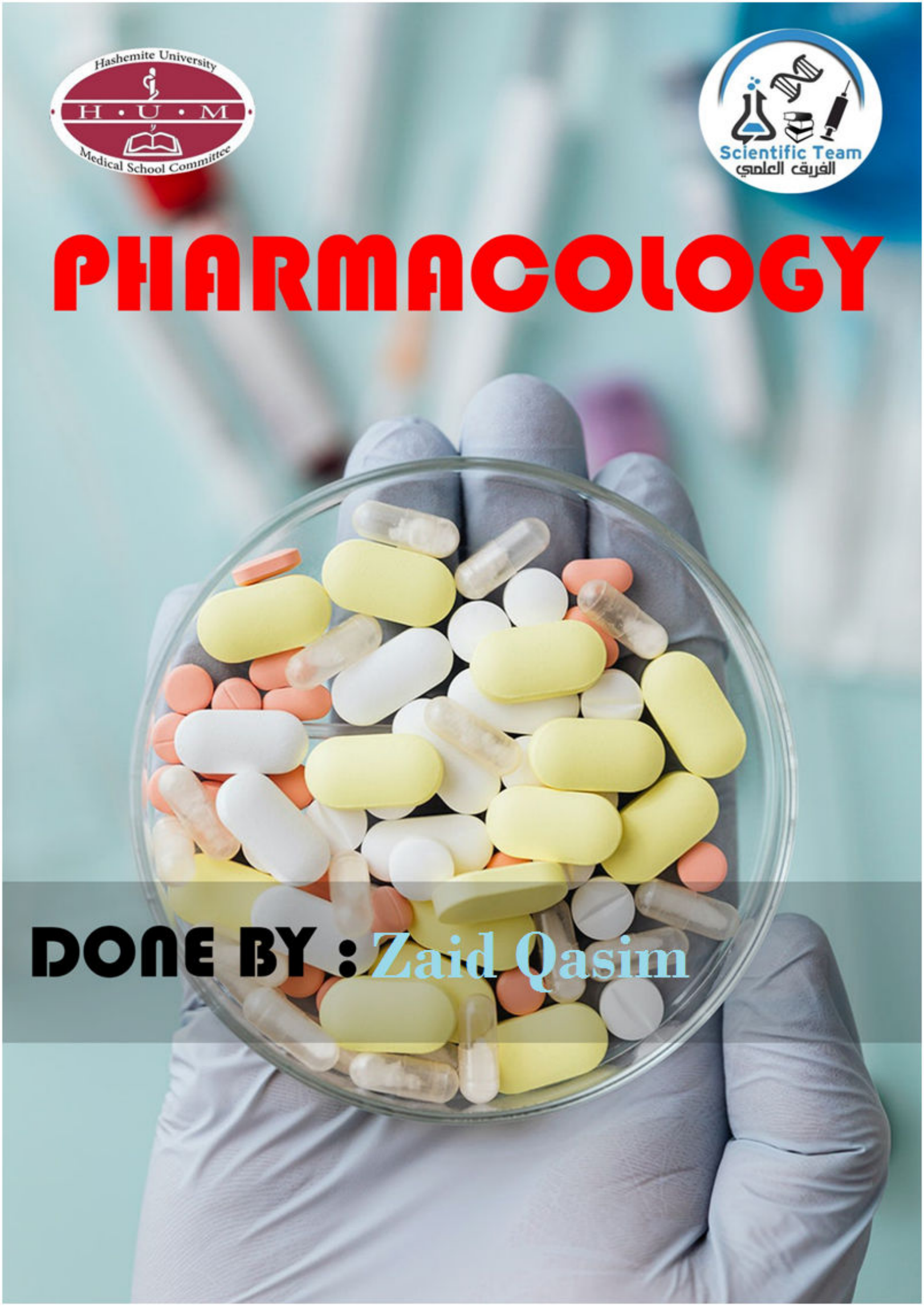
Hashemite University
H · U · M
Medical School Committee

