

Introduction to treatment of cancer

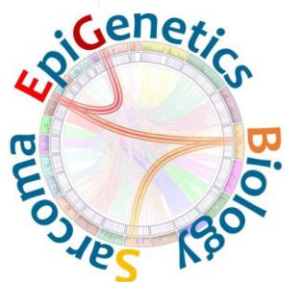
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Disclosures

- None

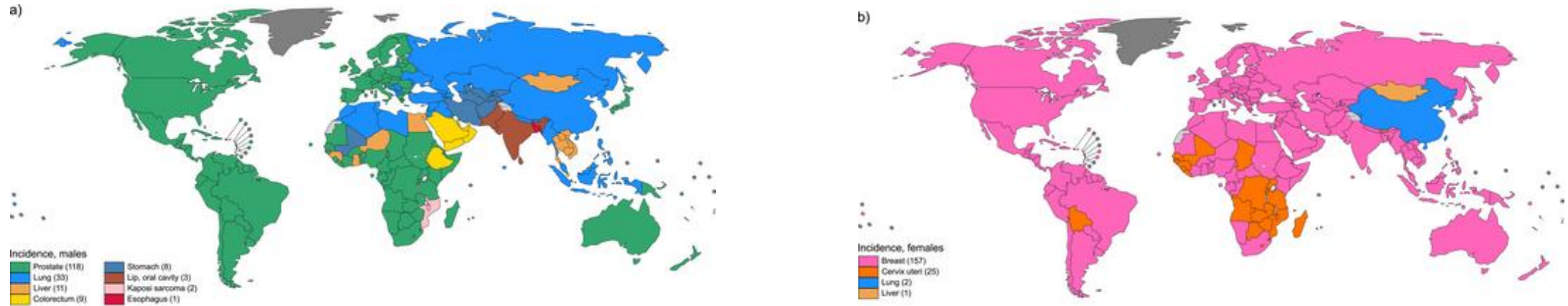
Objectives

- Understand the basic biology of cancer and its clinical implications.
- Identify the main modalities of cancer treatment (surgery, chemotherapy, radiotherapy, immunotherapy).
- Explain the principles behind treatment selection and multidisciplinary care.

Multidisciplinary approach



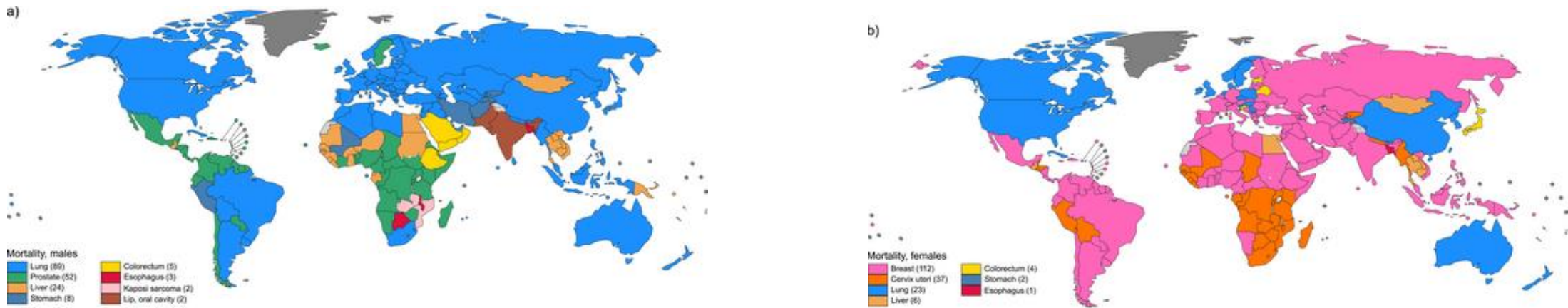
Introduction-Cancer Incidence



In **men**, **prostate** cancer ranks as the most frequently diagnosed cancer in 118 countries, followed by **lung cancer** in 33 countries, with liver, colorectal, and stomach cancer ranking in first place in 11, nine, and eight countries, respectively

Two cancer types dominate as the most commonly diagnosed cancers in women, namely, **breast cancer** (157 countries) and **cervical cancer** (25 of 28 remaining countries)

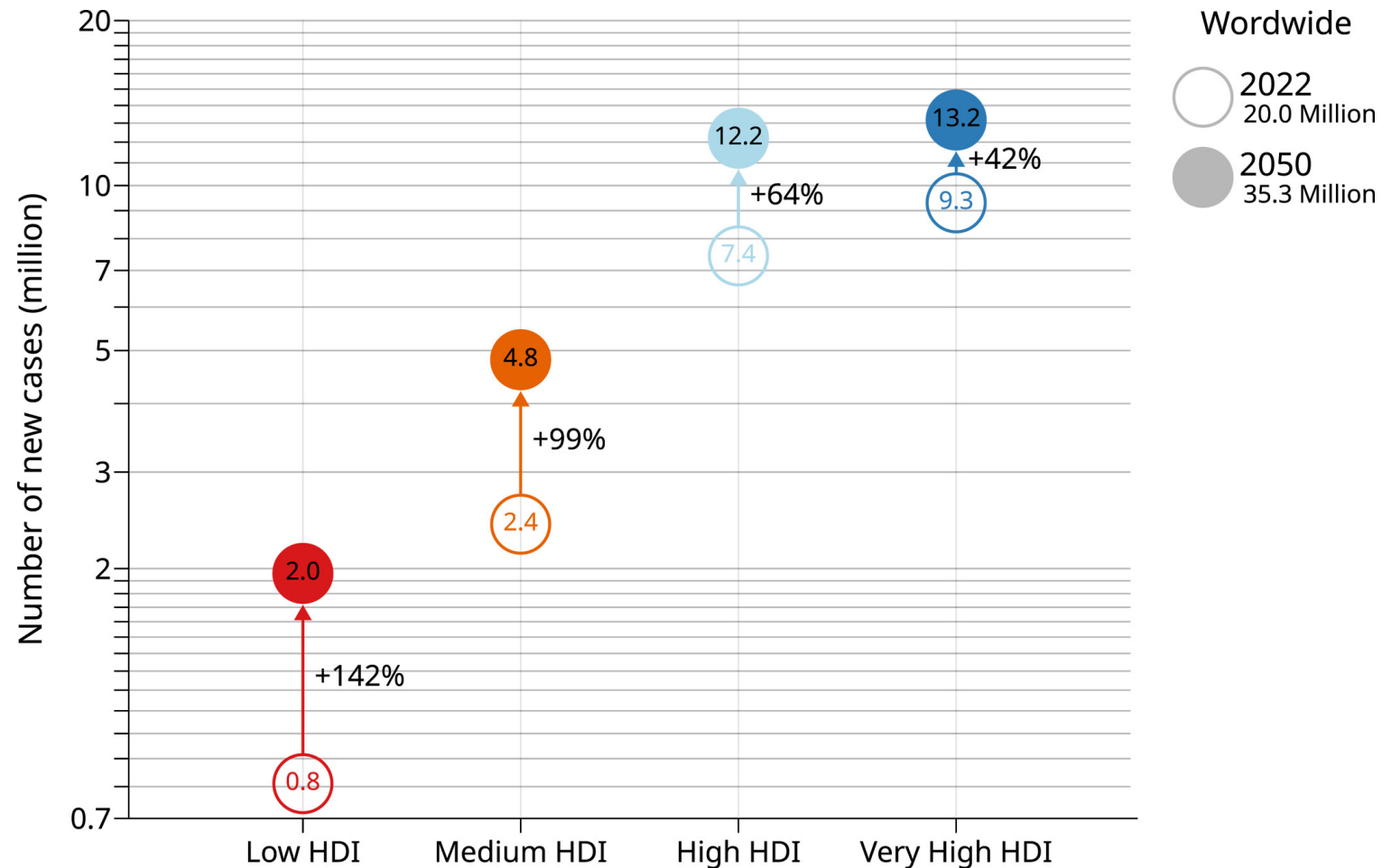
Introduction- Cancer mortality



In terms of cancer deaths, lung cancer leads in men in 89 countries, followed by cancers of the prostate (52 countries) and liver (24 countries)

The mortality profile in women is more heterogeneous than that of incidence, however, with breast and cervical cancer as the leading causes of cancer death in 112 and 37 countries, respectively, followed by lung cancer in 23 countries

Projected number of new cases



GLOBOCAN 2022

The greatest relative increases will take place in lower HDI settings

Risk factors

	Sufficient evidence in humans	Limited evidence in humans
<i>Dusts and fibers</i>		
Asbestos	Larynx, lung, mesothelioma, ovary	Colorectum, pharynx, stomach
Leather dust, wood dust	Nasal cavity and paranasal sinus	
<i>Radiation</i>		
Radium 226, radium 228	Bone, mastoid process, paranasal sinus	
<i>Biological agents</i>		
Epstein-Barr virus	Burkitt lymphoma, Hodgkin lymphoma, etc.	Lymphoepithelial-like carcinoma, stomach
Hepatitis B, C	Liver	Cholangiocarcinoma
Human papillomavirus 31, 35, 39, 45, 51, 52, 56, 58, 59	Cervix	
<i>Helicobacter pylori</i>	Lymphoma, stomach	

	Sufficient evidence in humans	Limited evidence in humans
<i>Personal habits</i>		
Alcoholic beverages	Breast, colorectum, larynx, liver, esophagus, oral cavity, pharynx	Pancreas
Tobacco smoking	Bone marrow, cervix, colorectum, kidney, larynx, liver, lung, nasal cavity and paranasal sinus, esophagus, pancreas, pharynx, stomach, ureter, urinary bladder, in smokers' children: hepatoblastoma	Breast, in smokers children: leukemia

	Sufficient evidence in humans	Limited evidence in humans
<i>Chemicals and mixtures</i>		
Formaldehyde	Leukemia, nasopharynx	Nasal cavity and paranasal sinus
Benzene	Leukemia	
<i>Occupations</i>		
Aluminum production	Lung, urinary bladder	
Isopropyl alcohol production	Nasal cavity and paranasal sinus	
<i>Metals</i>		
Chromium compounds	Lung	Nasal cavity and paranasal sinus
Nickel compounds	Lung, nasal cavity, and paranasal sinus	

Importance of treatment strategies

- **Personalization of Care**: Every cancer type, stage, and patient profile is different. Strategies ensure treatments are tailored to maximize effectiveness and minimize harm.
- **Combination of Modalities**: Surgery, chemotherapy, radiotherapy, and immunotherapy often work best in combination. A strategy defines the sequence and integration.
- **Optimizing Outcomes**: Strategic planning improves survival rates, reduces recurrence, and enhances quality of life.
- **Resource Management**: Helps allocate time, technology, and expertise efficiently.
- **Multidisciplinary Coordination**: Ensures oncologists, surgeons, radiologists, and other specialists work together toward a common goal.

