CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Chercher et soigner jusqu'à la guérison

Introduction to treatment of cancer

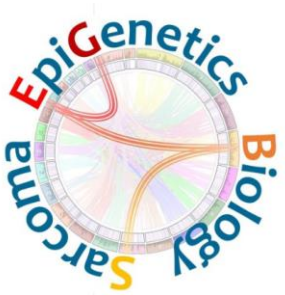
Waisse WAISSI MD. PhD.

Département de Radiothérapie

Centre Léon Bérard

Génétique Epigénétique et Biologie des sarcomes

Centre de Recherche en Cancérologie de Lyon



CRCL CENTRE DE RECHERCHE EN CANCÉROLOGIE DE LYON

unicancer

Disclosures

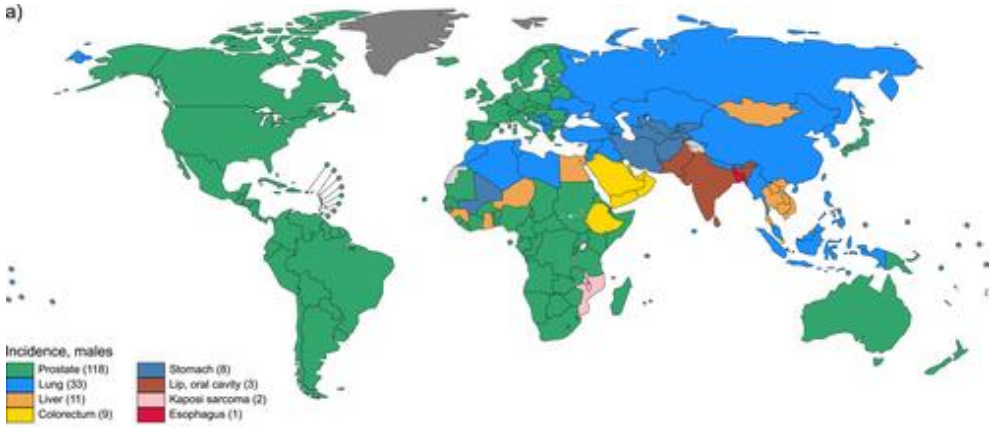
- None

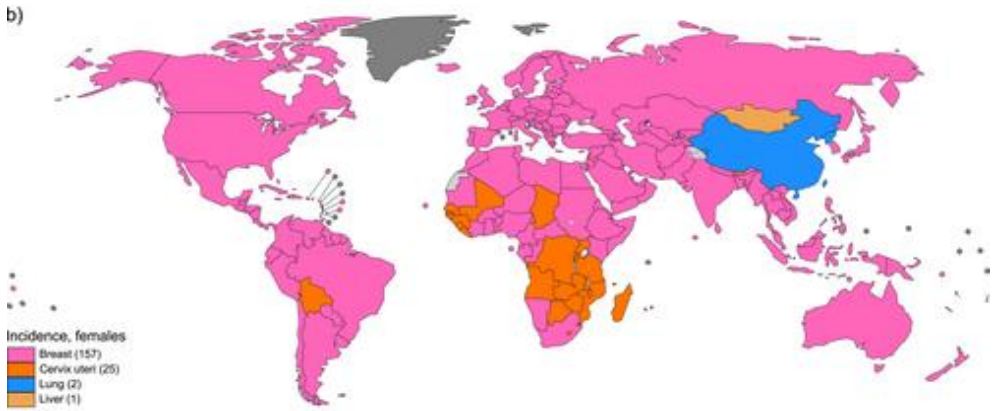
Objectives

- 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



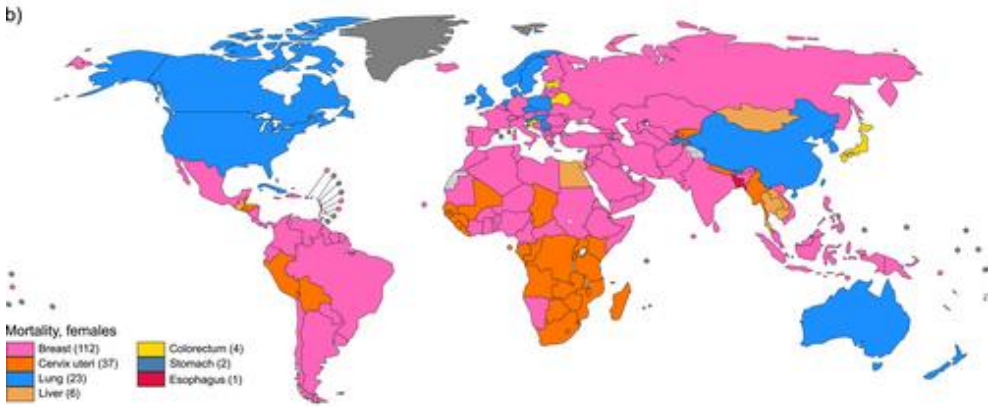


In **men**, **prostate** cancer ranks as the most frequently diagnosed cancer in 118 countries, followed by **lung cancer** in 33 countries, with liver, colorectal, and stomach cancer ranking in first place in 11, nine, and eight countries, respectively

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)

GLOBOCAN 2022

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)

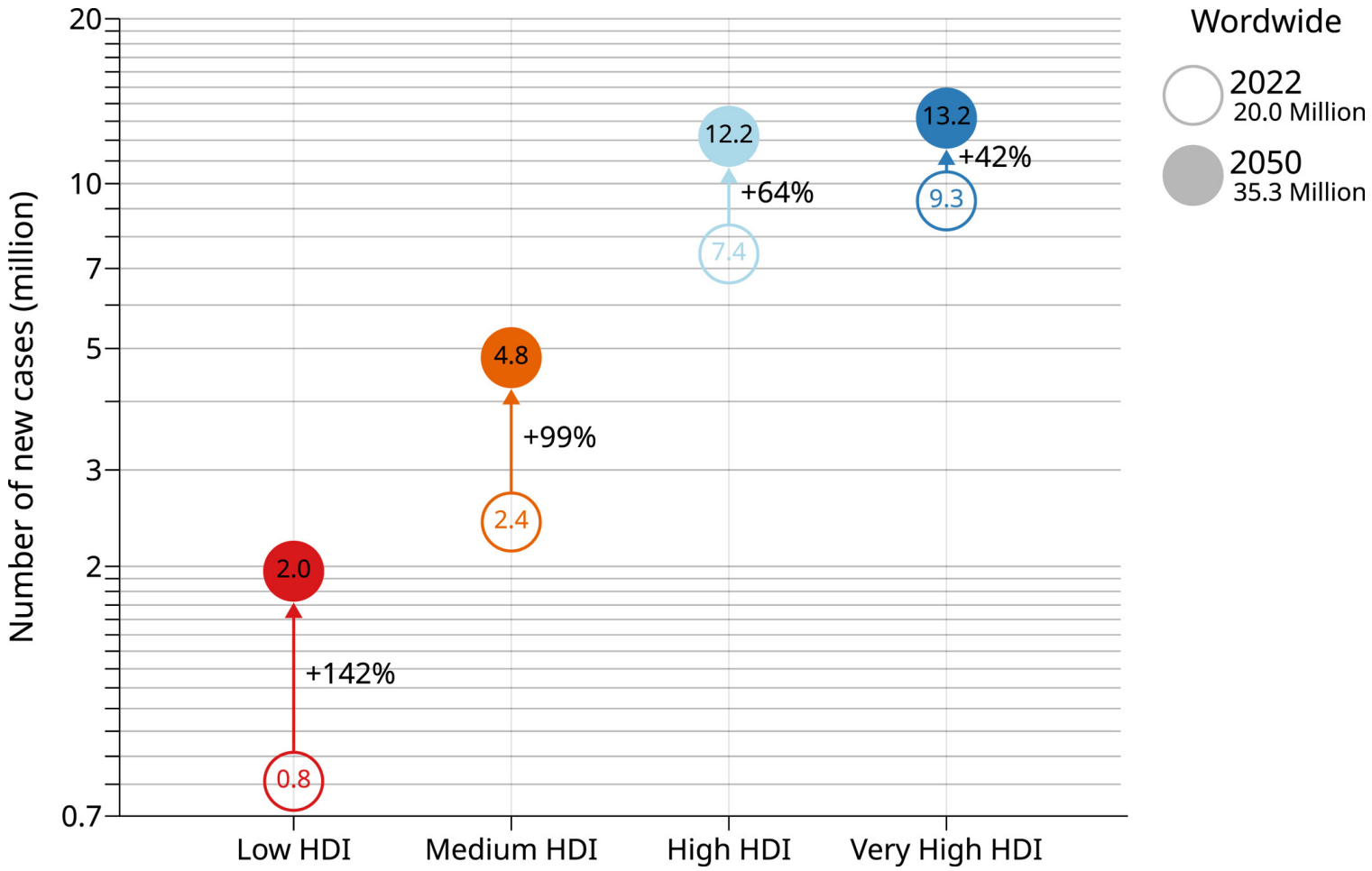
The mortality profile in women is more heterogeneous than that of incidence, however, with breast and cervical cancer as the leading causes of cancer death in 112 and 37 countries, respectively, followed by lung cancer in 23 countries

GLOBOCAN 2022

unicancer

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD
Chercher et soigner jusqu'à la guérison

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
Dusts and fibers		
Asbestos	Larynx, lung, mesothelioma, ovary	Colorectum, pharynx, stomach
Leather dust, wood dust	Nasal cavity and paranasal sinus	
Radiation		
Radium 226, radium 228	Bone, mastoid process, paranasal sinus	
Biological agents		
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	
Helicobacter pylori	Lymphoma, stomach	

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

From IARC

unicancer

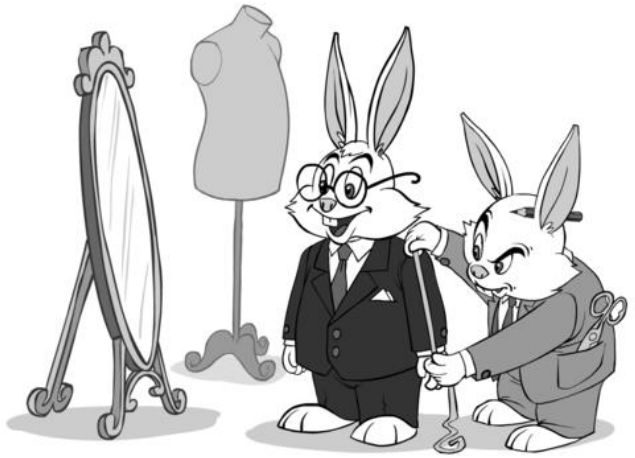
CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD
Chercher et soigner jusqu'à la guérison

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.