Scientific Team
الفريق العلمي

PHARMACOLOGY



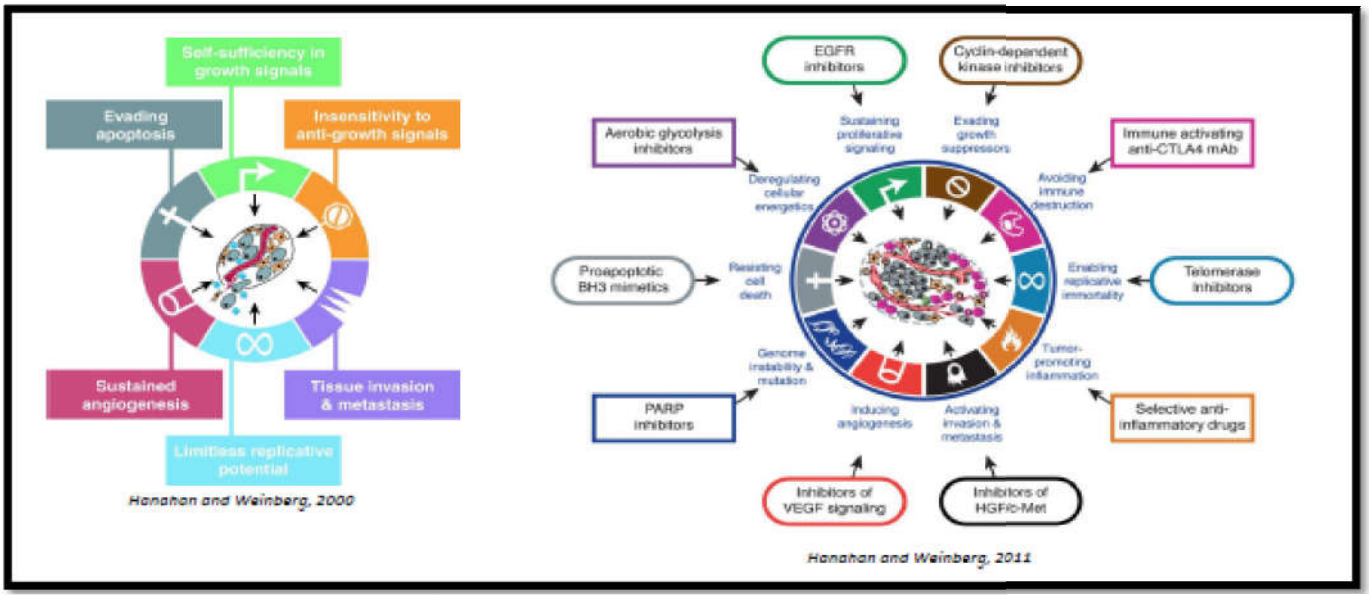
DONE BY : Zaid Qasim

بسم الله الرحمن الرحيم

Lecture 8 **:** *Selected Recent Advances for The Pharmacological Treatment of Breast Cancer*

- In this summary we're going to talk about the different types of the pharmacological treatment of breast cancer that are used in the clinical medical practice . . .
- The treatment of different types of human cancers, specifically the breast cancer , has undergone for large advancement of methods and modalities in the recent decades. Moreover, the survival rates as well as the cure rates of breast cancer are becoming high and the mortality rate from the breast cancer is largely decreasing . . .

- As with other cancers, the surgical removal of the breast tumors remains the mainstay curative treatment. Breast cancer of *Stages from I to III* are surely treated by surgery in combination with pharmacological therapy that we're going to discuss here. *Stage IV* of breast cancer, that is when the cancerous cells metastasize by lymphatics or blood vessels to other distant tissues is really bad and surgical intervention is not advised as it won't be useful. Therefore, pharmacological treatment is the only option we can use for patients with late stages of breast cancer.
- The recent huge better understanding of the pathology of breast cancer enabled us to innovate new different advanced modalities in the treatment of the cancer.
  For example, immunotherapy for cancer treatment has been improved in 2019 after we understand more about the cancer and how it can evades the immune system.
  Therefore, different agents were improved to enable our immune system to recognize cancer cells and kill them. In the past, our conventional (traditional) methods in the treatment of breast cancer were limited to cytotoxic chemotherapy such as DNA-damaging agents or microtubule inhibitors which have many harmful adverse effects.
  This figure shows us the different pathophysiological ways that cancerous cells may follow to maintain their survival and how we can target such processes by different drugs. *Notice the development of these drugs between 2000 and 2011.*



- We can classify the subtypes of breast cancer according to many considerations such as the histopathologic characteristics or clinical-based classification in terms of stage and grade of the cancer. However, in the context of pharmacological treatment for the breast cancer we can classify the breast cancer into ***three*** main subtypes according to the cell surface receptors expressed by the tumor cells:

(1) ***Hormone receptor (HR) –positive breast cancer*** : Estrogen Receptor (ER) –positive and/or Progesterone Receptor (PR) –positive. *[Remember that the normal mammary epithelial tissues -a type of typical epithelium- of the breast are responsive for estrogen and progesterone hormones to maintain their growth]*.

- These receptors contribute to the rapid proliferation of the breast cancer cells. So, hormonal therapy targeting these receptors will effectively arrest the growth of the tumor cells by interfering with estrogen or progesterone binding with the receptors on the surfaces of these cells.

(ER+) breast cancer is the most common subtype based on this classification.

(2) Human Epidermal Growth Factor Receptor 2 (HER2) –positive breast cancer : Liable for the treatment with (HER2) targeted therapies.

- A biopsy from every breast cancer tissue is taken from any patient diagnosed with breast cancer to determine if the cancer cells express (HR: ER & PR) → [HR+ or HR-] & (HER2) → [HER2+ or HER2-] and therefore, we can select the most proper hormonal treatment.

(3) Triple –negative breast cancer : Negative for (ER),(PR) and (HER2).

It compromises about 15-20% of patients with breast cancer and it is the most difficulty treated subtype of breast cancer as the breast cancer tissue won't respond to the hormonal therapy.