Importance of treatment strategies

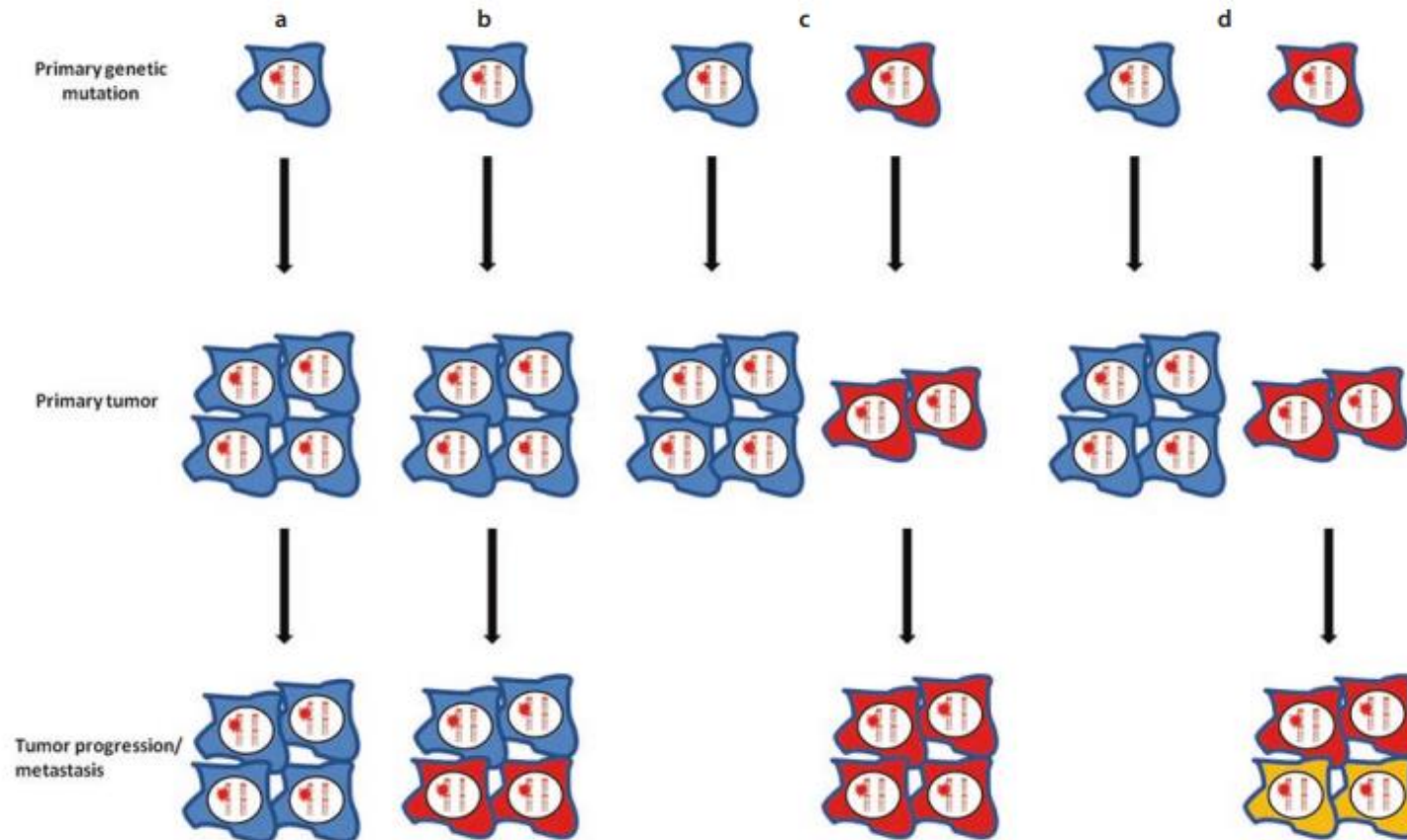


ONE SIZE
FITS ALL



MADE TO
MEASURE

Model of cancer



Monoclonal Hypothesis

Clonal divergence

Polyclonal

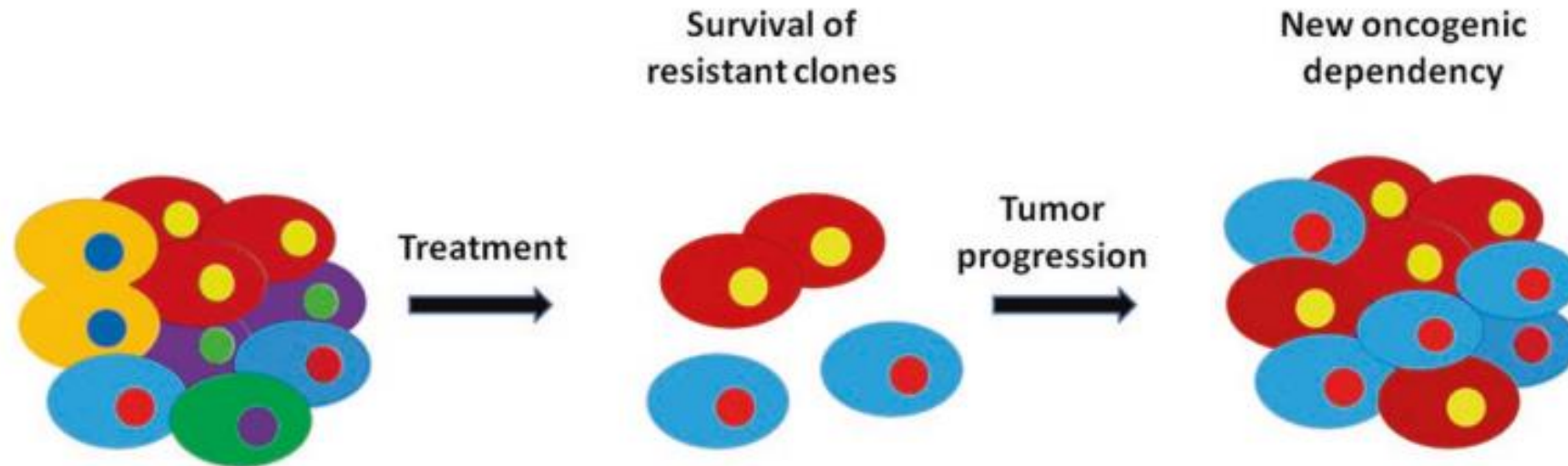
Clonal convergence

Polyclonal

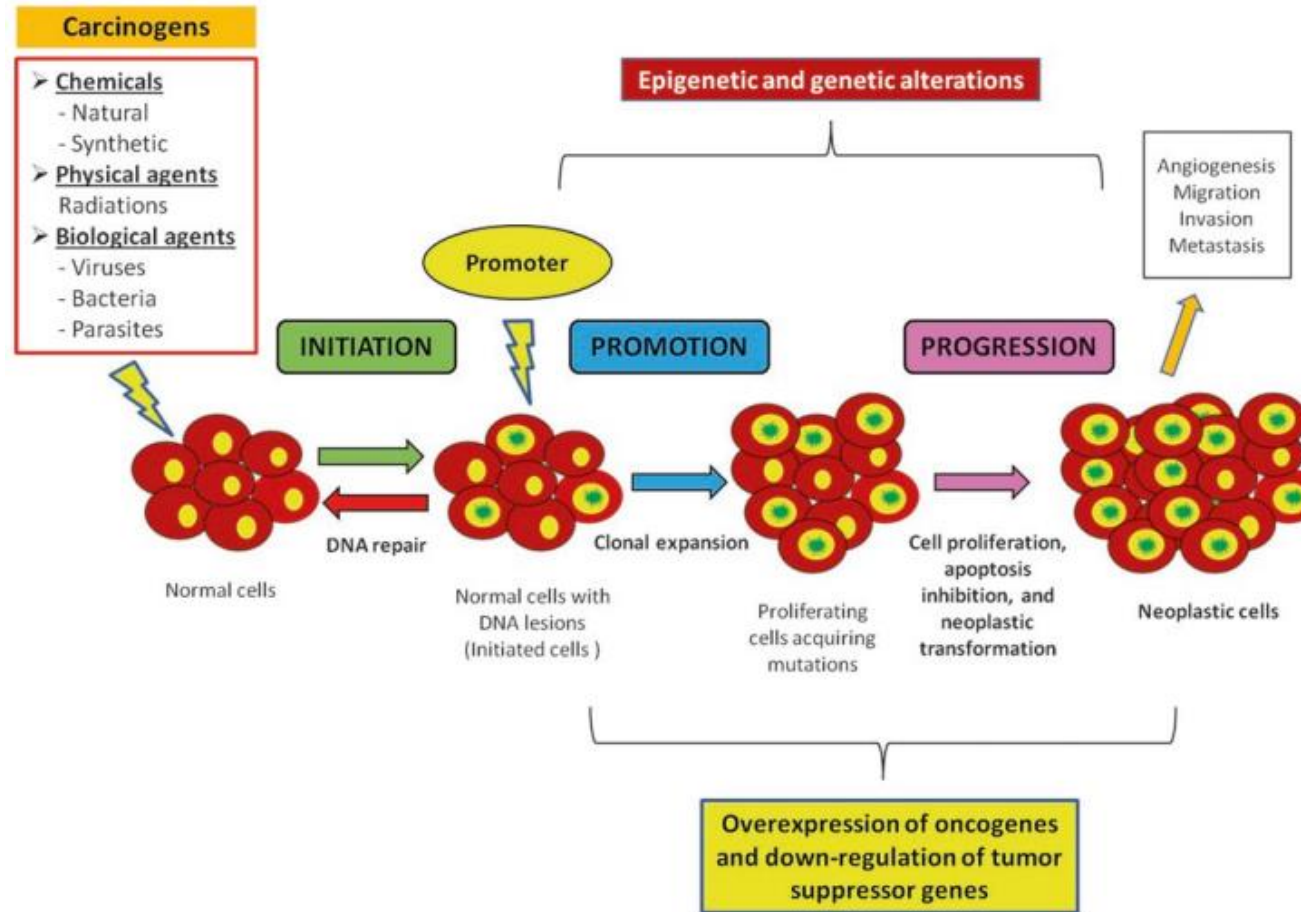
Early Clonal convergence

Late Clonal divergence

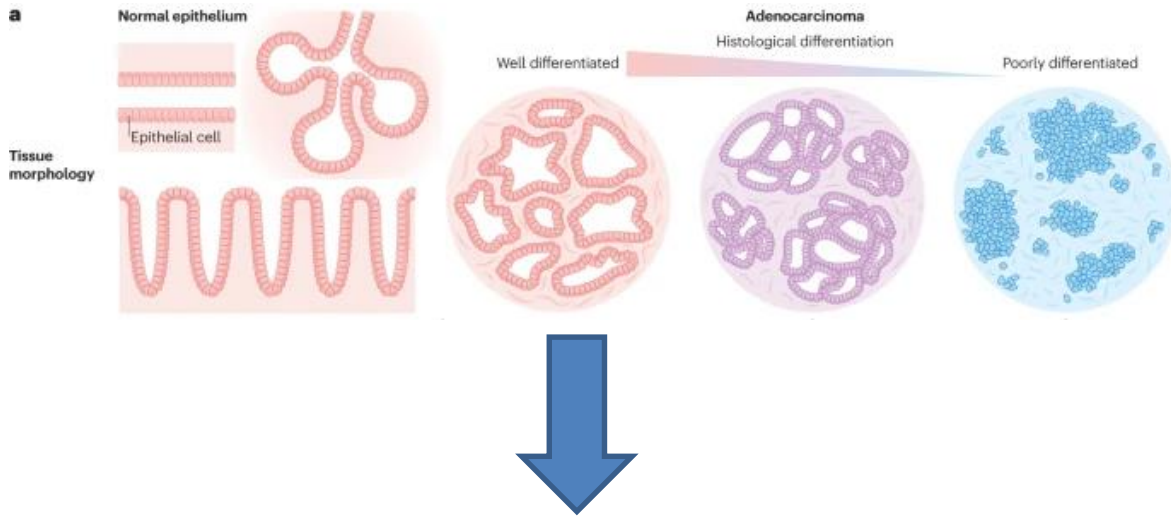
Intratumoral heterogeneity



Carcinogenesis stage



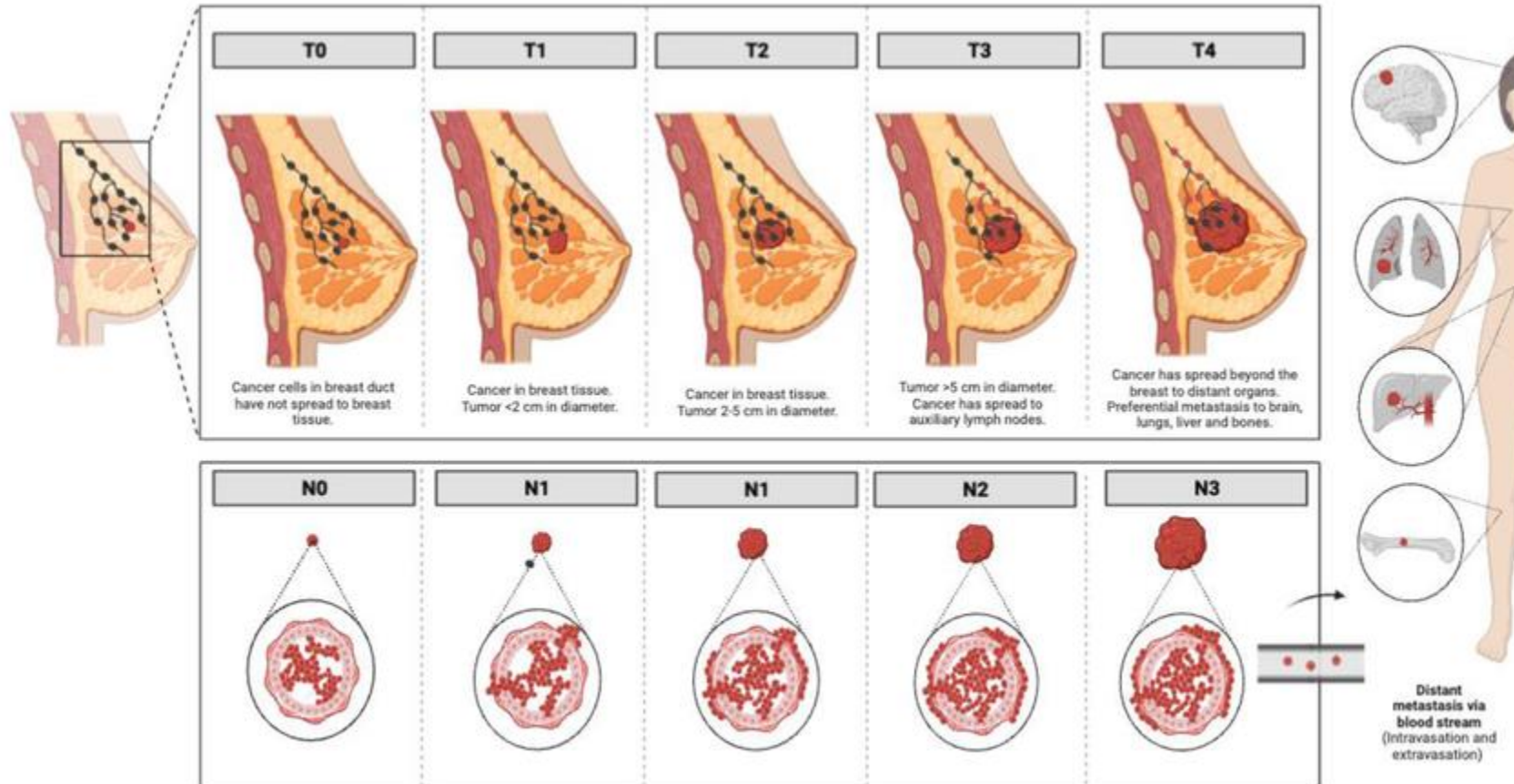
Histopathology



- The cystic structure is gradually lost along with the loss of histological differentiation, and poorly differentiated adenocarcinoma exhibit a solid morphology without apparent apico-basal polarity

Tumor Type : Carcinoma ? Sarcoma?
Grading : well to poorly differentiated
Tumor size?
Nodal invasion ?
Metastasis

Tumor progression and TNM stage





Treatment modalities

- Surgery: indications and limitations.