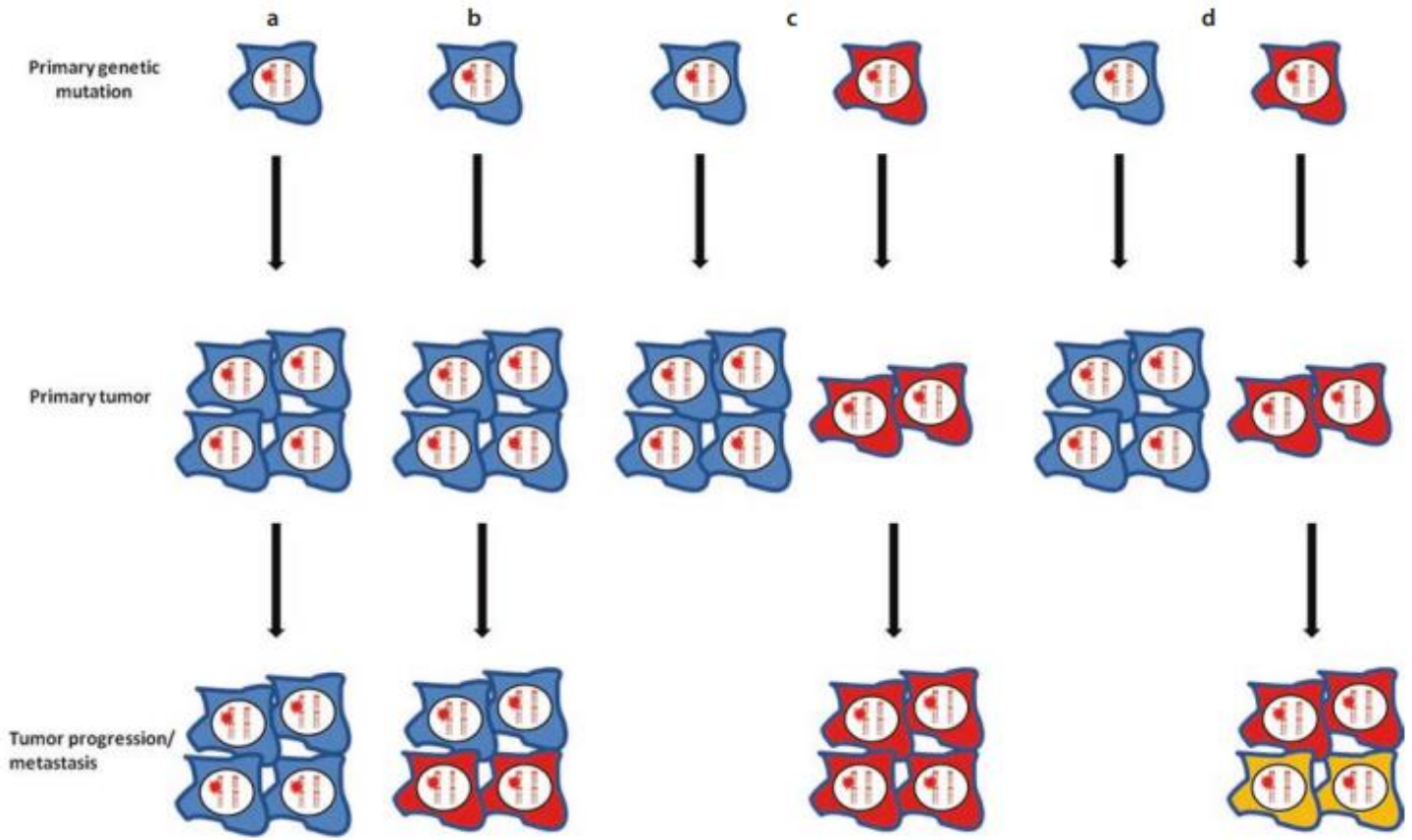
Importance of treatment strategies

ONE SIZE
FITS ALL



MADE TO
MEASURE

Model of cancer



Monoclonal Hypothesis

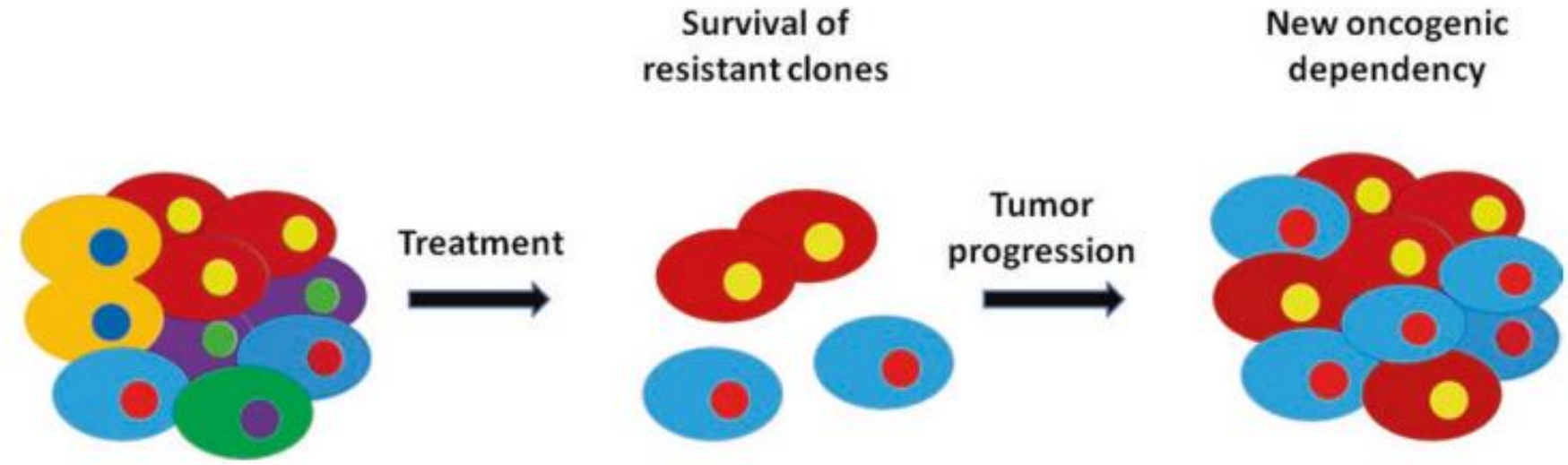
Clonal divergence

Polyclonal Clonal convergence

Polyclonal Early Clonal convergence Late Clonal divergence

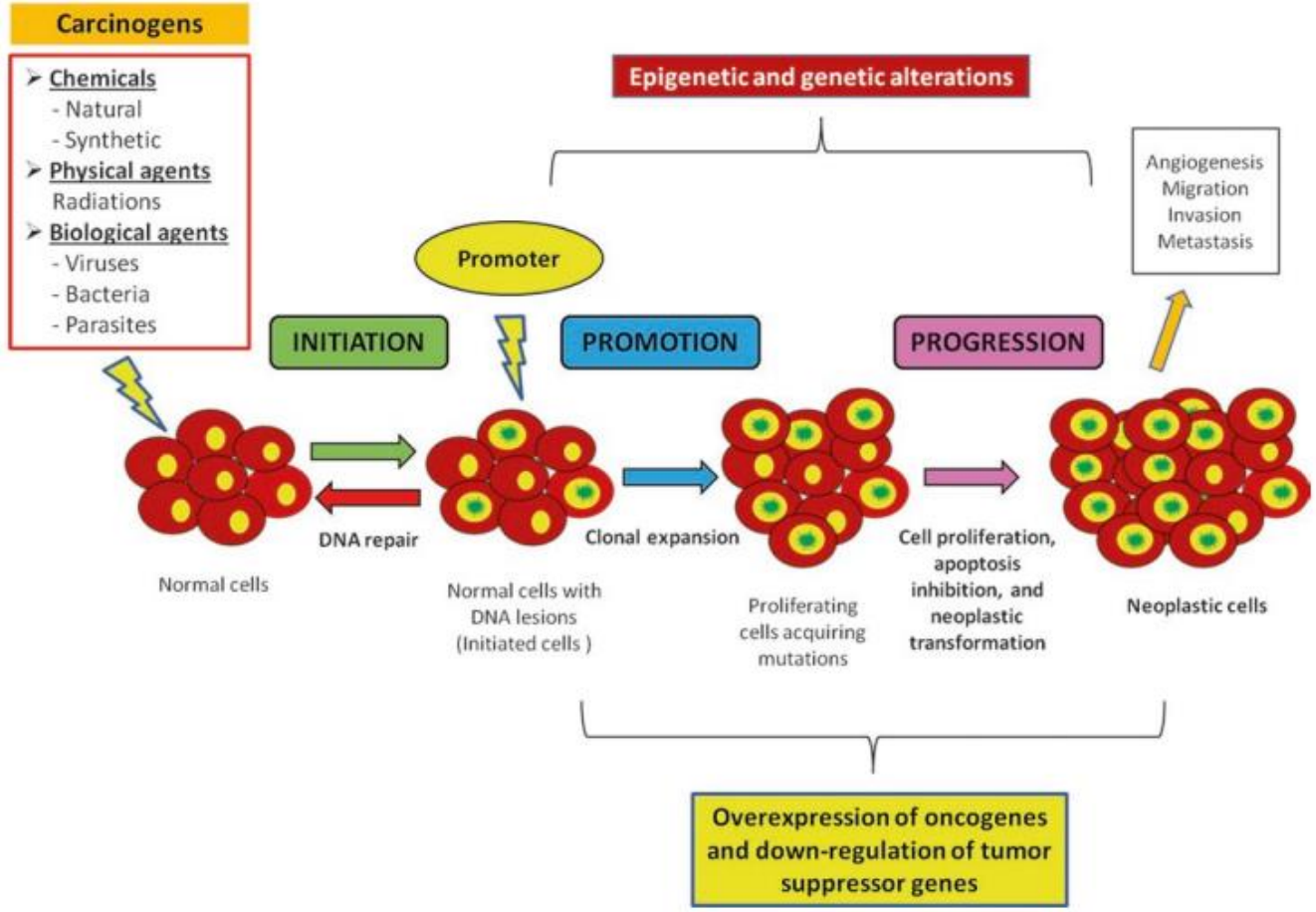
Russo et al. Practical Medical Oncology Textbook