-Remember that the treatment of breast cancer is multimodal as we can use surgery + chemotherapy + hormonal therapy ...etc

- Now, we are going to talk about the treatment of the three main subtypes of the breast cancer and talk briefly about the neoadjuvant chemotherapeutic agents combinations

. . .

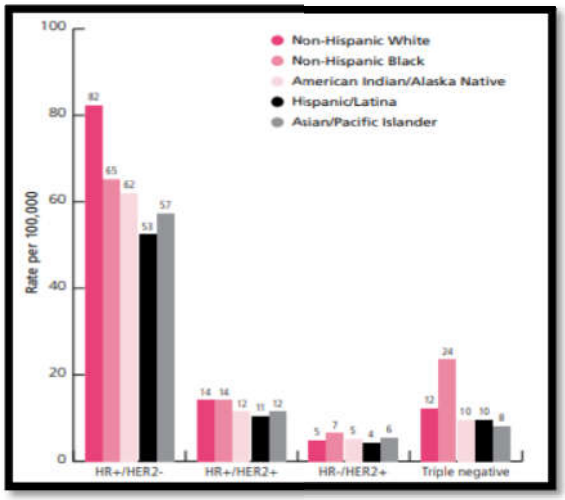
(1) Treatment of ER+ breast cancer.

- ER –positive breast cancer is the most frequently encountered type as it accounts for up to 60-80% of total breast cancer. It is further divided into :
  1- **Luminal A subgroup → (HR+) but (HER2-)** → Liable for hormonal treatment only.
  2- **Luminal B subgroup → (HR+) And (HER2+)** → they are the luckiest patients as we can affect breast cancer cell growth by two types of drug therapy.

[more receptors on the tumor cell surface → more targets are blocked by drugs and higher cure rate]

The following figure represents the female breast cancer incidence rates by subtypes in the period from 2010 – 2014 in the US

...



- Hormonal treatment is the mainstay of therapy:

1. **Tamoxifen**.
2. **Fulvestrant**.
3. **Aromatase Inhibitors.**
4. **Luteinizing hormone-releasing hormone analogs.**

All these drugs interfere with normal estrogen stimulation on the breast tissues . . .

A Historical overview : How hormonal therapy was developed ?

- In the 19th century , many physicians observed breast cancer regression in female patients after the menopause.
- In 1886, Thomas William Nunn reported disease regression in a perimenopausal woman with breast cancer 6 months after menopause → *This established the fact that breast tumor growth are dependent on the stimulation by estrogen which decreases highly after menopause.*
- In 1889, Albert Schinzinger proposed ovarian resection for the treatment of breast cancer. Later on 1895, George Thomas Beatson performed a bilateral oophorectomy (*surgical removal of both ovaries*) on a woman with extensive soft tissue recurrent breast cancer.

- **Nowadays, instead of doing oophorectomy we use the following drugs to antagonize the estrogen effect of breast cancer tissue :**

1.Tamoxifen.

- The mainstay treatment of (ER+) breast cancer and approved for those patients older than 40 years old.
- Strong evidence that 5-year adjuvant tamoxifen therapy(i.e. after surgery) results in a 47% reduction in recurrence and a 22% reduction in mortality.

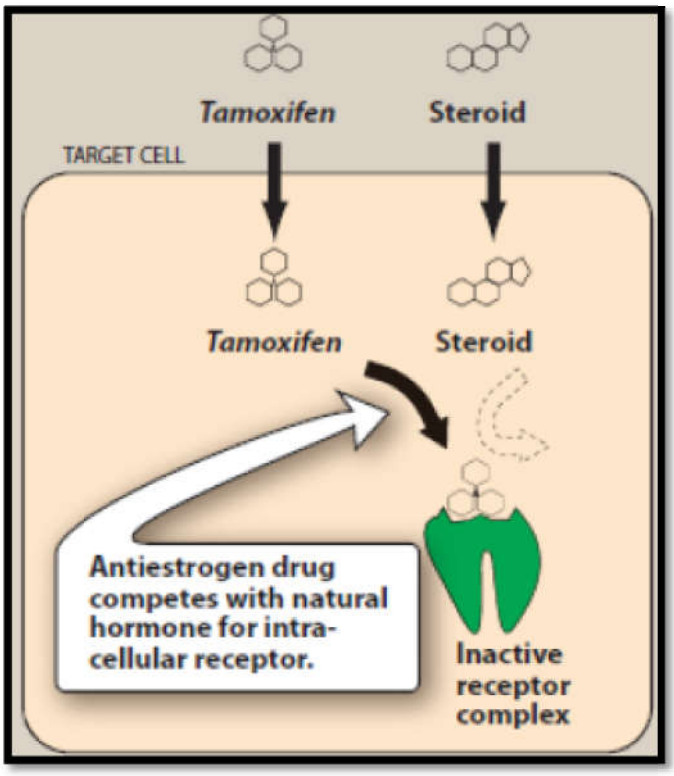
2014 American Society of Clinical Oncology (ASCO) recommendations:

- Women with stage I to III ER+ disease consider taking tamoxifen for 10 years (premenopausal *VS* postmenopausal).