- Chemotherapy: mechanisms, systemic effects.
- Radiotherapy: basic concept.
- New kids on the block : Immunotherapy and targeted therapy



Surgery: Indications

- Localized tumors with clear margins
- Resectable disease without major invasion
- Early-stage cancers
- Symptom relief (e.g., obstruction, bleeding)
- Diagnostic or staging purposes

Surgery: Limitations

- Advanced or metastatic disease
- Poor patient performance status or comorbidities
- High surgical risk or anatomical constraints
- Potential functional impairment post-surgery
- Limited benefit compared to other modalities

Targeted Therapy : EGFR and RAF

EGFR INHIBITORS

Non-small cell lung cancer (NSCLC):

EGFR TKIs:

Gefitinib
Erlotinib
Afatinib
Osimertinib

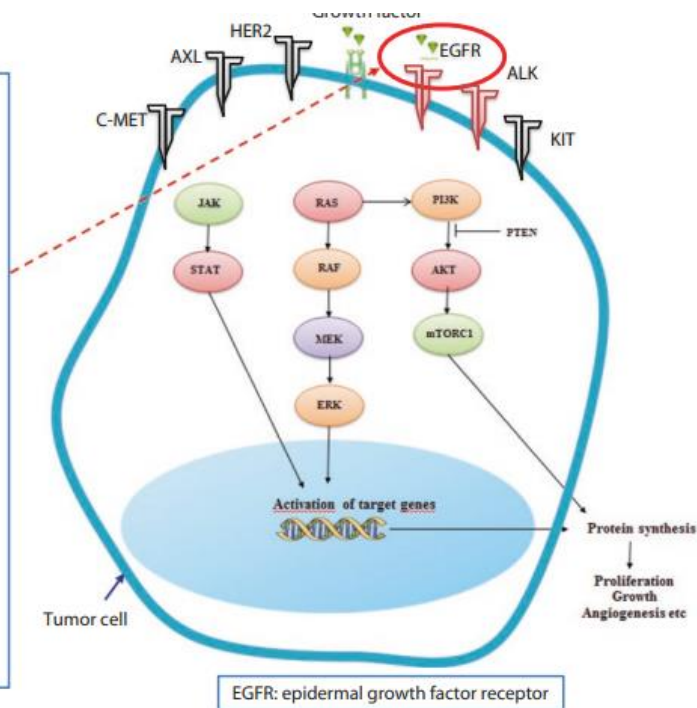
EGFR-targeted monoclonal antibodies:

Necitumumab

Colorectal cancer (CRC):

EGFR-targeted monoclonal antibodies:

Cetuximab
Panitumumab



BRAF/MEK/ERK INHIBITORS

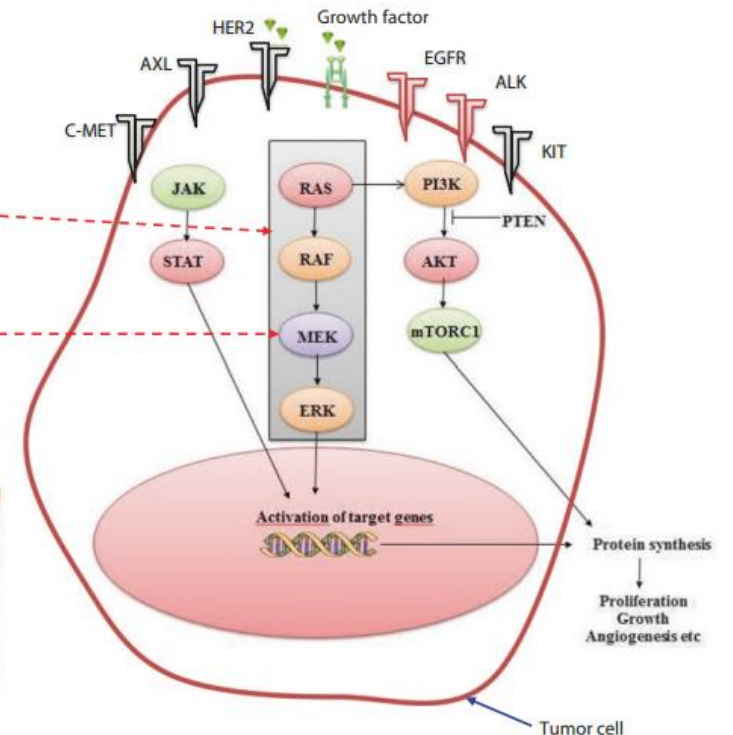
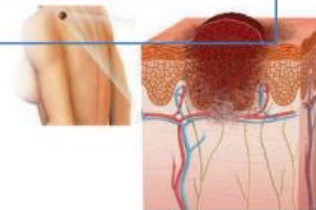
MELANOMA

BRAF Inhibitors:

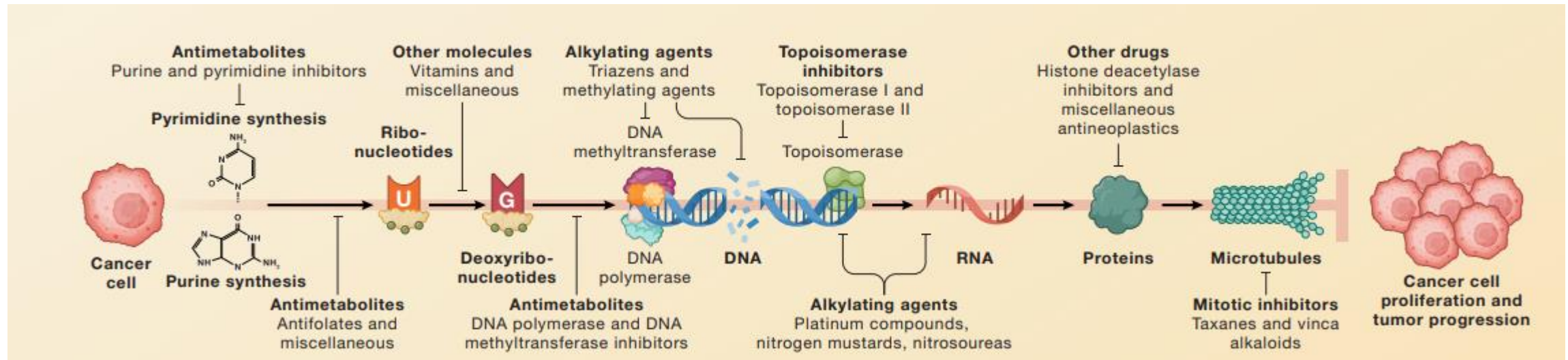
Vemurafenib
Dabrafenib
Encorafenib

Inhibitors of MEK1/2:

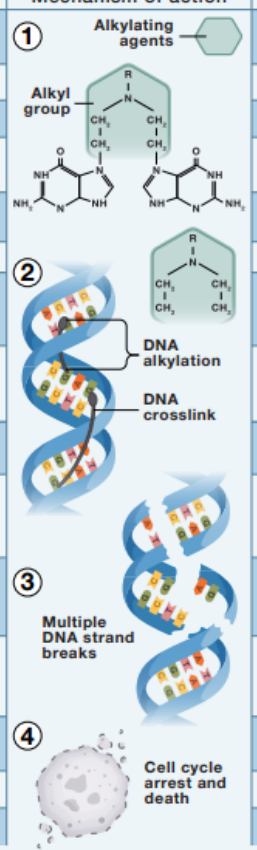
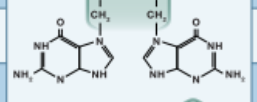
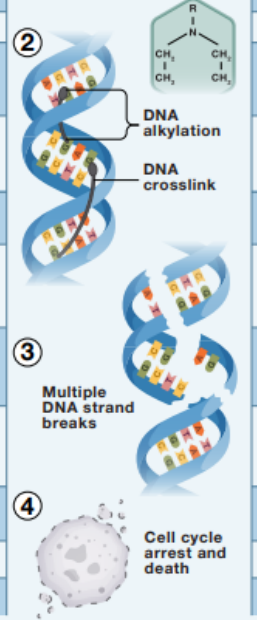

Trametinib
Cobimetinib
Binimetinib



Treatment modalities-Chemotherapy

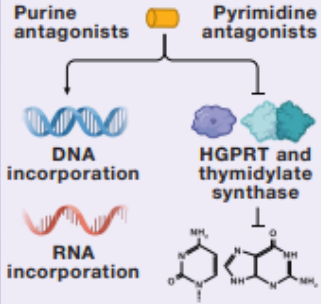
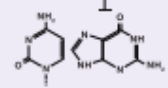
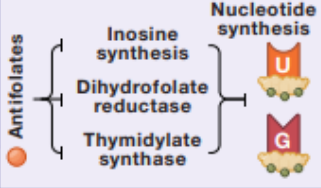
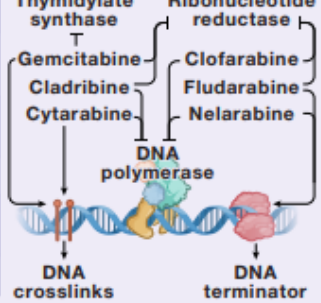


Chemotherapy-Alkylating agents

ALKYLATING AGENTS			
	Drug	Mechanism of action	Therapeutic applications
Platinum compounds	Cisplatin	 <p>① Alkylating agents</p> <p>Alkyl group</p> <p>② DNA alkylation</p> <p>DNA crosslink</p> <p>③ Multiple DNA strand breaks</p> <p>④ Cell cycle arrest and death</p>	Bladder, testicular, ovarian, head and neck, uterus, lung cancer
	Carboplatin		Lung cancer, ovarian cancer
	Oxaliplatin		Colorectal cancer
Nitrosoureas	Carmustine	 <p>Brain tumor, lymphoma, multiple myeloma</p>	Brain tumor, lymphoma, multiple myeloma
	Lomustine		Brain and lung tumor, malignant melanoma, Hodgkin's lymphoma
	Streptozocin		Pancreatic cancer
Nitrogen mustards	Bendamustine	 <p>Chronic lymphocytic leukemia, B-cell non-Hodgkin's lymphoma, multiple myeloma</p>	Chronic lymphocytic leukemia, B-cell non-Hodgkin's lymphoma, multiple myeloma
	Chlorambucil		Hodgkin's lymphoma, chronic lymphocytic leukemia, giant follicular lymphoma
	Cyclophosphamide		Multiple solid tumors
	Ifosfamide		Sarcoma, testicular, ovarian, bronchial, breast, pancreatic, endometrial cancer, lymphoma
	Mechlorethamine		T-cell lymphoma, B-cell lymphoma, chronic leukemia, lung cancer, medulloblastoma
	Melphalan		Multiple myeloma, ovarian cancer, neuroblastoma, melanoma, sarcoma
Triazines	Dacarbazine	 <p>Malignant melanoma, Hodgkin's lymphoma, sarcoma</p>	Malignant melanoma, Hodgkin's lymphoma, sarcoma
	Temozolomide		Brain tumors
	Procarbazine		Hodgkin's lymphoma

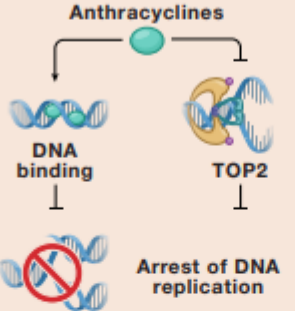
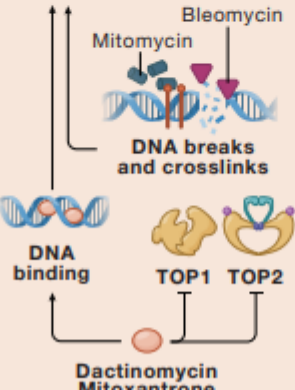
- Alkylating agents are classified as nitrogen mustards, platinum compounds, nitrosoureas, triazanes, and methylating agents.
- All these drugs can alkylate nucleic acids and proteins leading to the formation of intra- and inter-strand crosslinks responsible for multiple DNA breaks.

Chemotherapy-Antimetabolites

ANTIMETABOLITES			
	Drug	Mechanism of action	Therapeutic applications
Pyrimidine antagonists	Fluorouracil		Colorectal, breast, stomach, pancreatic, head and neck cancer
	Capecitabine		Colorectal, breast and gastric cancer
	Floxuridine		Digestive system cancers
Purine antagonists	6 - mercaptopurine		Acute lymphoblastic or lymphocytic leukemia
	Thioguanine		Acute myeloblastic or lymphoblastic leukemia
Antifolates	Methotrexate		Leukemia, breast, skin, head and neck, lung, uterine cancer
	Pemetrexed		Non-squamous non-small cell lung cancer, malignant pleural mesothelioma
	Pralatrexate		T-cell lymphoma
Enzyme Inhibitors	Cladribine		Hairy cell leukemia
	Fludarabine		B-cell chronic lymphocytic leukemia
	Gemcitabine		Pancreatic, lung, ovarian, breast cancer
	Clofarabine		Acute lymphoblastic leukemia
	Nelarabine		T-cell lymphoblastic leukemia and lymphoma
	Cytarabine		Acute myeloid and other leukemias

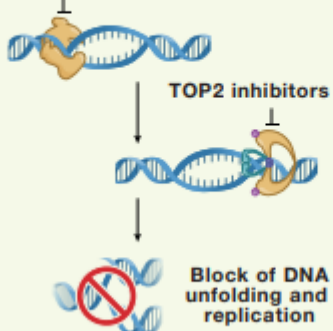
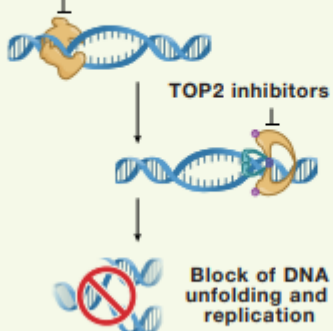
- **Antimetabolites** interfere with both DNA and RNA synthesis.
- This category contains: purine and pyrimidine antagonists, which are incorporated in the nascent DNA and RNA structure, or are able to interfere with enzymes involved in the production of nitrogenous bases;
- Besides these classes of antimetabolites there are also DNA Methyltransferase inhibitors and other drugs with non-specific mechanisms of action.