Intratumoral heterogeneity



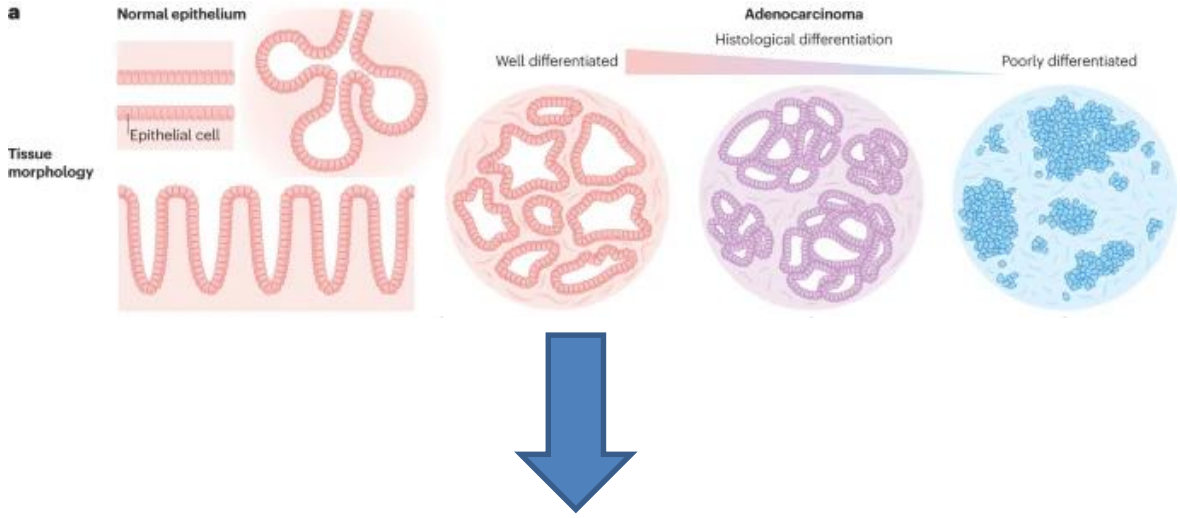
Russo et al. Practical Medical Oncology Textbook

Carcinogenesis stage



Russo et al. Practical Medical Oncology Textbook

Histopathology

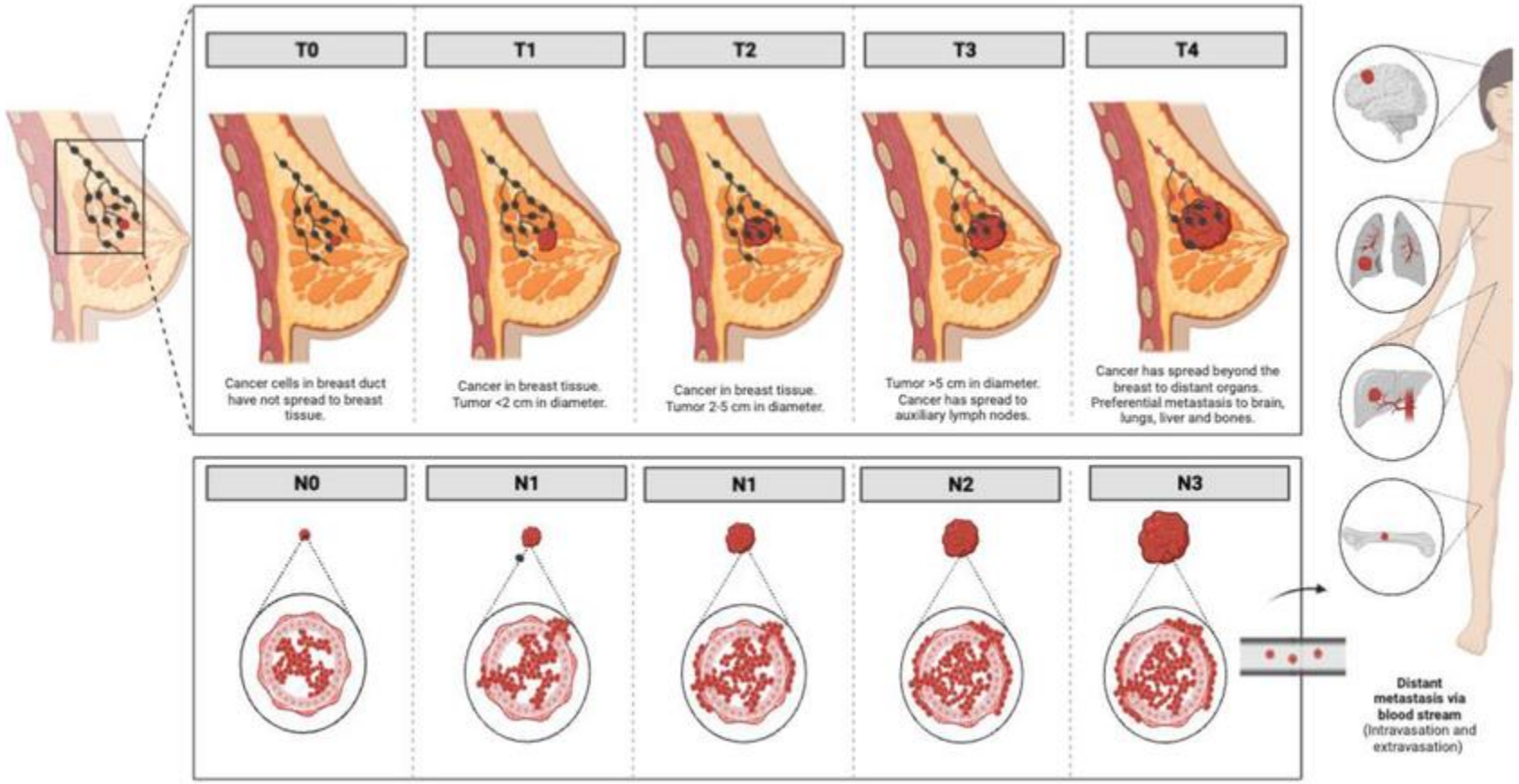


Tumor Type : Carcinoma ? Sarcoma?
Grading : well to poorly differentiated
Tumor size?
Nodal invasion ?
Metastasis

- 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

Fujii et al. Nat Rev Cancer 2023

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

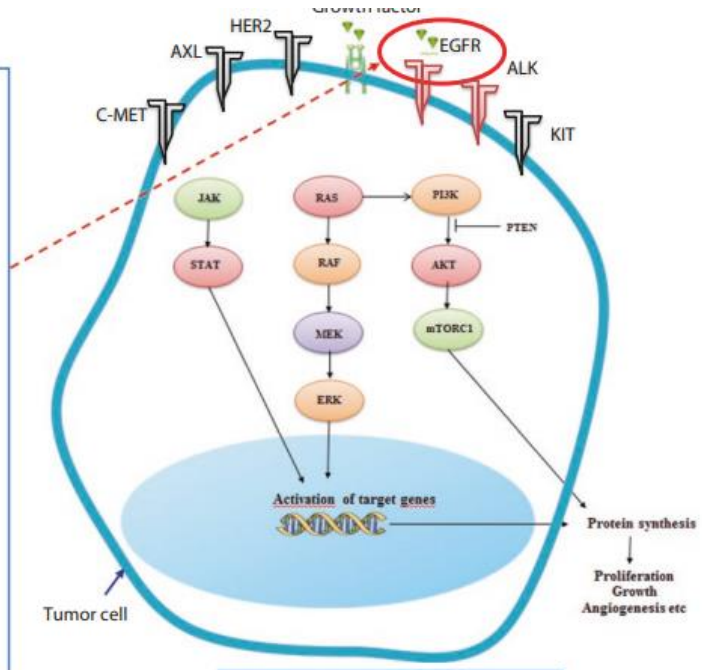
Non-small cell lung cancer (NSCLC):

EGFR TKIs:
Gefitinib
Erlotinib
Afatinib
Osimertinib

EGFR-targeted monoclonal antibodies:
Necitumumab

Colorectal cancer (CRC):