> *Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update, J Clin Oncol, 2014*

- Early on, tamoxifen was only prescribed for premenopausal patients with ER+ breast cancer. In present, tamoxifen is also offered for pre-or postmenopausal women with increased risk for breast cancer to reduce the risk of invasive ER+ breast cancer.
- " Estrogen is a steroid-derivative lipid soluble hormone which can penetrate the cell membrane of the mammary epithelial tissue and bind with an intracellular gene active receptor (ER) forming a hormone-receptor complex which translocates into the nucleus to bind with a specific DNA sequence and acts as a transcription factor affecting the proliferation of the mammary epithelium."

MOE: Selective estrogen receptor modulator (SERM) = not full estrogen antagonist as it may induce some slight estrogenic activity i.e. modulator rather than full-antagonist. It has a strong antiestrogenic effect on the mammary epithelium but slight estrogenic activity on other tissues which is responsible for many adverse effects.



- **Adverse Effects:**

- Hot flashes, nausea & vomiting, menstrual changes/discharge (these are the same signs of premature menopause).

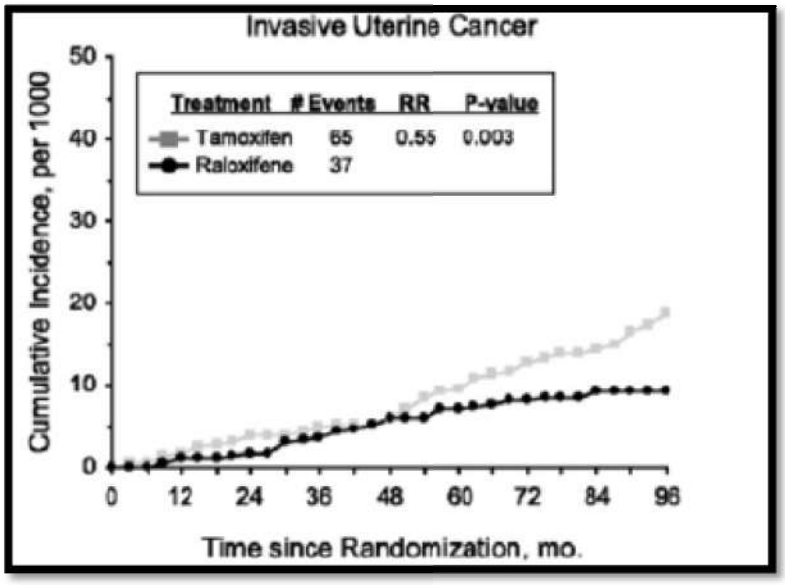
- **Contraindicated** in **(1)** pregnant patients, **(2)** patients with uterine malignancies & **(3)** patients with thromboembolic events such as stroke.

- *Why do tamoxifen cause menstrual irregularities ?* → because it has some estrogenic activity on the endometrial epithelium of the uterus which can result in constant endometrial hyperplasia and causes irregular menstrual discharge. From this point, long-term tamoxifen administration for breast cancer has been implicated in the increased the risk to develop an invasive uterine cancer.

↑Duration of treatment

↓

↑ Risk for invasive uterine cancer



2.Fulvestrant.

MOE: Classical competitive estrogen receptor antagonist on the mammary epithelium. It has less adverse effects on other body tissues compared to tamoxifen.

INDICATIONS:

- **(ER+) & (HER2-) in POSTMENOPAUSAL women not previously treated with endocrine therapy.**

- **HR+ in POSTMENOPAUSAL women with disease progression following endocrine therapy i.e. tamoxifen failure of treatment.**

