Selected Recent Advances for The Pharmacological Treatment of Breast Cancer

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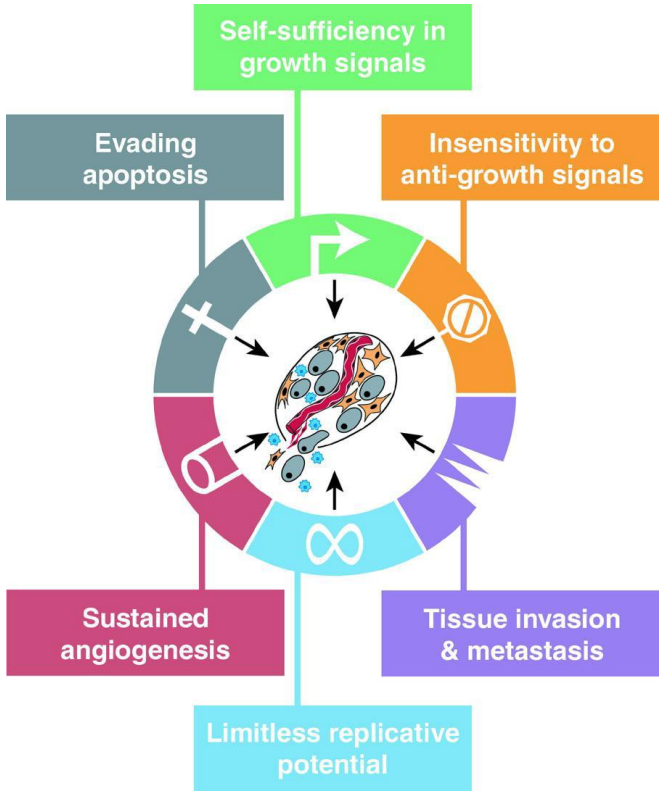
For Third Year Medical Students