EGFR-targeted monoclonal antibodies:
Cetuximab
Panitumumab



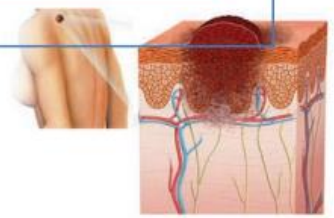
EGFR: epidermal growth factor receptor

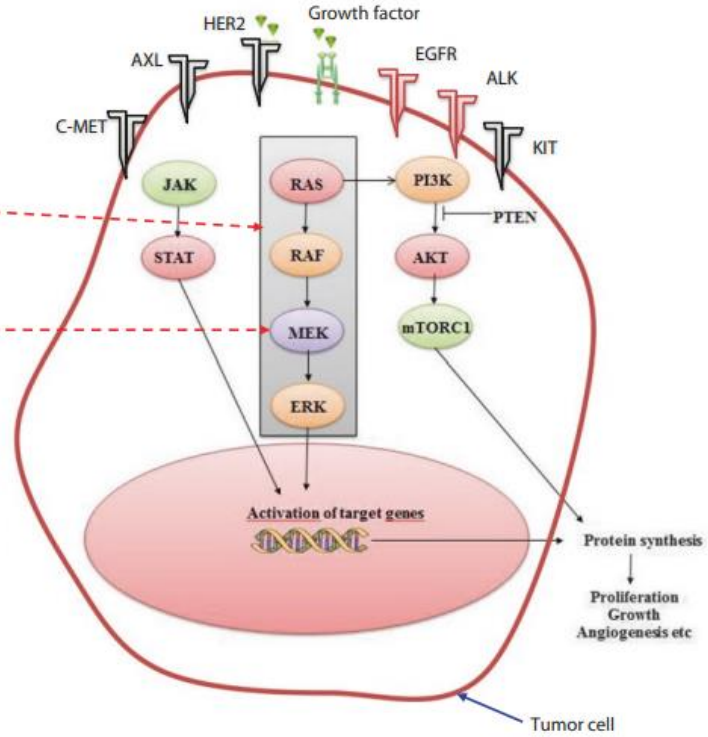
BRAF/MEK/ERK INHIBITORS

MELANOMA

BRAF Inhibitors:
Vemurafenib
Dabrafenib
Encorafenib

Inhibitors of MEK1/2:
Trametinib
Cobimetinib
Binimetinib



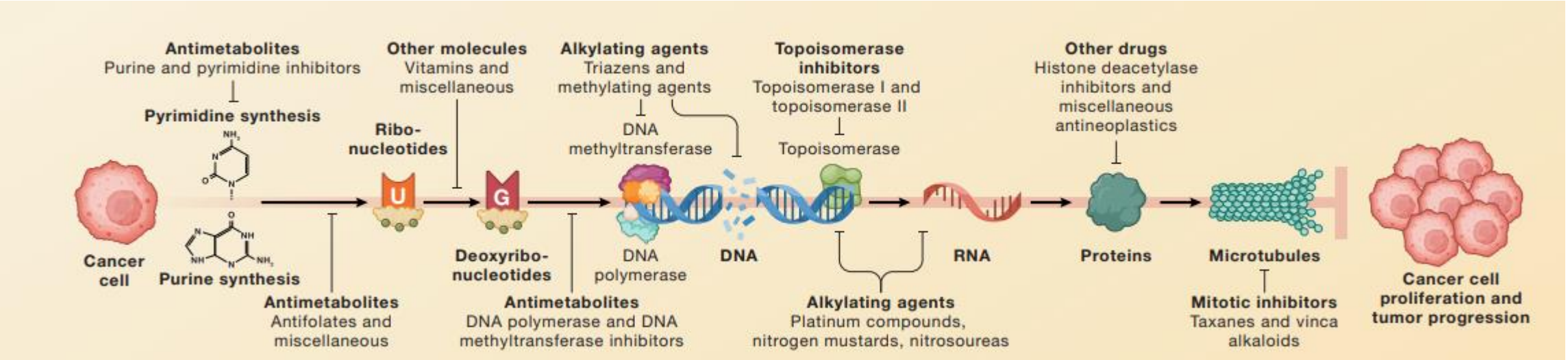


Russo et al. Practical Medical Oncology Textbook

unicancer

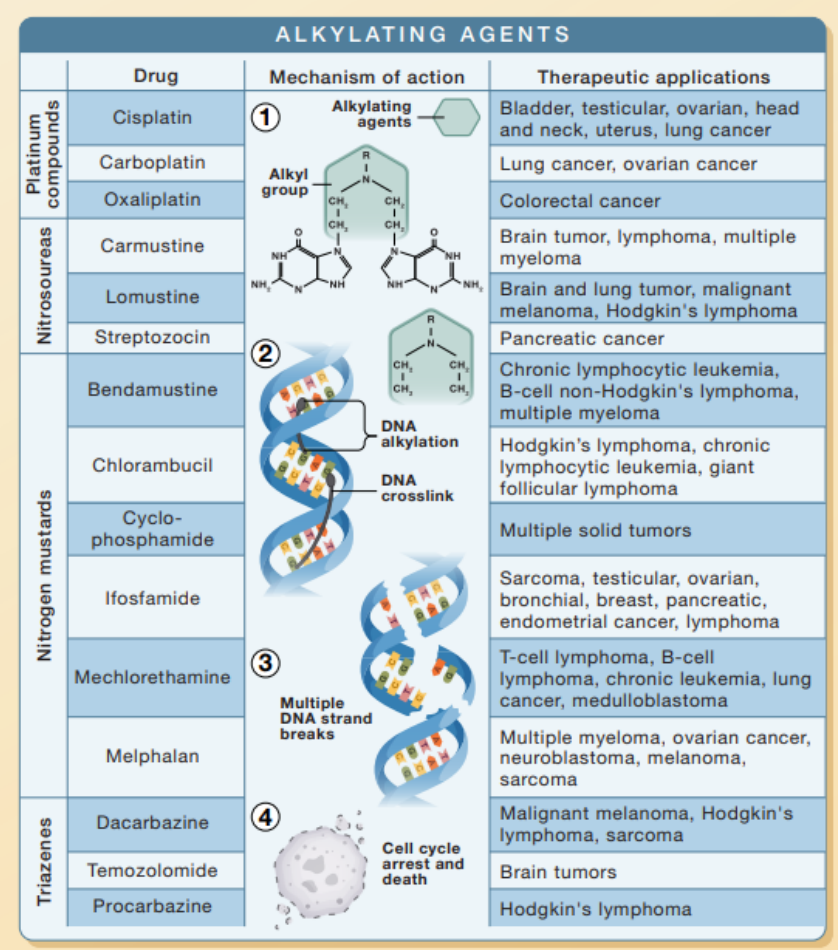
CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD
Chercher et soigner jusqu'à la guérison

Treatment modalities-Chemotherapy



Falzone et al. Cell 2023

Chemotherapy-Alkylating agents



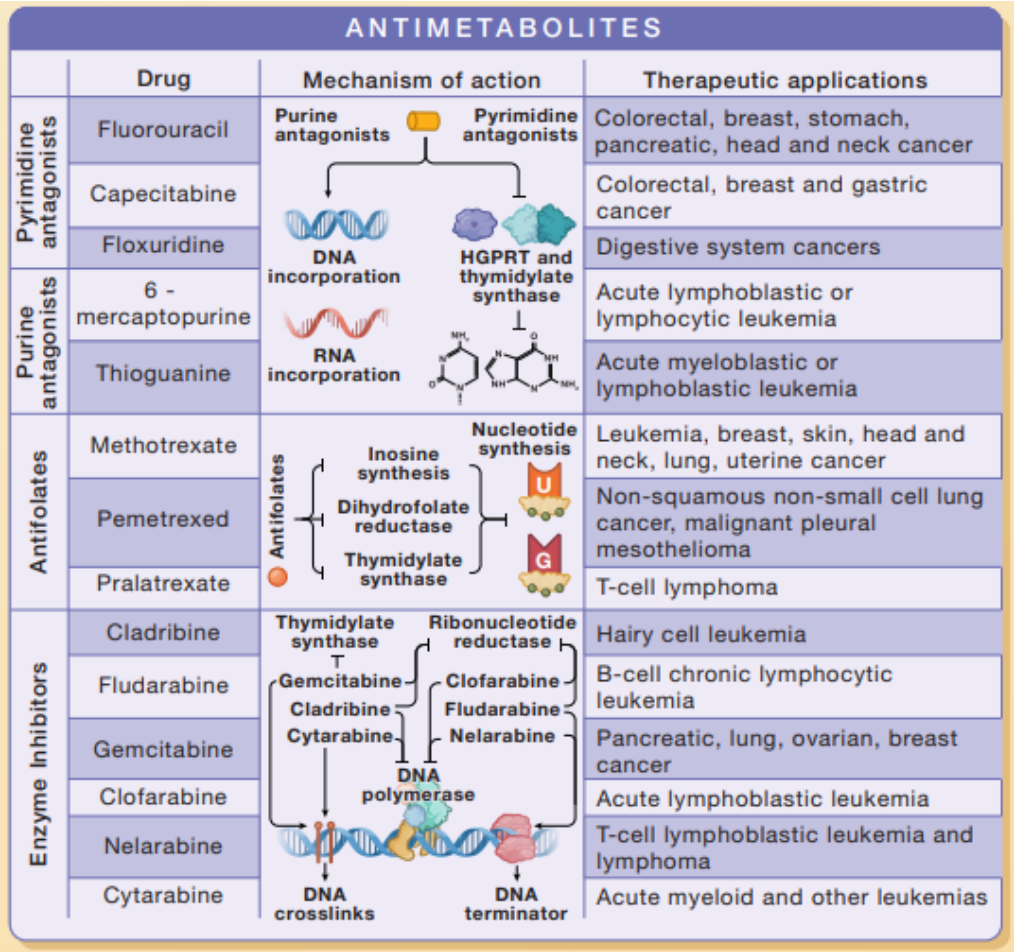
- **<u>Alkylating agents</u>** are classified as nitrogen mustards, <u>platinum compounds</u>, nitrosoureas, triazanes, and methylating agents.
- All these drugs can alkylate nucleic acids and proteins leading to the **<u>formation of intra- and inter-strand crosslinks responsible for multiple DNA breaks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

Falzone et al. Cell 2023

unicancer

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD
Chercher et soigner jusqu'à la guérison

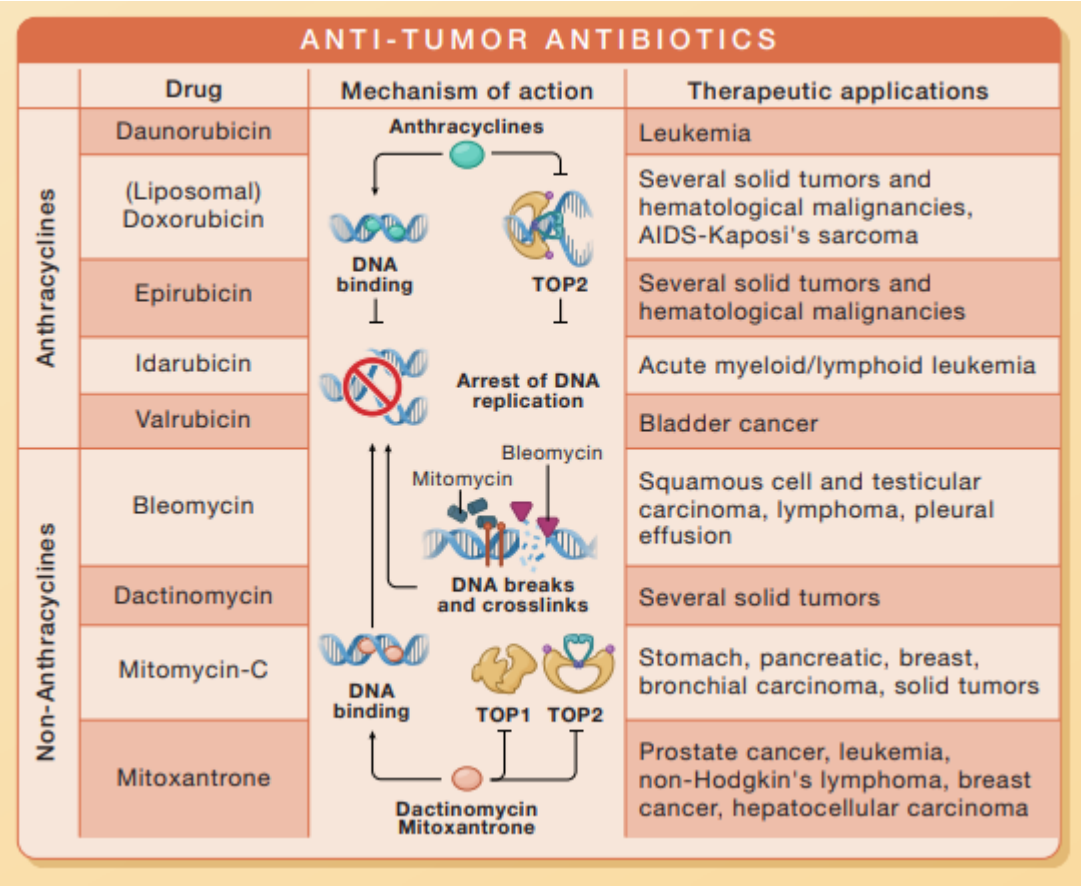
Chemotherapy-Antimetabolites



- **<u>Antimetabolites</u>** interfer 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.