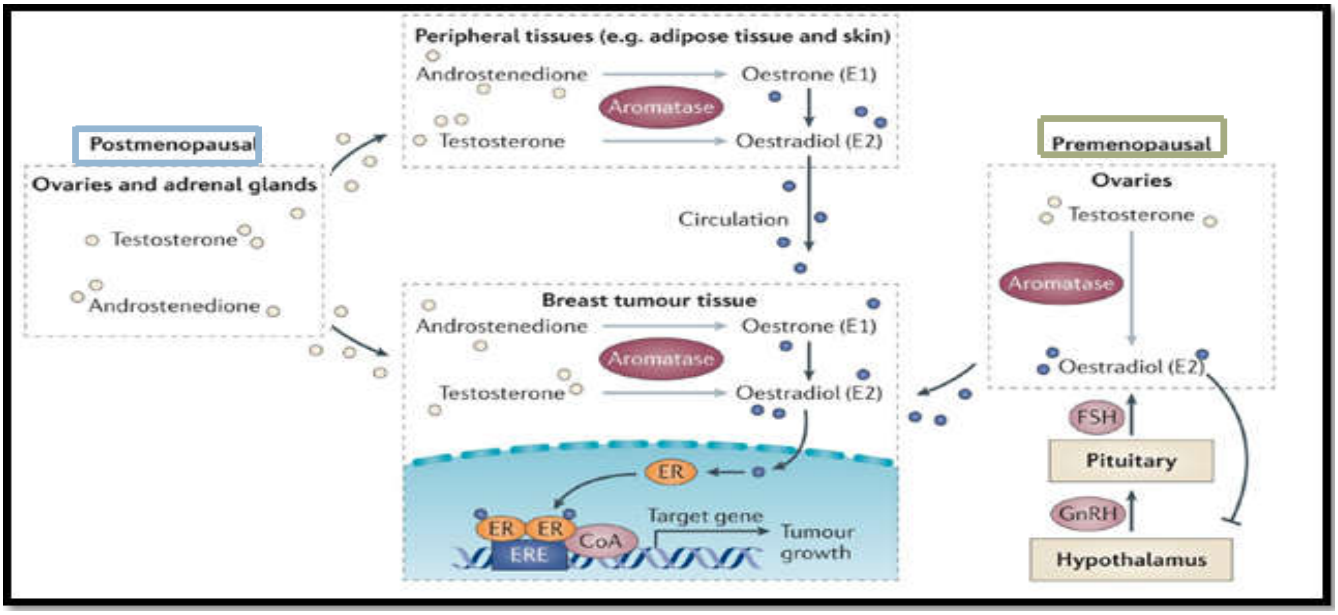
Tamoxifen remains the mainstay treatment of ER+ breast cancer.

- It is very effective in postmenopausal women with breast cancer if taken in combination with CDK4/6 inhibitors . So, to sum up ---------►

Tamoxifen	selective estrogen receptor modulator (SERM)	first line of treatment (the mainstay)	premenopausal & postmenopausal women	many adverse effects similar to signs of menopause
Fulvestrant	Competitive antagonist	can be used when tamoxifen therapy fails	postmenopausal women only	less adverse effects

3.Aromatase Inhibitors.

- Aromatase enzyme, in addition to many other enzyme, synthesizes estradiol (the main active form of estrogen) from its testosterone precursor inside the ovaries (the main site for estrogen synthesis) and many other extra-adrenal tissues.
- In postmenopausal women, the ovaries fails to produce more estrogen. Therefore, testosterone and androstenedione precursors after being secreted into the plasma, will undergo aromatization reactions by the aromatase enzyme in the other aromatase-rich tissues like mammary epithelial tissue, liver, adipose tissue and skin to produce estrogen but in a much lesser extent than the ovaries.
- Breast tumor tissue can benefit from any testosterone or androstenedione secreted into the plasma to keep it survival and proliferation.



- Aromatase inhibitor agents, as their name indicate, can block the ability of the peripheral aromatase enzyme found in the extra-adrenal tissues like adipose or breast tissues to produce estradiol from testosterone and androstenedione therefore, decrease the proliferation of breast cancer cells.
- Aromatase inhibitors are becoming very popular and replacing tamoxifen in the context of medical treatment of breast cancer
- They are the current standard-of-care adjuvant therapy for the treatment of ER+ breast cancer.
- Trials have shown superiority of aromatase inhibitors over tamoxifen in terms of tumor regression
- Initially, used (and were effective) only in postmenopausal women, but now considered for premenopausal women (as same as tamoxifen).

هاي ثانية عائلة تُستخدَم قبل وبعد الـ menopause ، الـ Fulvestrant يُستخدم فقـــط **بعـد** الـ Menopause!

- **Adverse Effects:** hot flashes (12-36%), arthralgia/arthritis (17%), headache (9-13%), vaginal dryness (2%) and mood changes (19%).
- Arthralgia/arthritis may decrease the acceptance of these drugs by the patients :(

- Aromatase inhibitors can be generally divided into steroidal and non-steroidal agents:

(1) *Non-Steroidal Aromatase Inhibitors include **Anastrazole** and **Letrozole**.
(2) Steroidal Aromatase Inhibitors include **Exemestane**.

Anastrazole Letrozole	non-steroidal in nature	First line adjuvant therapy for the treatment of (ER+) breast cancer in postmenopausal women	taken orally
Exemestane	steroidal	alternative to tamoxifen to reduce the risk of invasive (ER+) breast cancer	taken orally

***Unlike tamoxifen they don't have an established risk for endometrial cancer.**

4.(GnRH) Analogues – Luteinizing hormone-releasing hormone analogues.

- Remember: *Hypothalamic-Pituitary-Gonadal axis*:
The hypothalamus secret (GnRH) into the hypophyseal portal circulation to stimulate anterior pituitary gland to secrete (LH) and (FSH). These two hormones go via the circulation into ovaries in female and testes in males to secrete Estradiol & Progesterone and Testosterone respectively. The sex hormones then have a negative feedback inhibition on both hormones secreted by the hypothalamus and anterior pituitary**.**

- We can also remember from the pharmacology of the endocrine system that the pulsatile administration of (GnRH) will ↑ gonadotrophin release but if (GnRH) is secreted continually it will cause down regulation of anterior pituitary receptors and causes ↓ gonadotrophin release. So, synthetic (GnRH) analogues can be used to decrease the secretion of estrogen from the ovaries by inhibiting (LH) and (FSH) secretion from the anterior pituitary.