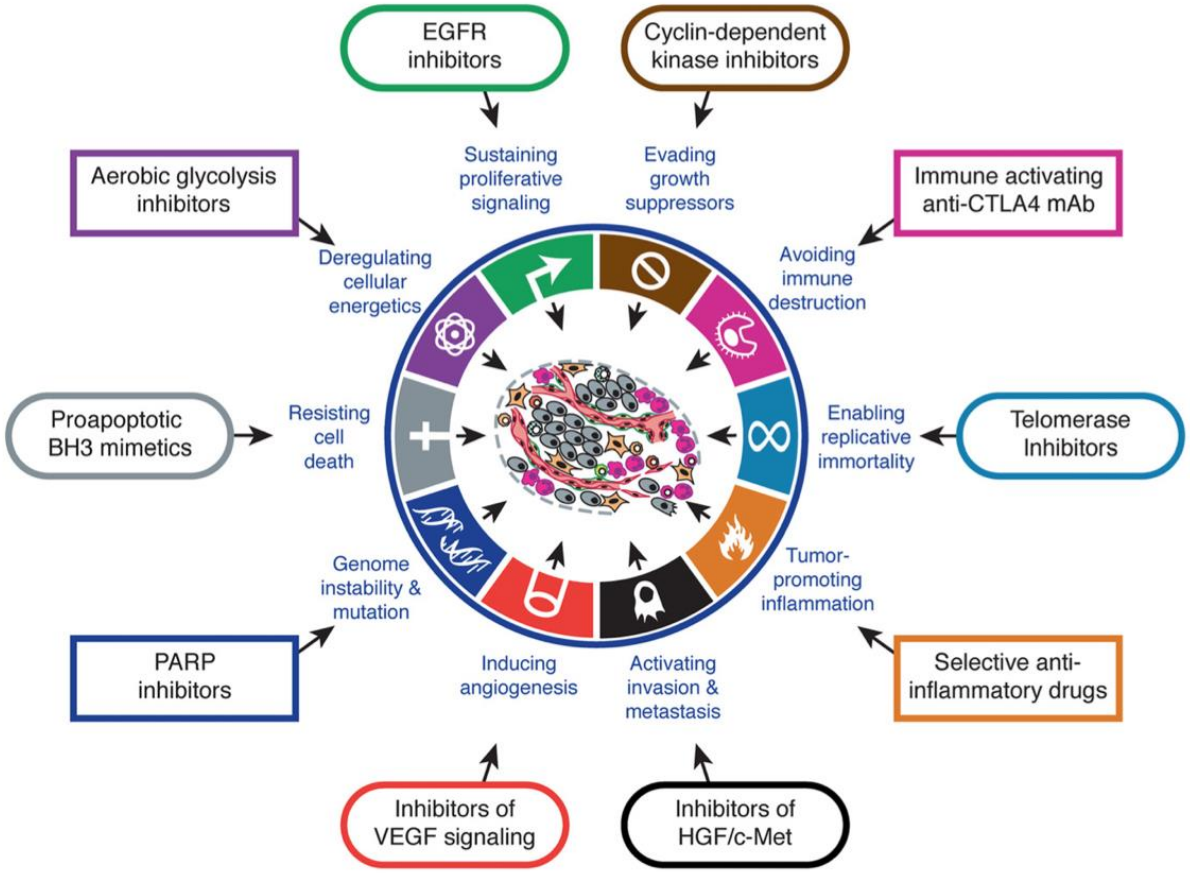
Genitourinary Module

Spring 2020

Evolution of Targeted Anticancer Therapy



Hanahan and Weinberg, 2000



Hanahan and Weinberg, 2011

How Do We Classify Breast Cancer Subtypes For Therapy?

- Hormone receptor (HR)-positive breast cancer:
  - estrogen receptor (ER)-positive and/or
  - progesterone receptor (PR)-positive.

  ❑Liable for the treatment with hormonal therapies
- Human epidermal growth factor receptor 2 (HER2)-positive breast cancer.

  ❑ Liable for the treatment with HER2 targeted therapies.
- Triple-negative breast cancer
  - Negative for ER, PR, or HER2.

Treatment of ER-positive Breast Cancer

ER-positive Breast Cancer

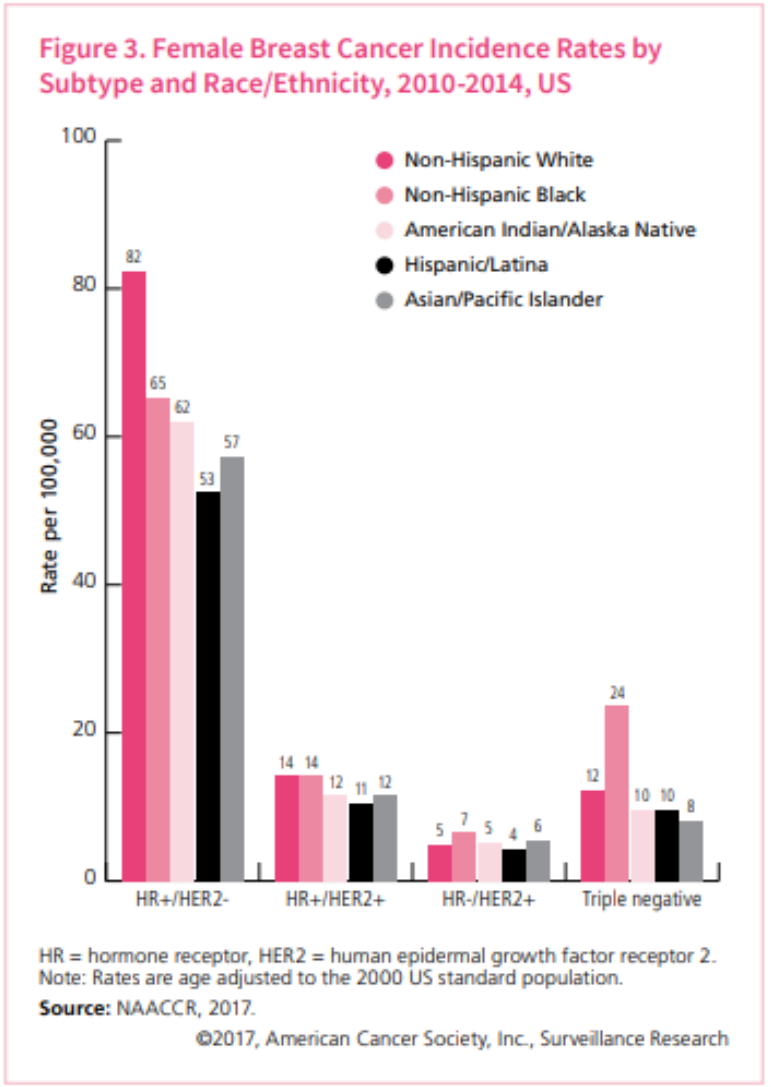
- Further divided into:
  - Luminal A subgroup (HR+/HER2–)
  - Luminal B subgroup (HR+/HER2+)
- Up to 60-80% of total breast cancer cases
- Hormonal Treatment is the mainstay of therapy:

-Tamoxifen

-Aromatase Inhibitors

-Luteinizing hormone-releasing hormone analogs

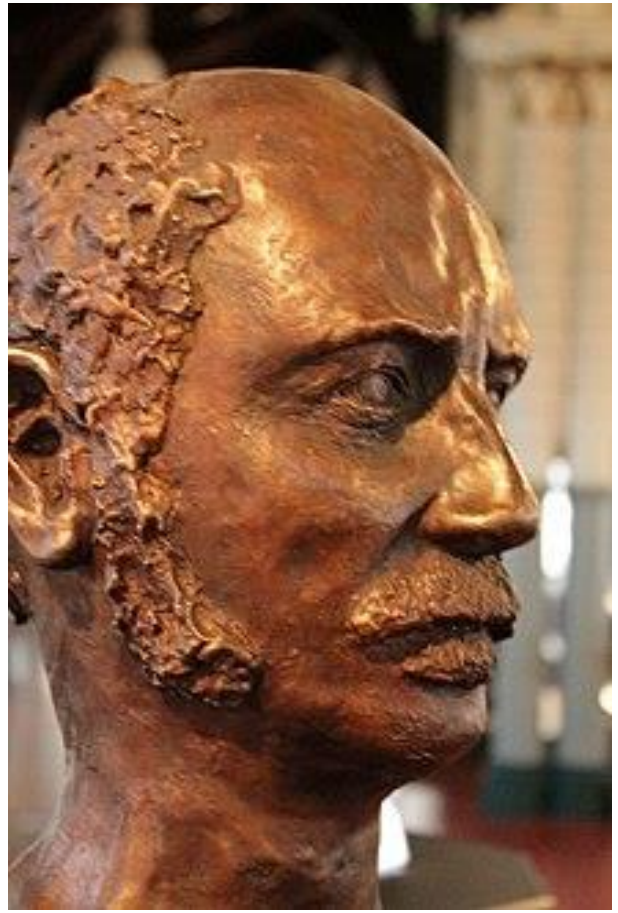
-Fulvestrant



Beatson's Oophorectomy

- 1886- Thomas William Nunn reported disease regression in a perimenopausal woman with breast cancer 6 months after menopause
- 1889- Albert Schinzinger proposed ovarian resection for the treatment of breast cancer
- 1895- George Thomas Beatson performed a bilateral oophorectomy on a woman with extensive soft tissue recurrent breast cancer

Oophorectomy for Breast Cancer: History Revisited by Richard R. Love, John Philips, 2002



Tamoxifen

- Approved for the treatment of ER+ breast cancer for > 40 years
- Strong evidence that 5-year adjuvant tamoxifen therapy 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 (pre- vs postmenopausal)

    Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update, J Clin Oncol, 2014
- Tamoxifen also offered for pre-or postmenopausal women with increased risk for breast cancer to reduce the risk of invasive ER+ breast cancer

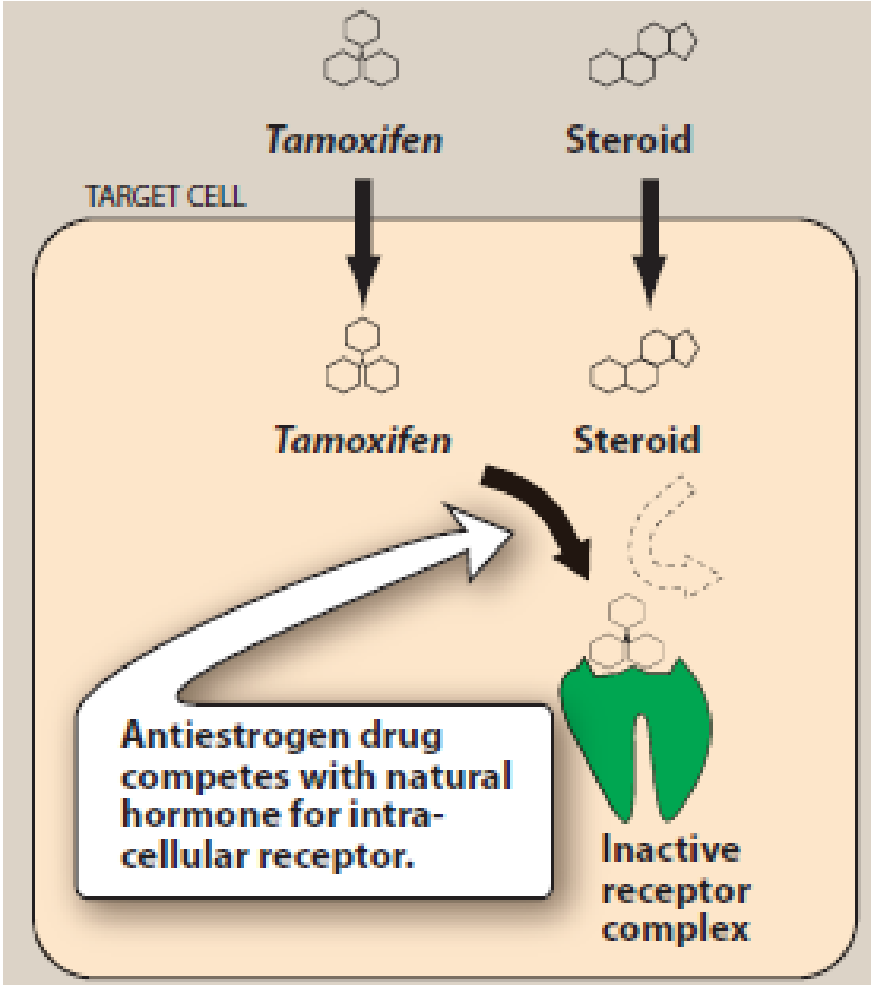
Tamoxifen

Mechanism of action:

- a selective estrogen receptor modulator (SERM).

"*estrogen antagonist with some estrogenic activity*"

- strongly antiestrogenic on mammary epithelium
- Inhibits estrogen-mediated proliferation of breast tumor cells