Chemotherapy-Cytotoxic antibiotics

ANTI-TUMOR ANTIBIOTICS			
	Drug	Mechanism of action	Therapeutic applications
Anthracyclines	Daunorubicin	 <p>Anthracyclines</p> <p>DNA binding</p> <p>TOP2</p> <p>Arrest of DNA replication</p>	Leukemia
	(Liposomal) Doxorubicin		Several solid tumors and hematological malignancies, AIDS-Kaposi's sarcoma
	Epirubicin		Several solid tumors and hematological malignancies
	Idarubicin		Acute myeloid/lymphoid leukemia
	Valrubicin		Bladder cancer
Non-Anthracyclines	Bleomycin	 <p>Bleomycin</p> <p>Mitomycin</p> <p>DNA breaks and crosslinks</p> <p>DNA binding</p> <p>TOP1 TOP2</p> <p>Dactinomycin Mitoxantrone</p>	Squamous cell and testicular carcinoma, lymphoma, pleural effusion
	Dactinomycin		Several solid tumors
	Mitomycin-C		Stomach, pancreatic, breast, bronchial carcinoma, solid tumors
	Mitoxantrone		Prostate cancer, leukemia, non-Hodgkin's lymphoma, breast cancer, hepatocellular carcinoma

- Cytotoxic antibiotics comprise two different classes of drugs, anthracycline and non-anthracycline agents.
- The main mechanism of action of anthracyclines is to form covalent bonds with nucleic acids and Topoisomerase-II (TOP2), thereby interfering with DNA replication.
- In contrast, non-anthracyclines exert different effects; while some agents (e.g. Dactinomycin and Mitoxantrone) directly interfere with topoisomerases, others induce DNA breaks (e.g. Bleomycin) or DNA crosslinks (e.g. Mitomycin).

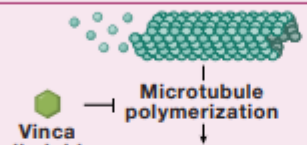
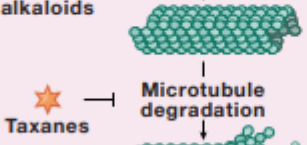
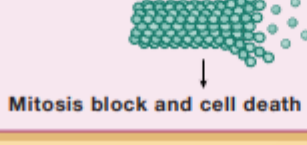
Chemotherapy-Topoisomerases inhibitors

TOPOISOMERASE INHIBITORS			
	Drug	Mechanism of action	Therapeutic applications
TOP1 Inhibitors	(Liposomal) Irinotecan		Colorectal, small-cell lung, pancreatic cancer
	Topotecan		Ovarian cancer, small cell lung cancer, cervical cancer
TOP2 Inhibitors	Etoposide (VP-16)		Lung, testicular and ovarian cancer, lymphoma, acute myeloid leukemia
	Mitoxantrone		Prostate, liver and breast cancer, leukemia, non-Hodgkin's lymphoma
	Teniposide		Leukemia

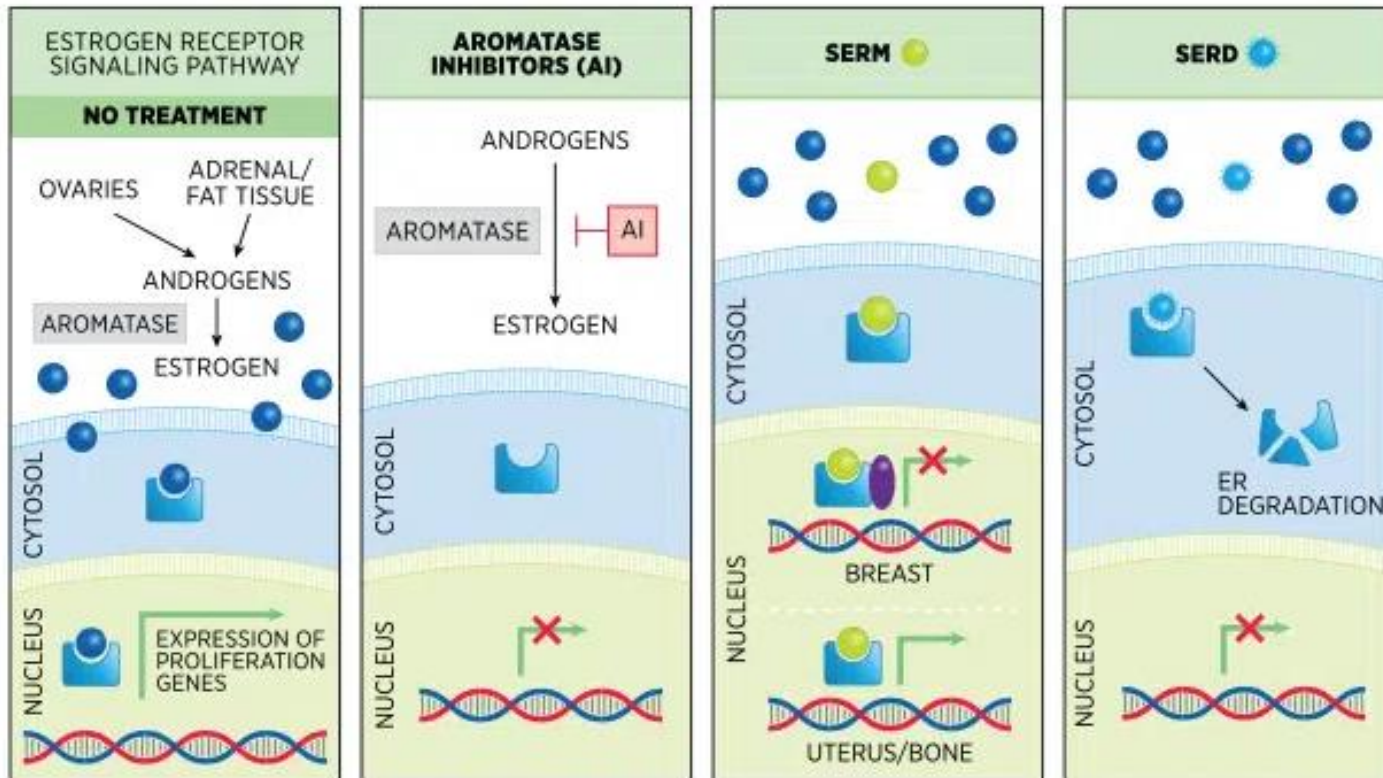
- This category of drugs contains both Topoisomerase-I (TOP1) and Topoisomerase-II (TOP2) inhibitors.
- Among the first group, Irinotecan and Topotecan bind to TOP1 to prevent DNA unwinding, which in turn inhibits DNA replication.
- Similarly, Etoposide and Mitoxantrone prevent DNA replication by binding TOP2. In addition, the inhibition of Topoisomerases induces the formation of single-strand and double-strand breaks of DNA leading to the arrest of the cell cycle.

Chemotherapy-Mitotic inhibitors

- Mitotic inhibitors are plant-derived agents able to induce cell cycle arrest by preventing the formation of microtubules.
- This category contains vinca alkaloids and taxanes
- The former can bind the tubulin of microtubules inhibiting their assembly, while the latter prevents microtubule disassembly by binding the same component.

MITOTIC INHIBITORS			
	Drug	Mechanism of action	Therapeutic applications
Taxanes	Cabazitaxel	 Microtubule polymerization	Metastatic castration-resistant prostate cancer
	Docetaxel		Breast, lung, prostate, stomach, head and neck cancer
	(Nab) Paclitaxel	 Microtubule degradation	Breast, ovarian, lung and pancreatic cancer, AIDS-related Kaposi's sarcoma
Vinca alkaloids	Vinblastine	 Mitosis block and cell death	Hodgkin's lymphoma, testicular and breast cancer, Kaposi's sarcoma
	(Liposome) Vincristine		Leukemia, lymphoma, neuroblastoma, sarcomas
	Vinorelbine		Lung cancer and breast cancer