- **MOE:** They occupy (GnRH) in the anterior pituitary and cause receptor desensitization and thereby they decrease (LH) and (FSH) secretion.

- This family include : **Leuprolide** and **Goserlin**.

- They are **last-line used drugs** for adjuvant treatment of advanced (ER+) breast cancer **in combination with tamoxifen**. (remember that anastrazole & letrozole are the 1st line).

- This table summarizes the main drugs used in hormonal therapy for (ER+) breast cancer . . .

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Tamoxifen	PO	Hot flashes, N,V, vaginal bleeding, hypercalcemia, thromboembolism	*Warfarin, rifampin*	Vaginal bleeding, new breast lumps	May cause endometrial cancer
Anastrozole and Letrozole	PO	Hot flashes, N, joint pain, ischemic cardiovascular events, osteoporosis	Estrogen-containing products	Hepatic function, bone mineral density monitoring, cholesterol monitoring	Contraindicated in premenopausal or pregnant women
Leuprolide, Goserelin, Triptorelin	Depot, Sub-Q, IM	Tumor flare, hot flashes, asthenia, gynecomastia		Bone mineral density monitoring, serum testosterone, PSA	

5.CDK4/6 Inhibitors.

- Cancer cells circulate in the cell-cycle at a very high rate as they are rapidly proliferating cells – basic definition.
- ***Cyclins*** (like A, B, D or E) are a family of regulatory proteins that control the progression of the cell cycle.
- In order to regulate and control the cell cycle progression, they bind with and activate ***Cyclin Dependent Kinases*** (***CDKs***) (like 1, 2, 4 or 6).
- From these cyclins we have the cyclin D which binds with CDK 4/6 to form a CDK complex that phosphorylates a specific protein called ***retinoblastoma protein*** (***Rb***).
- Rb normally inhibits the progression of the cell cycle from G1 phase to S phase cell i.e. a cell cycle suppressor. *When it is not phosphorylated it becomes active and prevent excessive cell growth by inhibiting cell cycle progression. However, when the cell is ready to divide, the Rb is phosphorylated by [cyclin D – CDK4/6 complex] to become inactive and allow for cell cycle to progress from G1 phase to S phase.*

- Around 15-30% of (ER+) have amplification of cyclin (D1) and (CDK4) in whom we can use the CDK4/6 inhibitors.

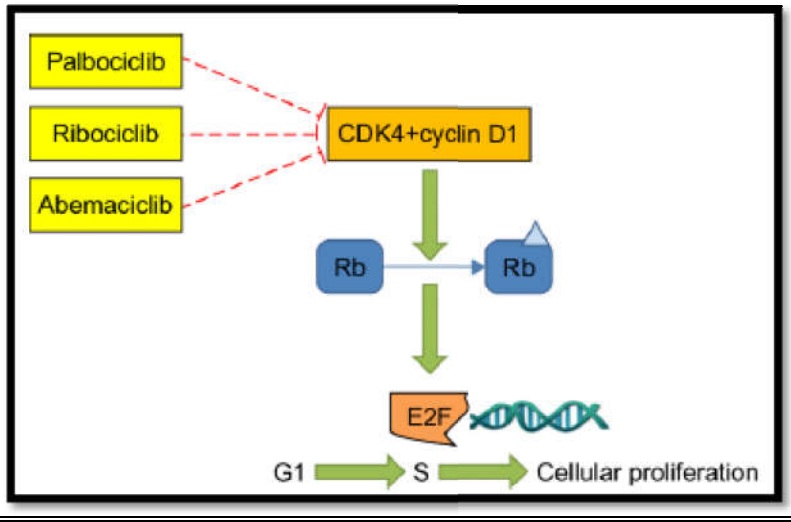
- **MOE:** They block the phosphorylation of retinoblastoma protein, thereby downregulating E2F-response genes to mediate G1-S arrest.

- **This family include:**

1- Palbociclib.

2- Ribociclib.

3- Abemaciclib.



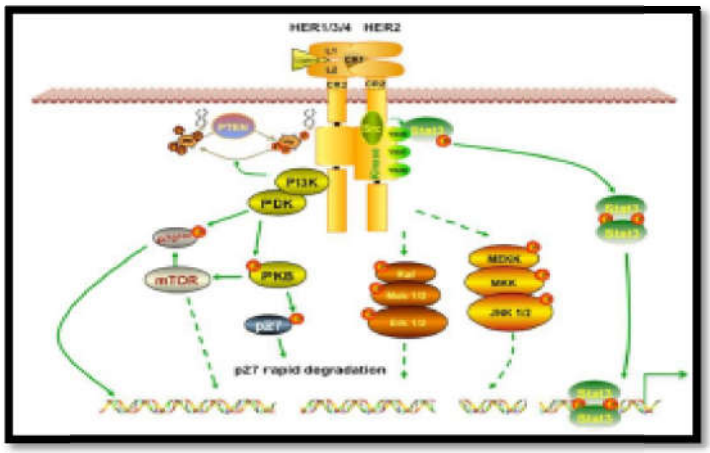
- Palbociclib is the most commonly used and is indicated for use (**in combination with fulvestrant or aromatase inhibitors**) for postmenopausal women with metastatic (*Stage IV*) (ER+) and (HER2-) breast cancer.

