or weight loss, comorbidities, risk of adverse effects, life expectancy, and goals of care.
- The primary benefits associated with these drugs are increased appetite and modest weight gain, not improved survival.

- **the ASCO guidelines** : if the decision is made to treat, we base the choice of agent on expected life expectancy and assessment of risks versus benefits.

- For patients in whom only days to weeks of therapy are anticipated, we suggest dexamethasone rather than another agent.
- For patients with longer life expectancies, we suggest a progesterone analog (megestrol acetate or medroxyprogesterone acetate) rather than another agent, but potential benefits must be balanced with risks (edema, thromboembolic events, increased mortality).

- We recommend against the use of hydrazine sulfate. We suggest not using inhaled cannabinoids, cannabis, inhibitors of tumor necrosis factor, insulin, or melatonin.

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 tumours 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

77