Endocrine therapy in Breast cancer

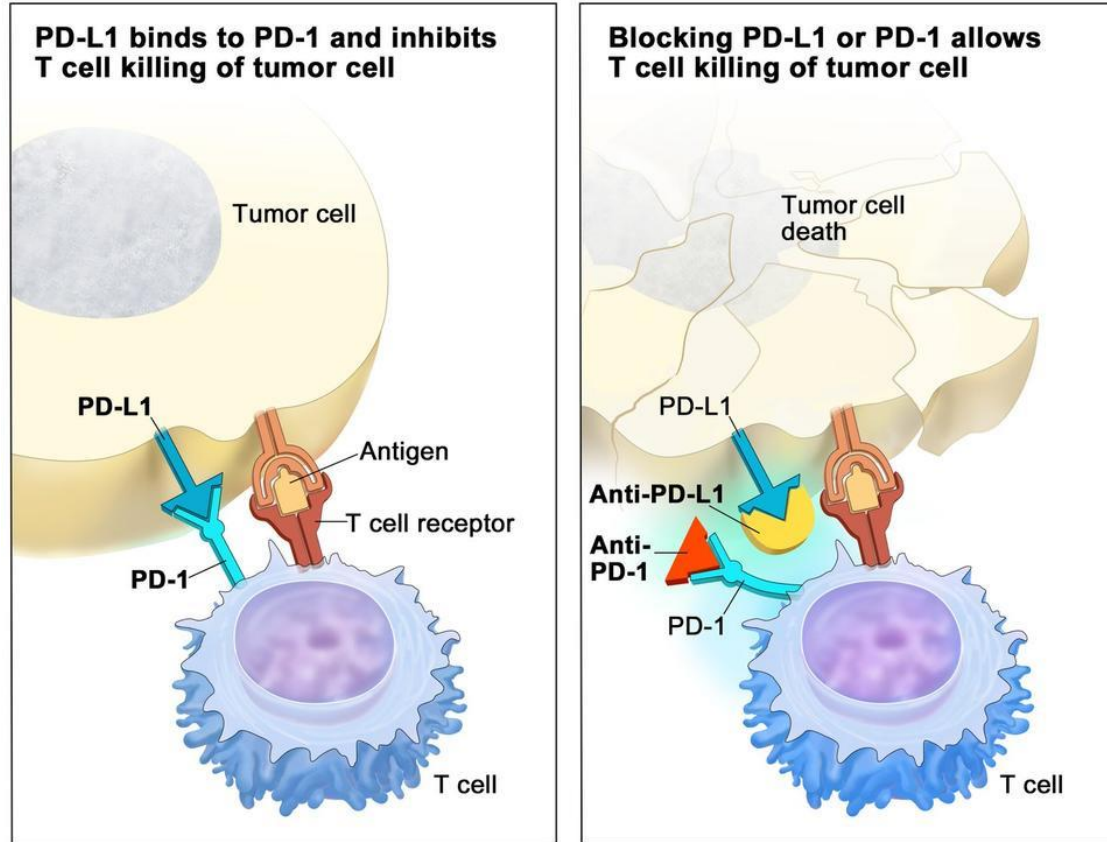


AI : block residual estrogen production in extra-ovarian tissues (fat tissue and the adrenal glands)

SERM : compete with estrogen to bind to the ER and have different effects depending on the tissue.

SERD : bind to ER, inhibit its translocation to the nucleus, and cause its destabilization and degradation

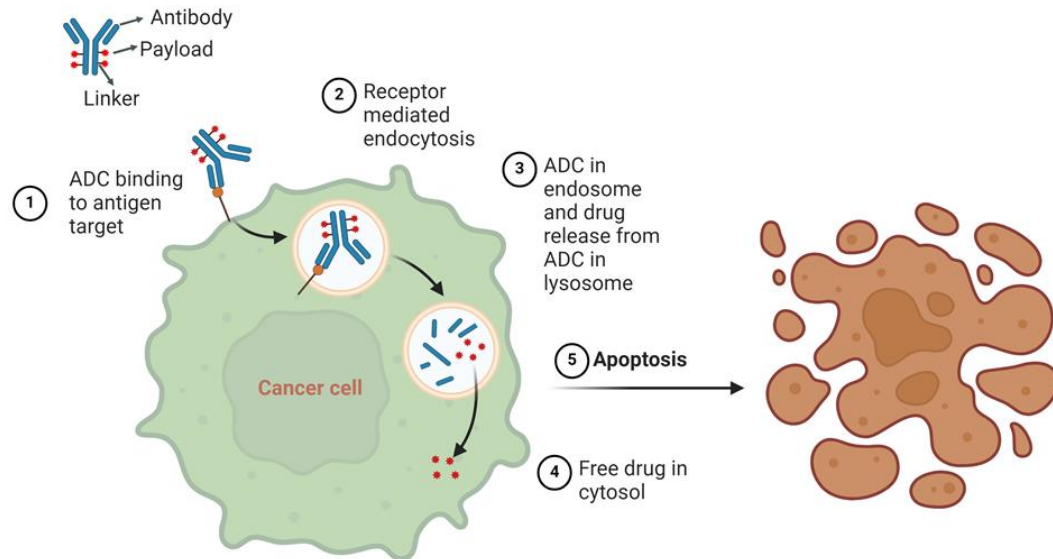
Immune checkpoint inhibitors



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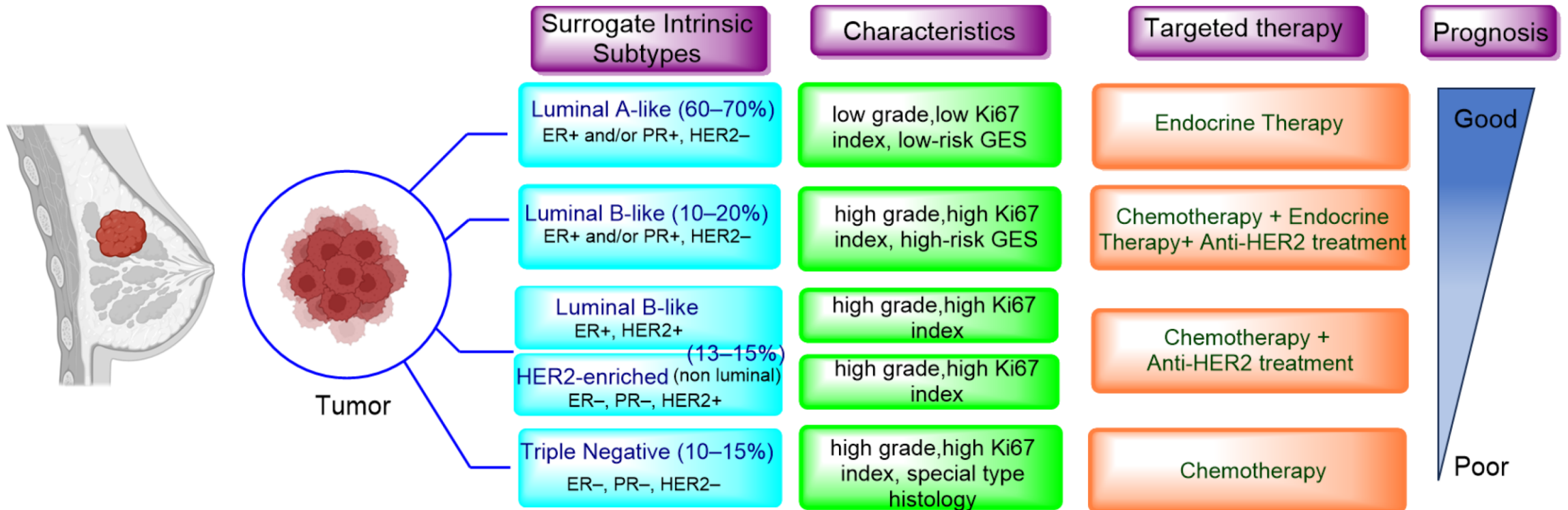
- Many tumors develop mechanisms that allow them to evade antitumor responses.
- Despite immunosurveillance, tumors can develop and become clinically evident.

New kids on the block- ADC

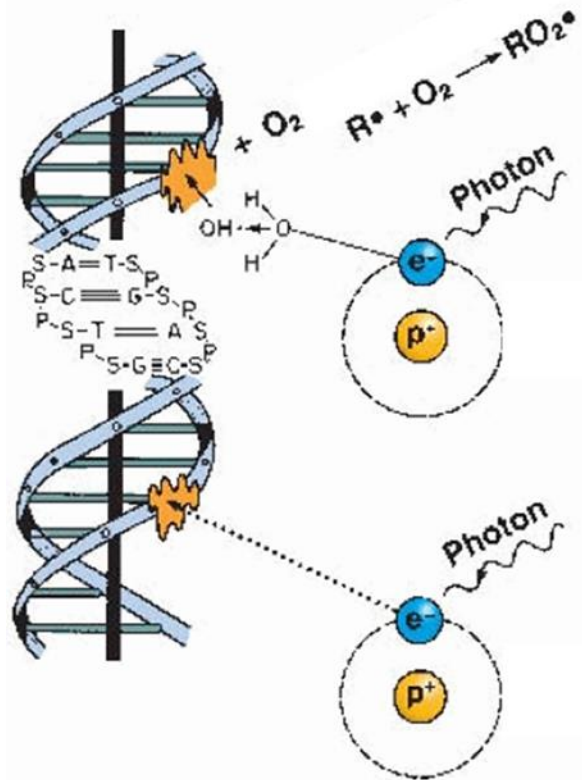


- Antibody linked with a cytotoxic payload
- ADCs combine :
 - Targeting properties of monoclonal antibody
 - Cancer cell-killing of cytotoxic drugs