Falzone et al. Cell 2023

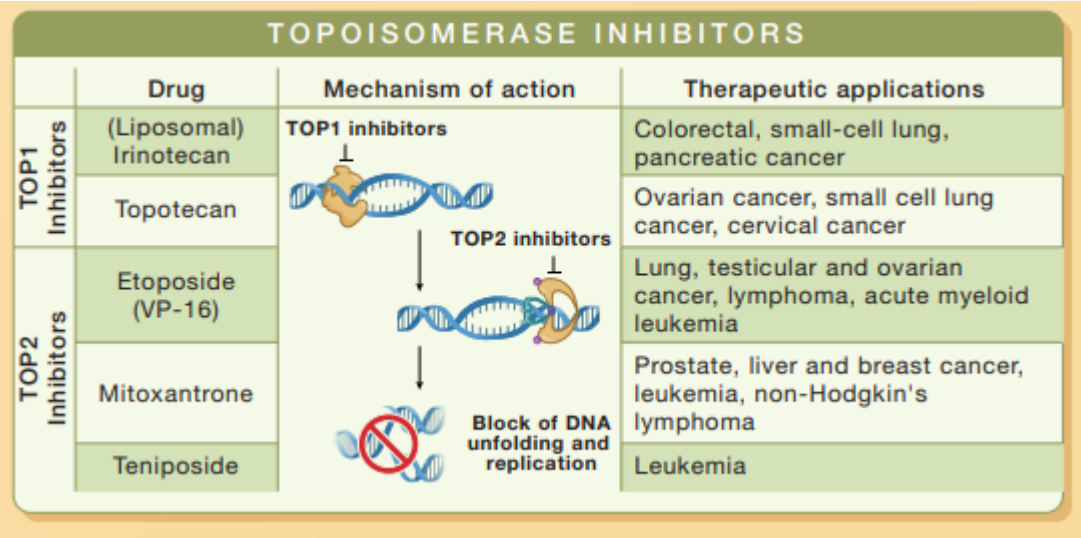
Chemotherapy-Cytotoxic antibiotics



- 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).

Falzone et al. Cell 2023
Falzone et al. Cell 2023

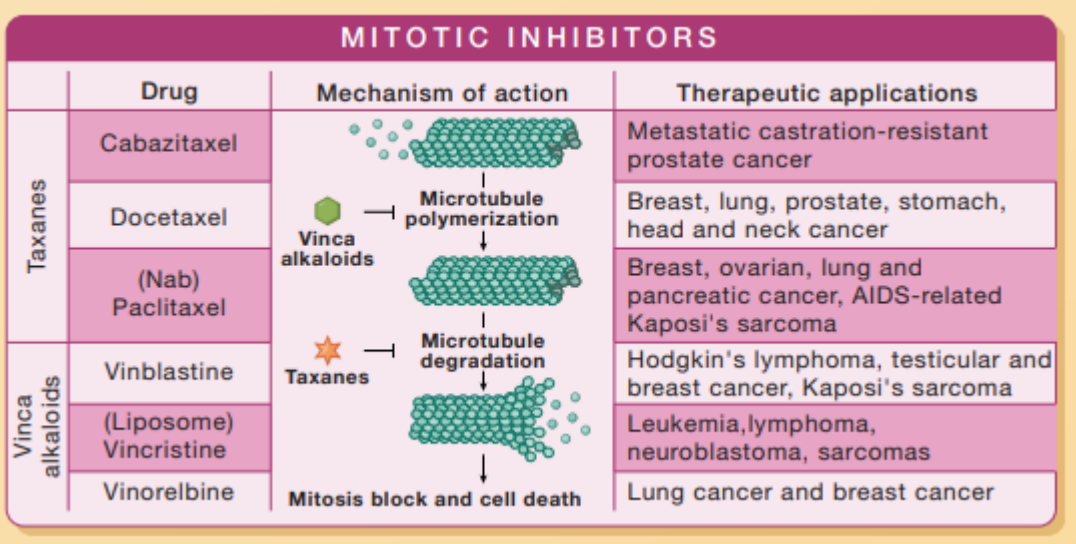
Chemotherapy-Topoisomerases inhibitors



- 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.

Falzone et al. Cell 2023

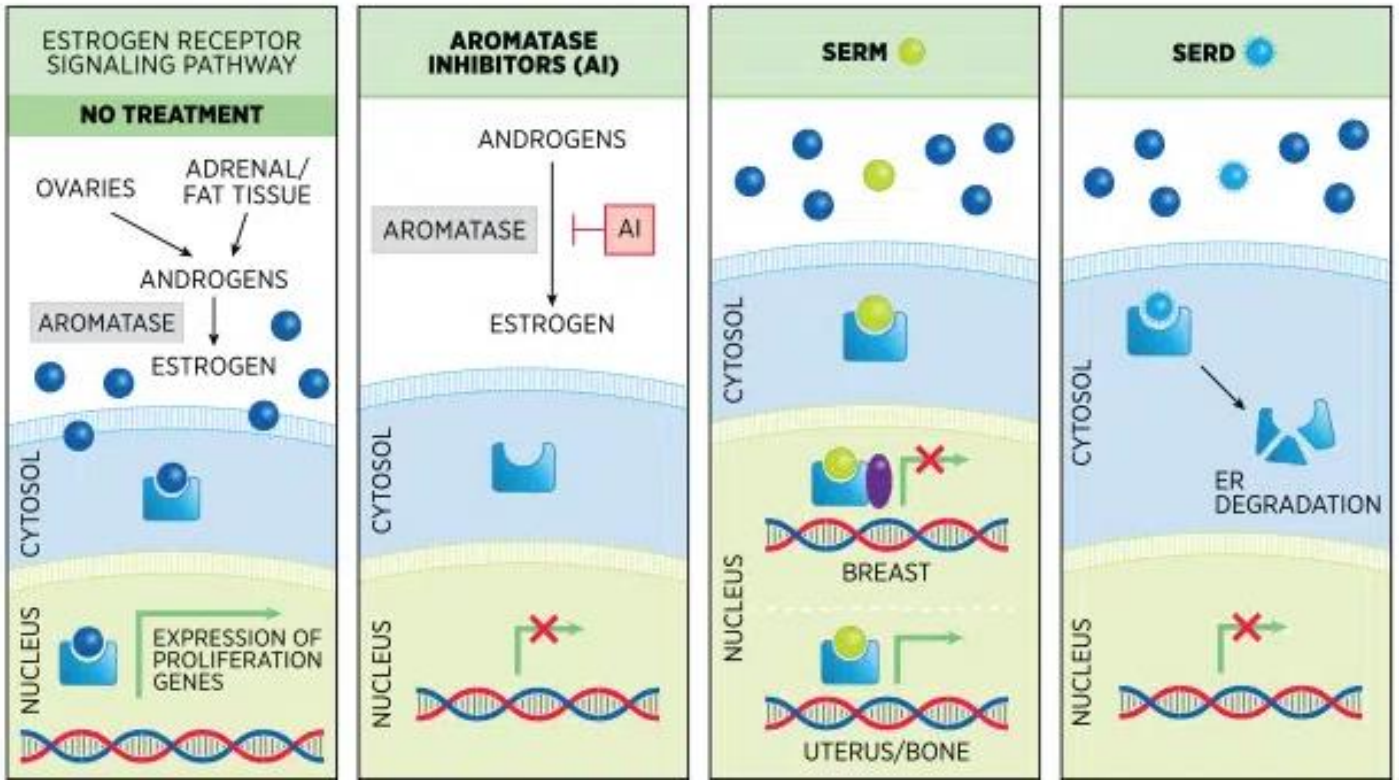
Chemotherapy-Mitotic inhibitors



- **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.