- **Adverse Effects:** neutropenia, fatigue and gastrointestinal symptoms.

(2) Treatment of HER2+ breast cancer.

- HER2 is a member of the human epidermal growth factor receptor (EGFR) family which is normally expressed at a low level on the surface of epithelial cells like breast, ovary, lung, liver, kidney, and central nervous system.
- In about 20-30% of patients with breast cancer HER2 has been overexpressed.
- Targeting this receptor with drugs is highly effective in the treatment of patients with HER2+ breast cancer.

- HER2 is activated by the formation of homodimers or heterodimers with other EGFR proteins e.g. HER2/HER3dimer causes autophosphorylation and/or transphosphorylation of specific tyrosine residues in EGFR intracellular domains resulting in the Activation of pro-proliferation signaling pathway. Look at the following figure . . .



- **Trastuzumab** (**Herceptin**) is a recombinant humanized monoclonal antibody designed against HER2. It was the first drug developed -in early nineties- in the targeted therapy as it works only on the overexpressed HER2 on the surface of breast tumor tissues.

- **MOE:**

  It (1)triggers HER2 internalization and degradation and (2) attracts immune cells to HER2-overexpressing tumor cells thus (3) inhibits pro-proliferation pathways e.g. MAPK and PI3K/Akt pathways and (4) suppresses cell growth and proliferation.

- **Adverse Effects:**

- Pain (47%) – Asthenia (42%) - Fever (36%) - Nausea (33%) - Chills (32%) - Cough (26%) – Headache (26%) – Diarrhea (25%) – Vomiting (23%).
- It also may result in Cardiotoxicity as it can bind with HER2 found on the surface of cardiomyocyte therefore, it may increase the risk to develop congestive heart failure (CHF) or result in deterioration in breast cancer patients with established (CHF).

- ***Other agents used in HER2+ breast cancer treatment:***

(1) **Pertuzumab**.
(2) **Ado-trastuzumab emtansine**.
(3) **Fam-trastuzumab deruxtecan** (new,2020).
→ **" HER2 Inhibitors"**

(4) Lapatinib
(5) Neratinib
→ **"EGFR Inhibitors"**

(3) Treatment of Triple –negative breast cancer (TNBC).

- (TNBC) is a breast cancer which lacks ER, PR and HER2. It accounts for 10-15% of primary breast cancers.
- This type of breast cancer is important because:

  a. It is a poor prognostic factor for disease-free and overall survival.
  b. It has no available effective specific targeted therapy.

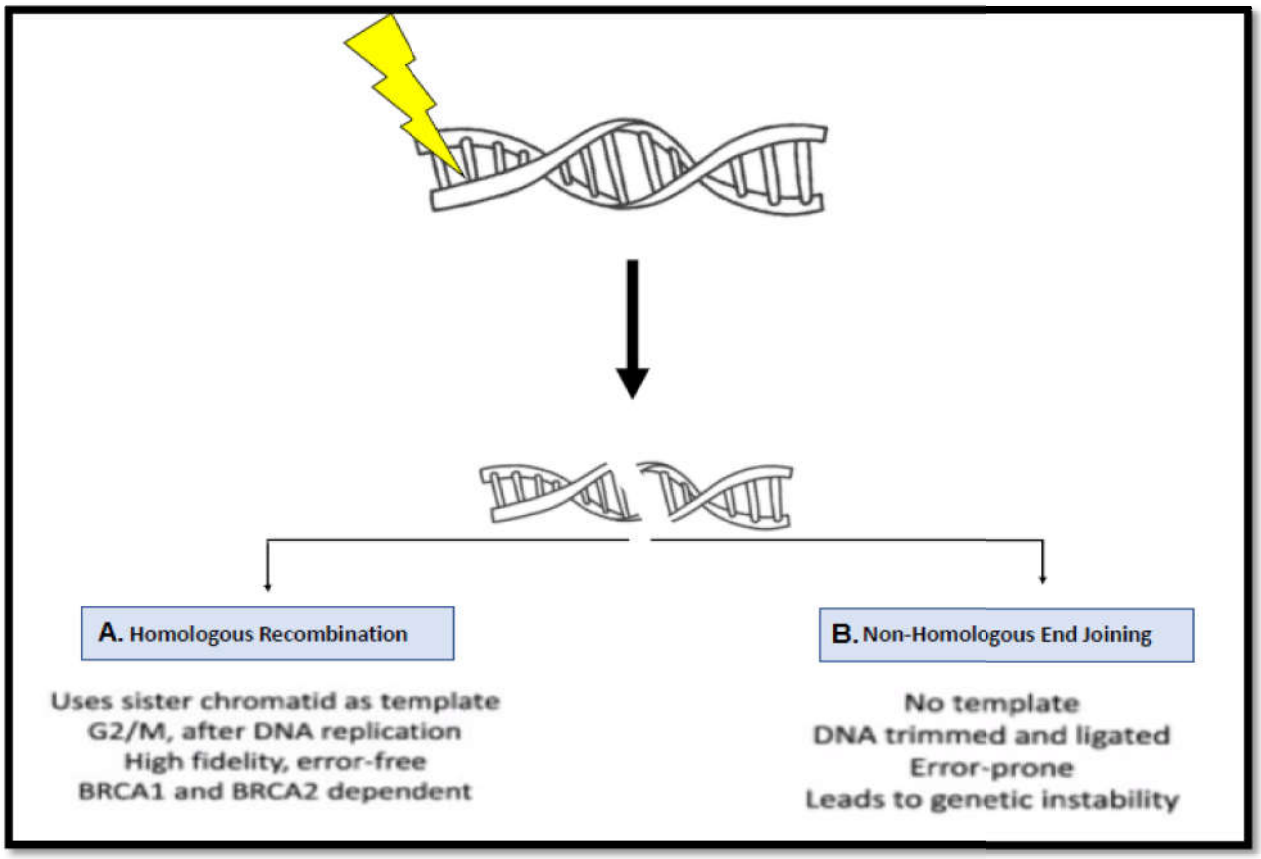
- Treatment of TNBC is done by cytotoxic chemotherapeutic agents including the following drugs →