Tamoxifen

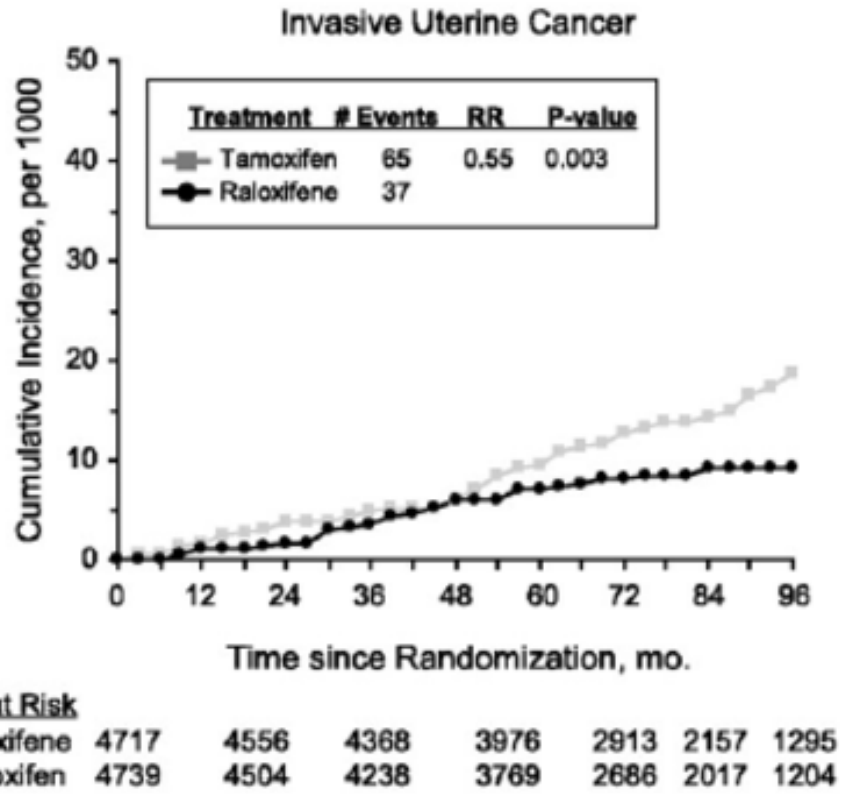
Adverse effects:

- Hot flashes (64%)
- Nausea and vomiting
- Menstrual changes/discharge (13-30%). *Why?*
- Contraindicated in pregnancy

Black Box Warnings

Uterine malignancies and thromboembolic events

- Serious and life-threatening events associated with tamoxifen in the risk reduction setting (women at high risk for cancer and women with DCIS) include uterine malignancies, stroke and pulmonary embolism
- Fatal cases of each type of event have occurred
- Discuss potential benefits versus risks of these serious events with women at high risk of breast cancer and women with DCIS considering tamoxifen to reduce their risk of developing breast cancer; benefits of tamoxifen citrate tablets outweigh its risks in women already diagnosed with breast cancer



STAR Trial, 2006

Fulvestrant

Mechanism of action:

- Competitive estrogen receptor antagonist

Monotherapy:

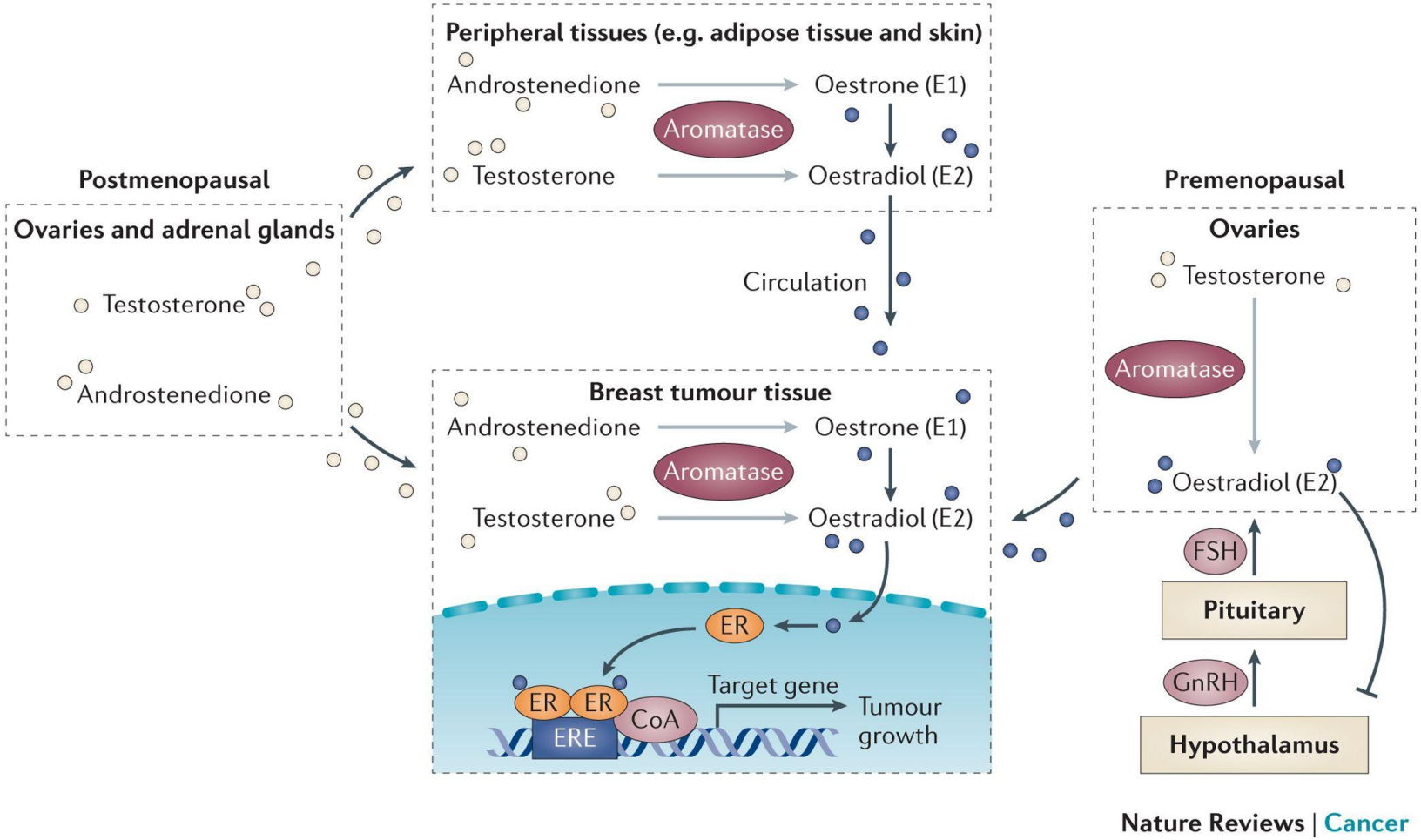
- Indicated for ER+, HER2- in postmenopausal women not previously treated with endocrine therapy
- Indicated for HR-positive in postmenopausal women with disease progression following endocrine therapy