Falzone et al. Cell 2023

Endocrine therapy in Breast cancer



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

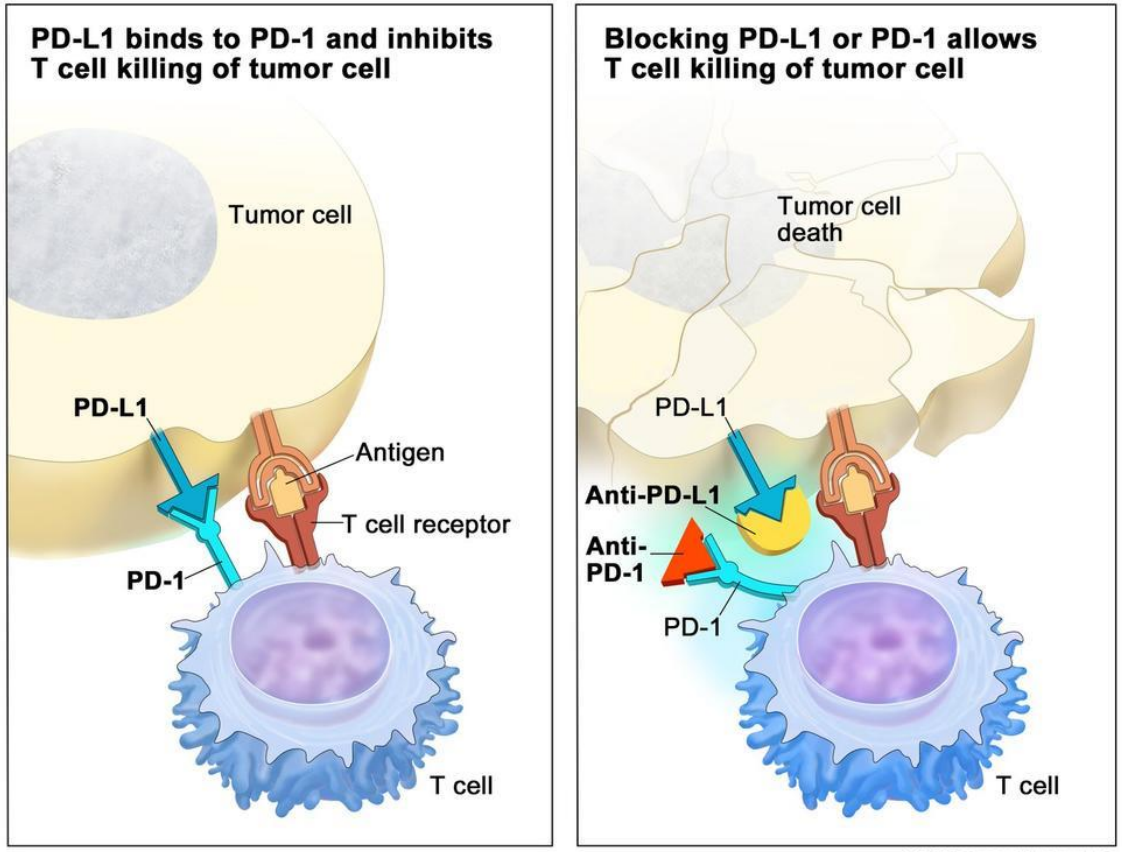
SERM : compete with estrogen to bind to the ER and have different effects depending on the tissue.

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

unicancer

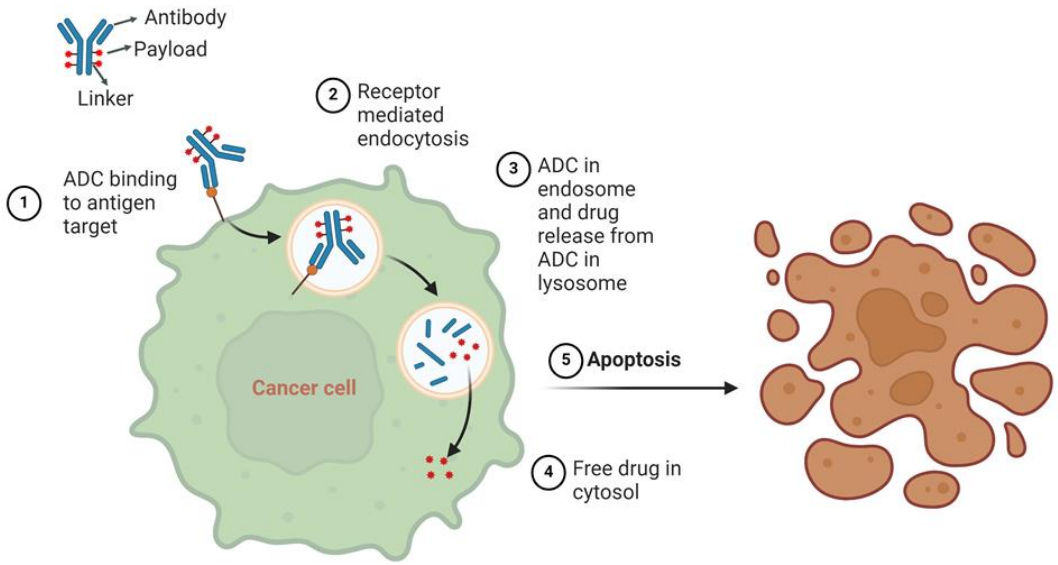
CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD
Chercher et soigner jusqu'à la guérison

Immune checkpoint inhibitors



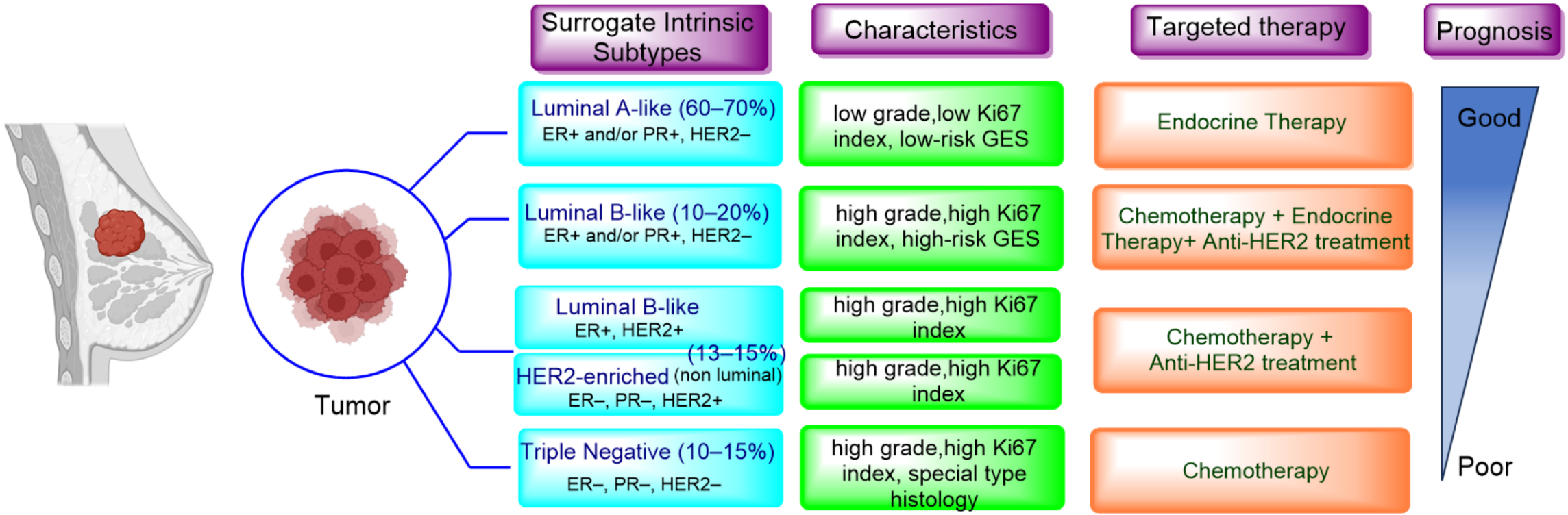
- Many tumors develop mechanisms that allow them to evade antitumor responses.
- Despite immunosurveillance, tumors can develop and become clinically evident.