Anthracyclines (**Topoisomerase Inhibitors)**	**Doxorubicin** & Epirubicin
Taxanes (**Microtubule inhibitors)**	Paclitaxel & **Docetaxel**
Antimetabolites	**Gemcitabine** & Capecitabine
Platinum-coordination complexes	Cisplatin & **Carboplatin**

*الي باللون الأحمر مهمات

- A new set of drugs is now approved for the targeted therapy of (TNBC).
- They work by inhibiting the repair of the DNA damage cause by ionizing radiation or conventional chemotherapeutic drugs. *But how do cells repair the DNA damage?*

  By two methods ⟶



- A new set of drugs is now approved for the targeted therapy of (TNBC).
- Homologous recombination is a very efficient method in DNA damage repair and it is dependent on [BRCA1] and [BRCA1] genes. Patients with deleterious BRCA1 mutations will more commonly develop (TNBCs). When there are mutations in the BRCA genes, the cancer cells will follow an error-prone non-homologous recombination to repair the DNA damage.
- One of the most important proteins that are implicated in the non-homologous end joining method of the DNA damage repair is Poly (ADP-Ribose) Polymerase (PARP).
- (PARP) inhibitors will decrease the chance for cancer cells to repair the DNA damage.
- **MOE:** Simply, they inhibit the ligation process performed by (PARP) - in the non-homologous end repair- and this cause the cancer cells to become full of unrepaired damages and mutations and therefore, cancerous cells die easily.
- (PARP) inhibitors are given in combination with cytotoxic DNA-damaging agents e.g. doxorubicin + PARP inhibitor like Olaparib.

- **Olaparib** is a (PARP) inhibitor agent , approved for use in women and men with deleterious germ-line [BRCA1] and [BRCA1] mutations and metastatic (stage IV) breast cancer (TNBC).

- Other potential approaches in the treatment of (TNBCs):

1. **PIK3 Inhibitors**.
2. **CDK4/6 inhibitors**.
3. **Immunotherapy**.

→ " **not yet approved until now** "

(4) Neoadjuvant Chemotherapy.

- A preoperative chemotherapy given to the patient before surgical removal of the breast tumor to induce tumor shrinkage and making it easier for the surgeon to remove it.

- **INDICATIONS:**

1- T3-T4 disease.
2- Node-positive disease.
3- ER-negative disease (can also be used in ER+ disease).
4- HER2-positive disease.
5- Tumors that need downsizing for surgery.

- **COMBINATIONS:**

Regimen	Dose and Schedule	Frequency	Cycles
TAC			
T - Docetaxel (Taxotere)	75 mg/m² IV day 1	Every 21 days	6
A – Doxorubicin	50 mg/m² IV day 1		
C - Cyclophosphamide	500 mg/m² IV day 1		
FEC100			
5-Fluorouracil (5-FU)	500 mg/m² IV day 1	Every 21 days	
Epirubicin	100 mg/m² IV day 1		
Cyclophosphamide	500 mg/m² IV day 1		

1- **TAC** [Docetaxel, Doxorubicin and Cyclophosphamide] – 6 cycles – given 21 days before surgery.

2- **FEC100** [Fluorouracil, Epirubicin and Cyclophosphamide] – given 21 days before surgery.

اللهمَّ صلِّ على نبيِّنا محمّدٍ وآله

وصحبه وسلِّمْ تسليمًا كثيرًا