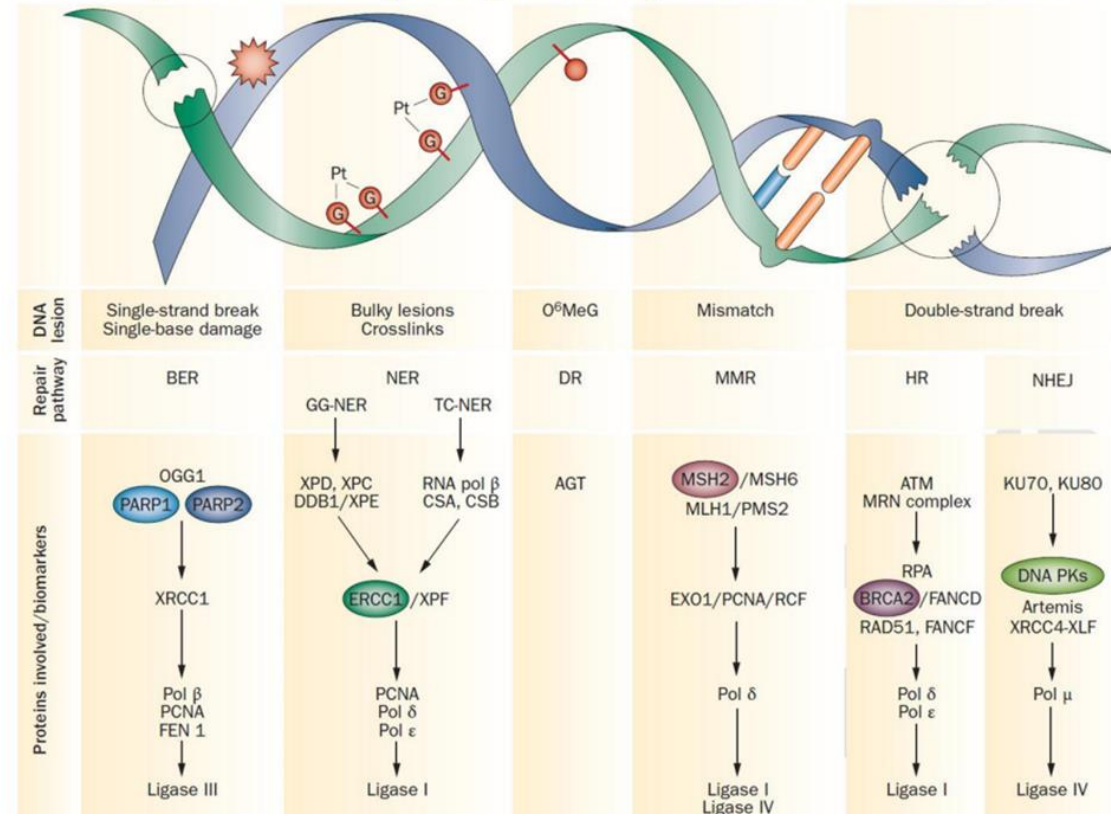
Multimodal strategies-Breast cancer



Radiotherapy



Major DNA repair pathways and biomarkers





Case Presentation

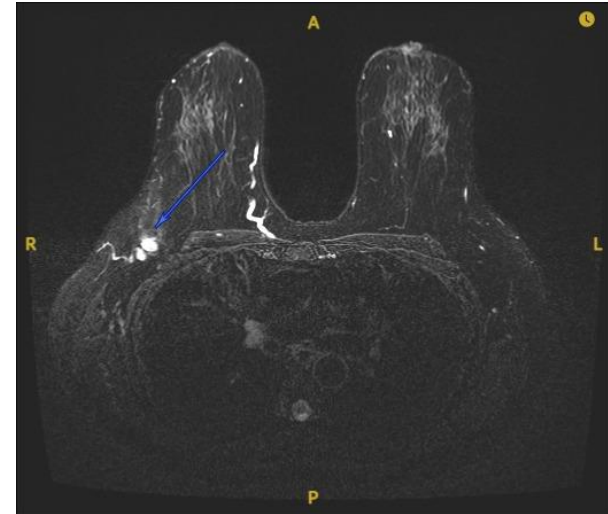
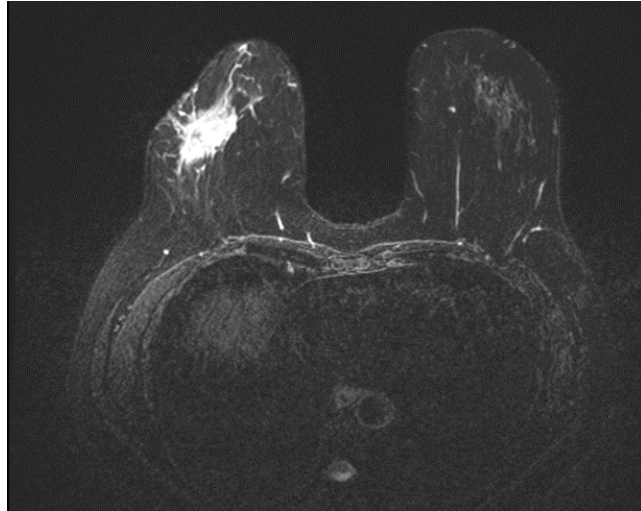
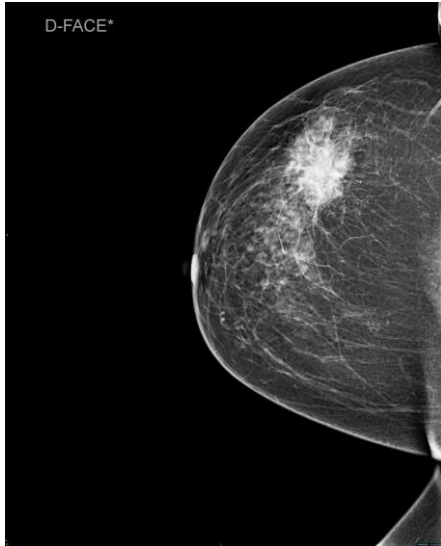
- Mrs R..
- 59 yo, post menopausal
- Initial presentation : January 2023, Autopalpation of right breast lump
- Medical history : None
- Family history : None



Clinical examination

- Right breast with 45 x 40 mm mobile mass in Right central outer
- Lymph nodes: Mobile Right axillary lymph nodes (2cm)

Breast image

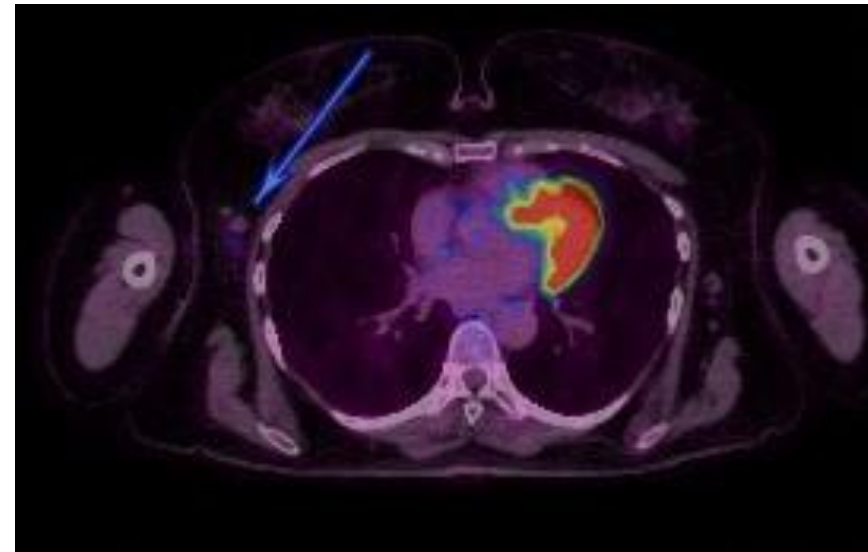
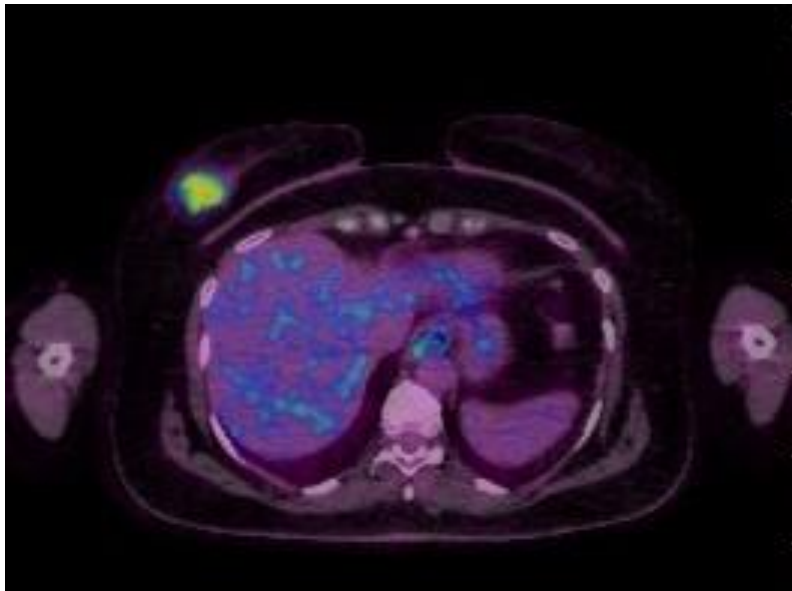


Architectural distortion with associated 35 mm irregular mass in the outer central right breast, posterior depth.
Enlarged lymph nodes in the right axilla.

Ultra sound guided biopsies

- Right breast mass (core needle),
 - Invasive ductal carcinoma, grade 2, No LVI
 - ER+(100%)PR-(0%)Her2-(IHC 2, FISH neg)
 - Ki-67 15%
- Right axillary lymph node (FNA)
 - Metastatic adenocarcinoma

PET-CT



→ cT2 cN1 M0

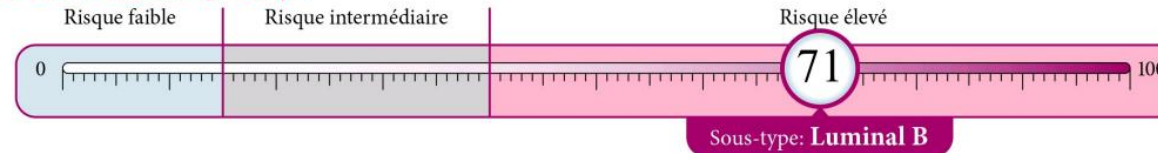
Surgery and Pathology

- Right simple mastectomy and axillary lymph node dissection.
No reconstruction
- Pathology:
 - Breast:
 - Lesion 1 : 35mm, Grade 2, LVI+
 - Lesion 2 : 5mm, Grade 2 + DCIS, ER+(100%), RP-
 - Lymph nodes: 2/13 involved, 2 macrometastases
- Stage pT2(m)N1a (Stage IIB, AJCC 8th Ed. Anatomic)
- Negative surgical margins

Adjuvant treatment

PAM 50

Risque de récurrence (ROR)*:



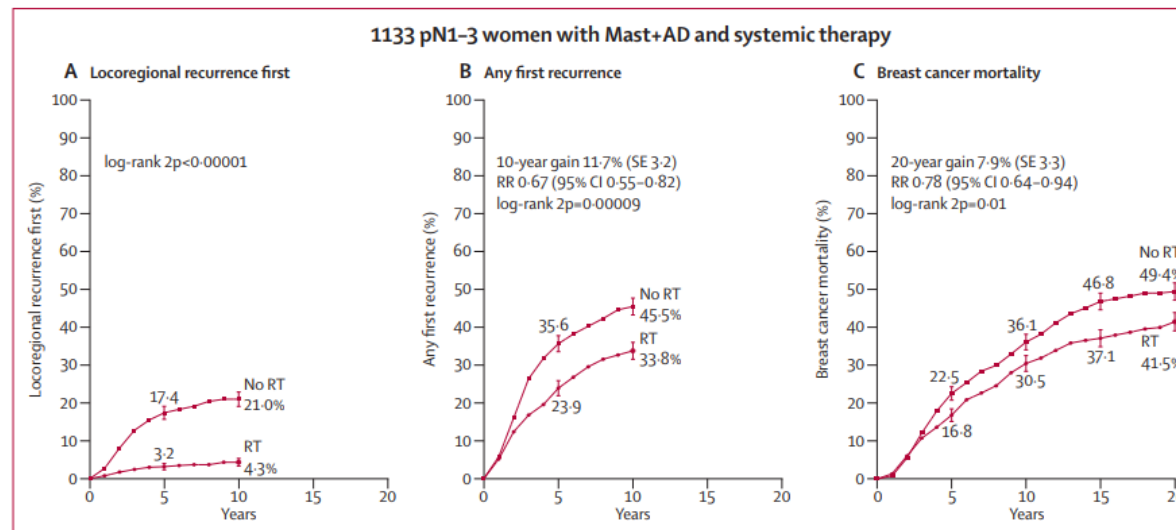
Adjuvant Chemotherapy : 3 AC and 9 Taxol

Radiotherapy

Hormonotherapy : AI

Rationale for post mastectomy radiotherapy

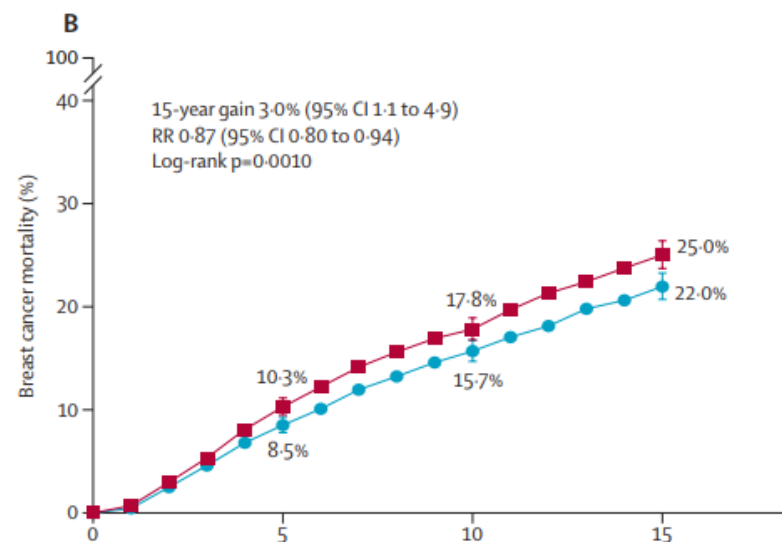
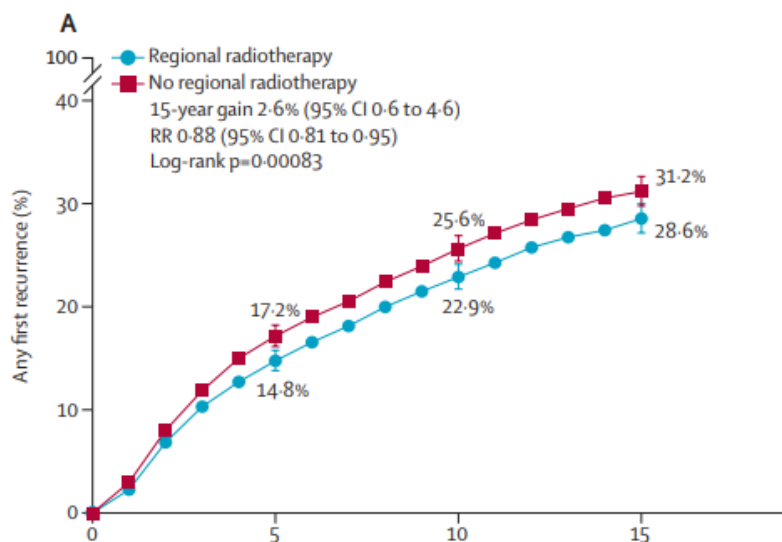
- EBCTCG meta analysis (Lancet 2014)



➔ Improves 20-yr locoregional recurrence and breast cancer-mortality in pN+ subsets

Rationale for post mastectomy loco regional radiotherapy

- EBCTCG meta analysis (Lancet 2023)

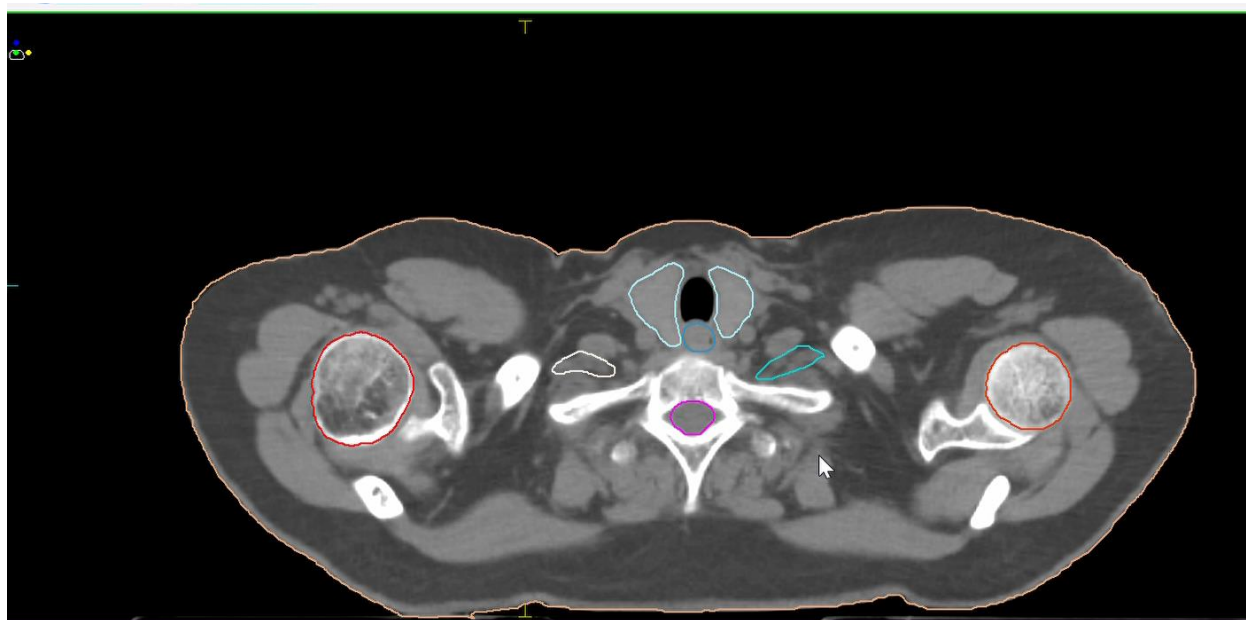


➔ Improves 15-yr recurrence and breast cancer-mortality

Volume definition

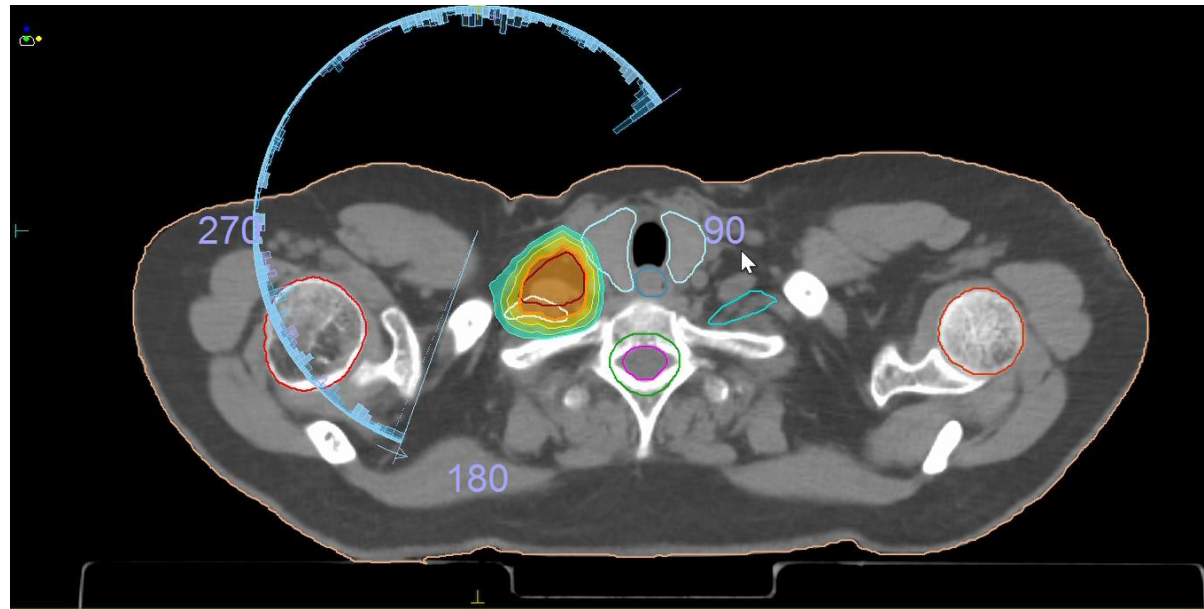
CTV T = CTV Chest wall R

CTV N = nL4+nL2+IP+IMC



Planning

➔ Dose prescription : 40Gy in 15 fractions
HypoG01 phase III RCT



Multidisciplinary approach

- Cancer treatment requires collaboration among specialists: surgeons, medical oncologists, radiation oncologists, radiologists, pathologists, and nurses.
- Tumor boards play a central role in reviewing cases and ensuring consensus on diagnosis, staging, and treatment plans.
- This approach promotes personalized medicine, tailoring therapy to tumor biology, patient comorbidities, and preferences.
- It improves treatment outcomes, reduces errors, and ensures comprehensive care.
- Communication and coordination are essential for integrating surgery, systemic therapy, and radiotherapy effectively.

Multidisciplinary approach



- Thank you for your attention



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