New kids on the block- ADC

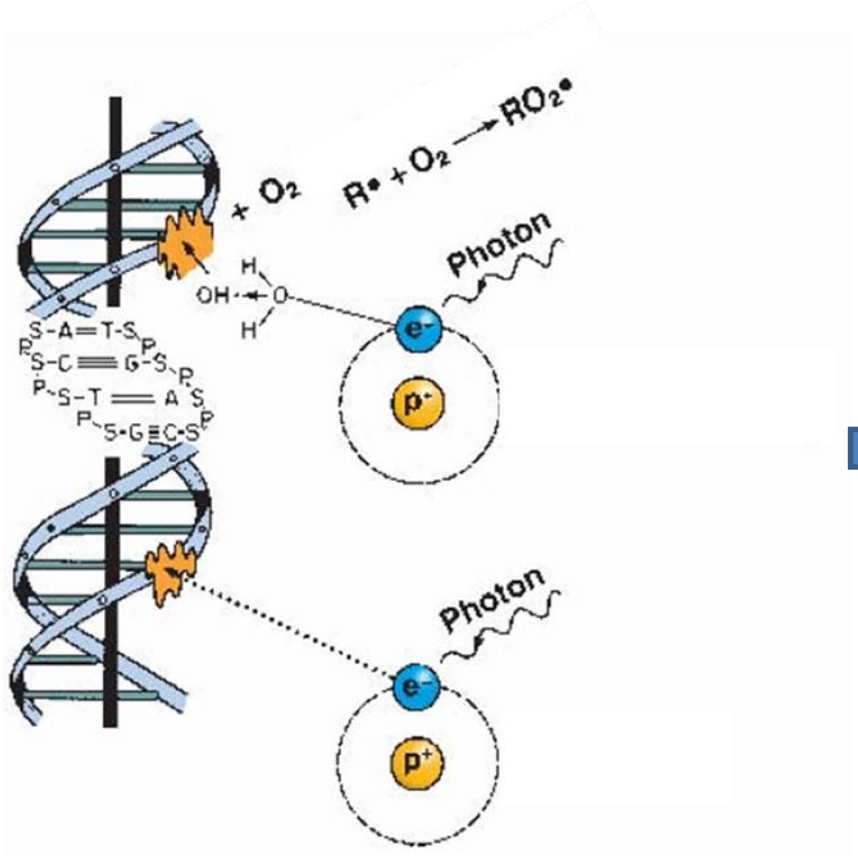


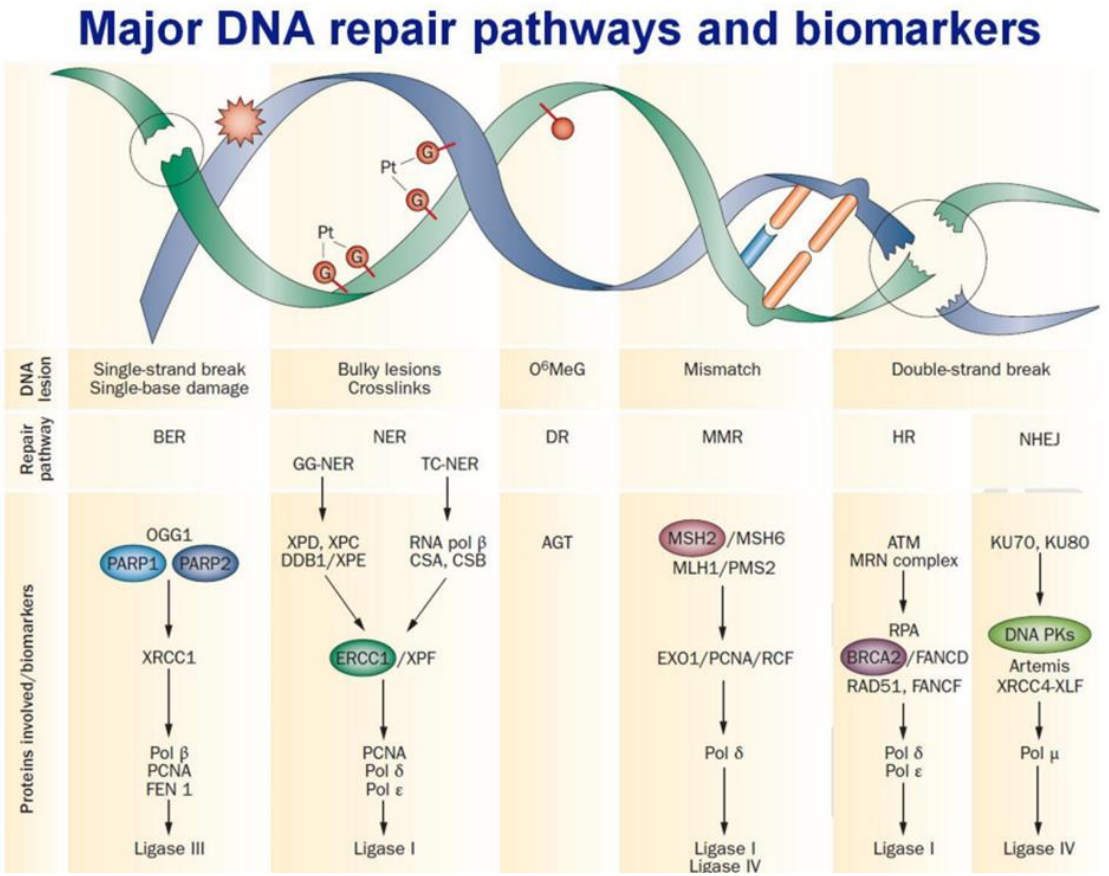
- Antibody linked with a cytotoxic payload
- ADCs combine :
  - Targeting properties of monoclonal antibody
  - Cancer cell-killing of cytotoxic drugs

Multimodal strategies-Breast cancer



Radiotherapy





unicancer

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD
Chercher et soigner jusqu'à la guérison

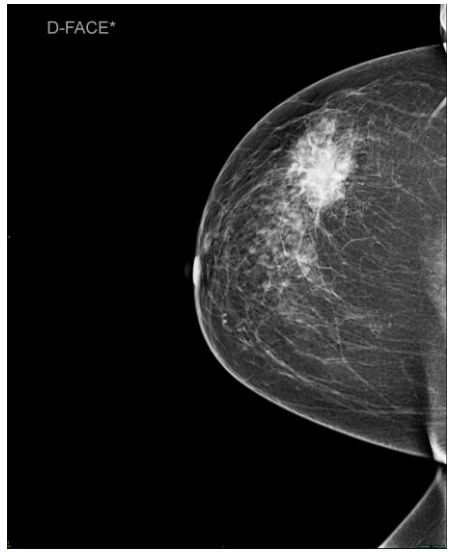
Case Presentation

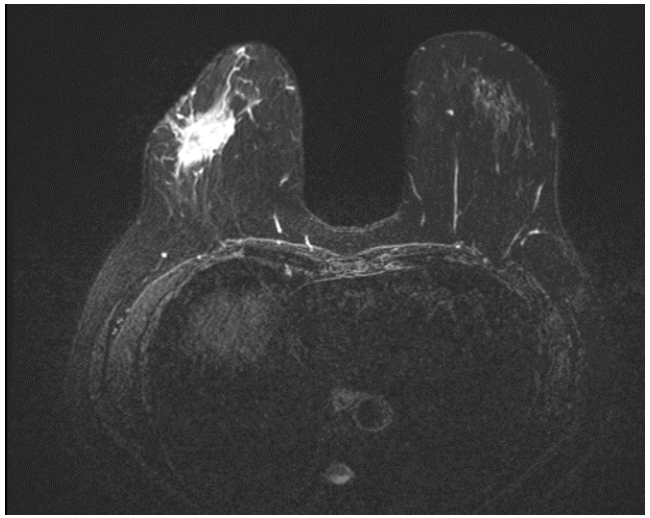
- Mrs R..
- 59 yo, post menopausal
- Initial presentation : January 2023, Autopalpation of right breast lump
- Medical history : None
- Family history : None

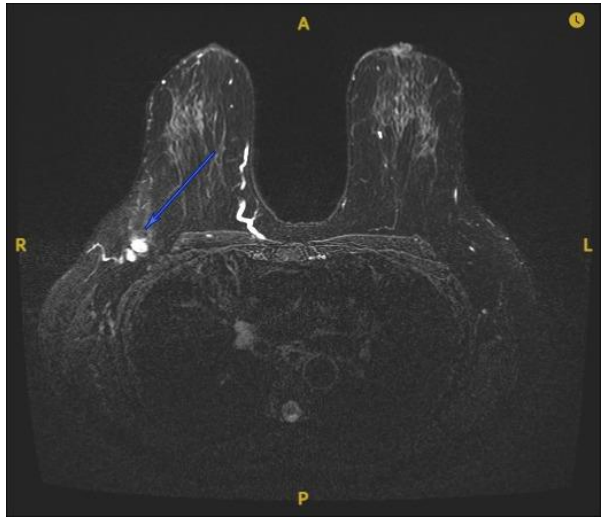
Clinical examination

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

Breast image





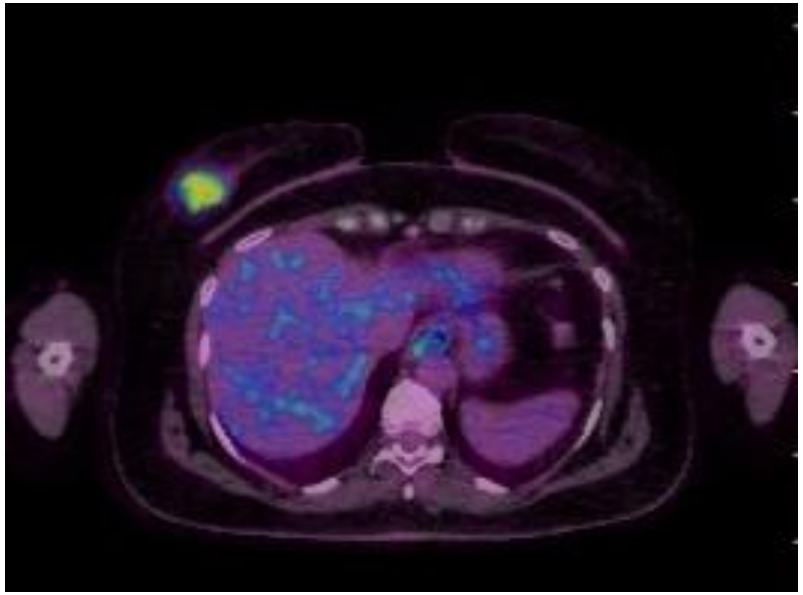


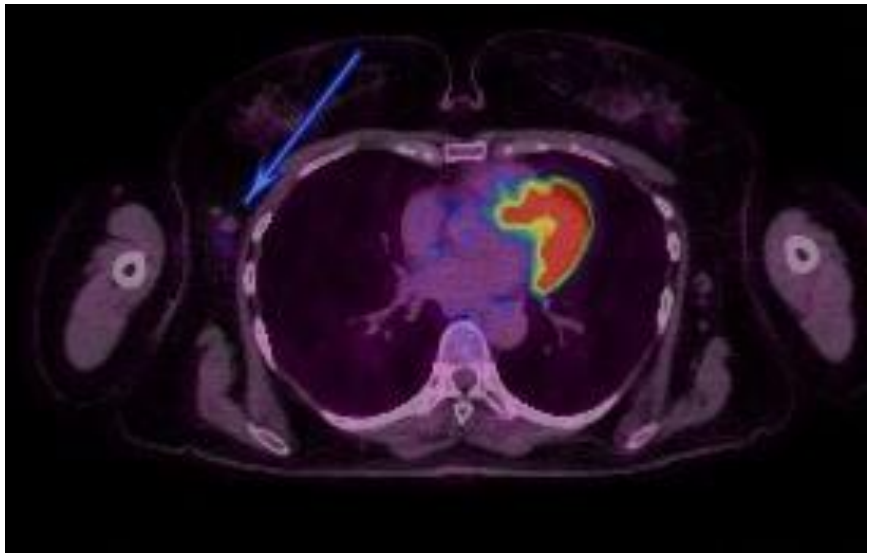
Architectural distortion with associated 35 mm irregular mass in the outer central right breast, posterior depth.
Enlarged lymph nodes in the right axilla.

Ultra sound guided biospies

- 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





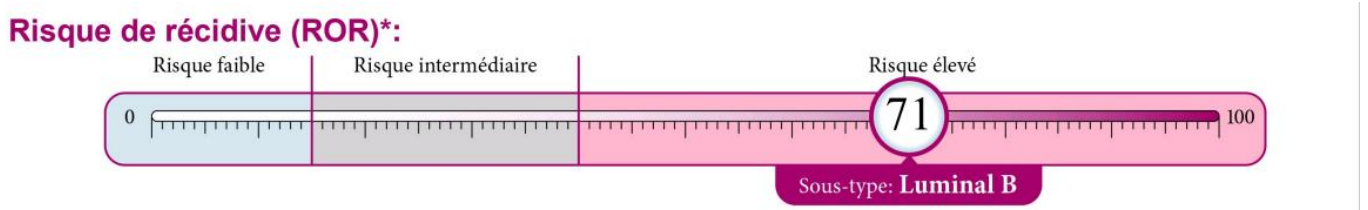
➔ cT2 cN1 M0

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

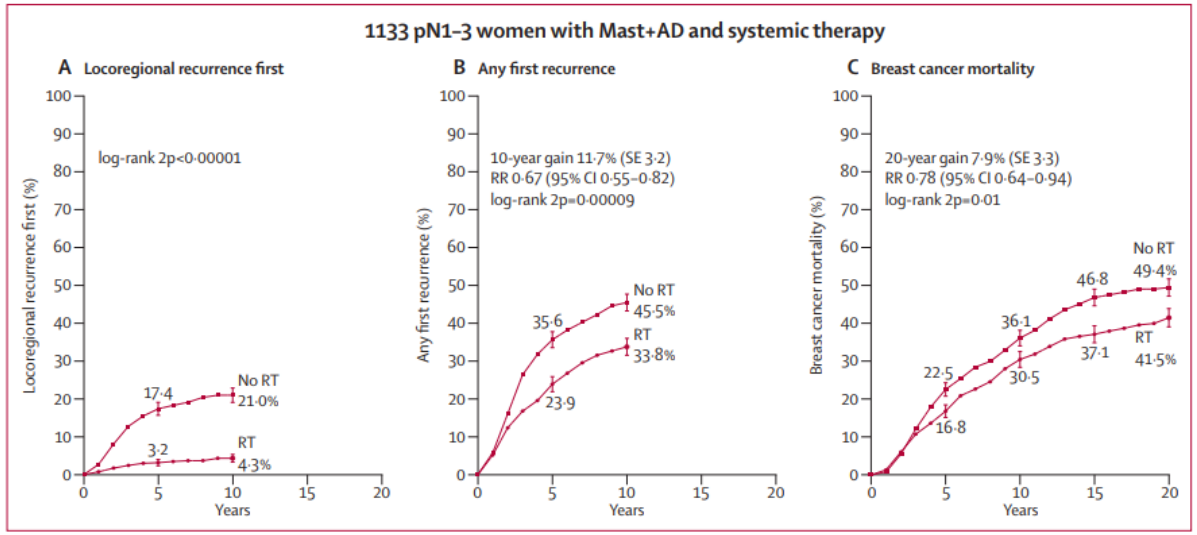
PAM 50



Adjuvant Chemotherapy : 3 AC and 9 Taxol
Radiotherapy
Hormonotherapy : AI

Rationale for post mastectomy radiotherapy

- EBCTCG meta analysis (Lancet 2014)



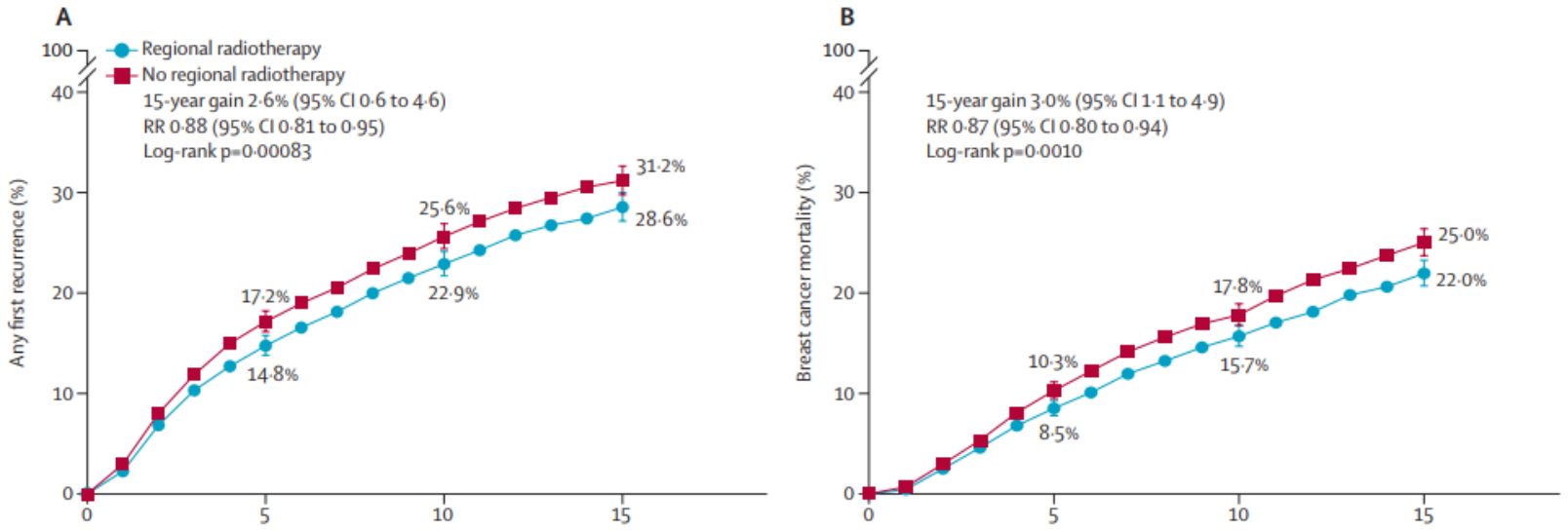
➔ Improves 20-yr locoregional reccurence and breast cancer-mortality in pN+ subsets

unicancer

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD
Chercher et soigner jusqu'à la guérison

Rationale for post mastectomy loco regional radiotherapy

- EBCTCG meta analysis (Lancet 2023)



➔ Improves 15-yr reccurence and breast cancer-mortality

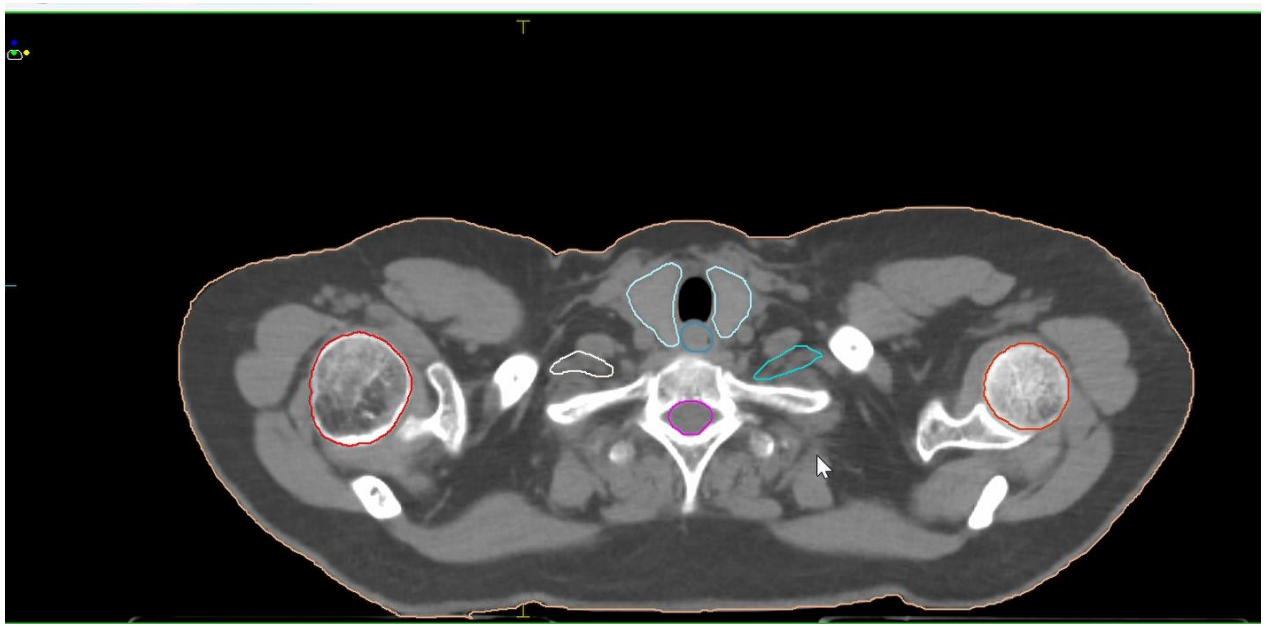
unicancer

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD
Chercher et soigner jusqu'à la guérison

Volume definition

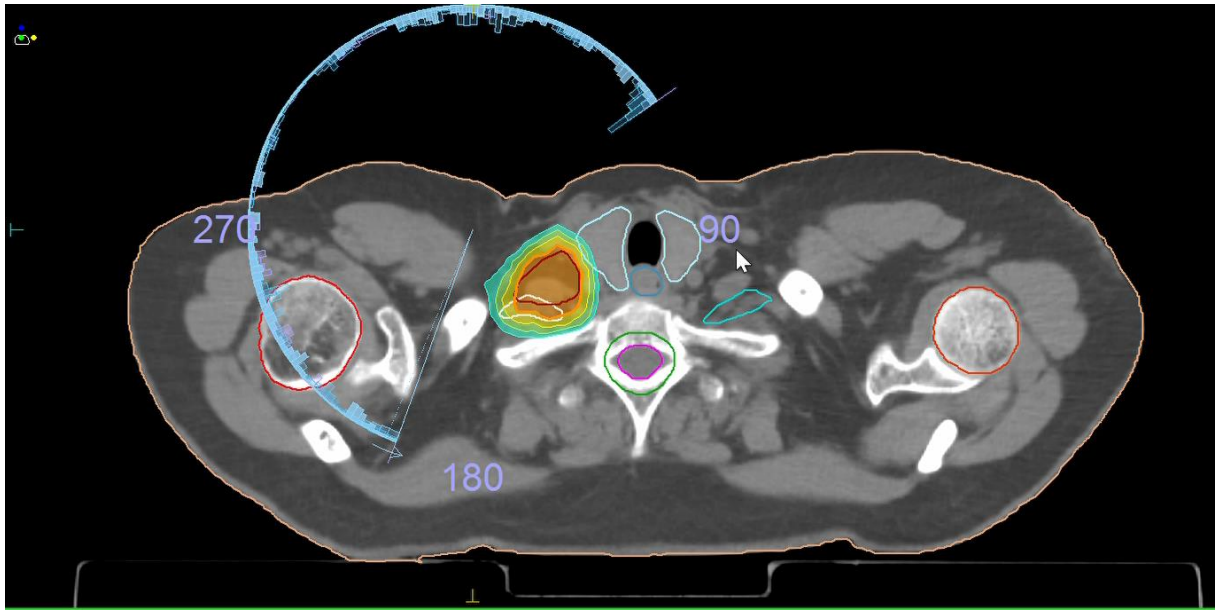
CTV T = CTV Chest wall R

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

Waisse.waissi@lyon.unicancer.fr