In combination with CDK4/6 inhibitors

Aromatase Inhibitors

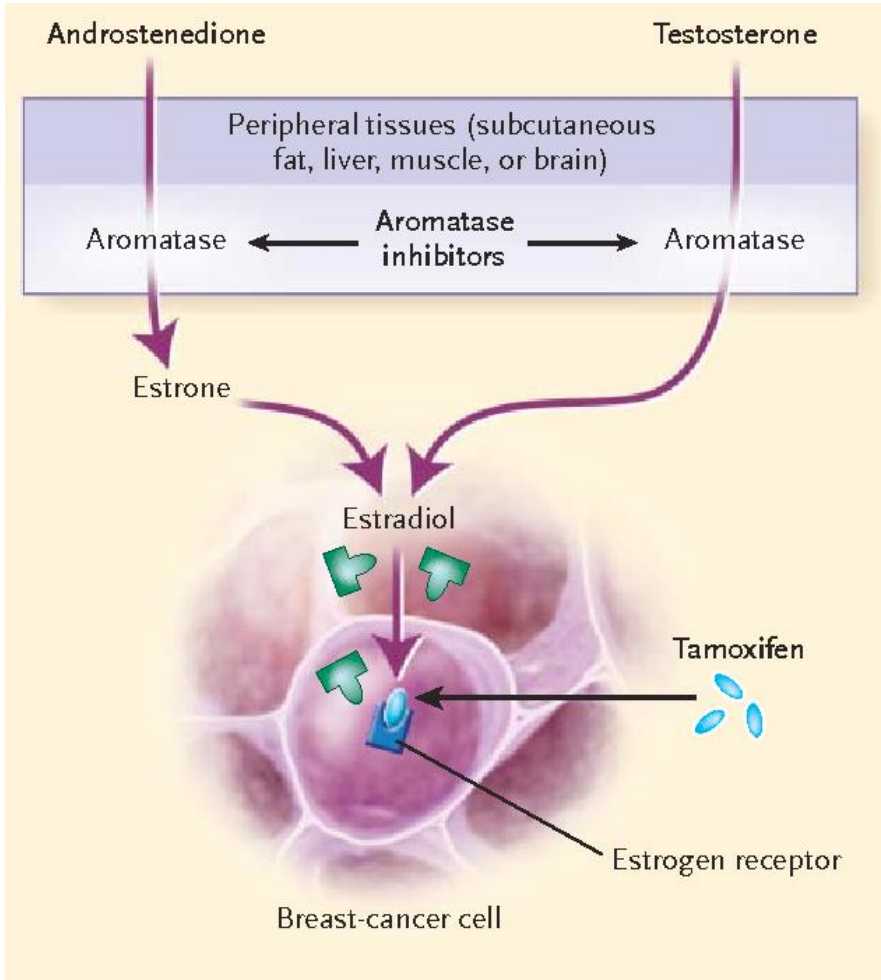
Aromatization:

- Extra-adrenal synthesis of estrogen (Adipose tissue, liver, skin, breast)
- Main source of estrogen in postmenopausal women



Aromatase Inhibitors

Mechanism of action

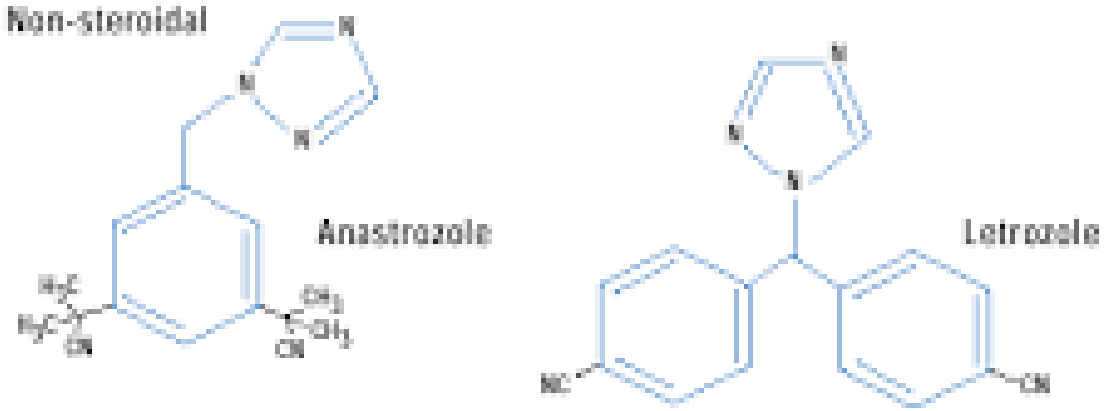


Aromatase Inhibitors

- Current standard-of-care adjuvant therapy for the treatment of ER+ breast cancer
- Trials have shown superiority of aromatase inhibitors over tamoxifen
- Initially, used (and effective) only in postmenopausal women, but now considered for premenopausal women
- **Adverse effect:** hot flashes (12-36%), arthralgia/arthritis (17%), headache (9-13%), vaginal dryness (2%), and mood changes (19%).

Anastrozole and Letrozole

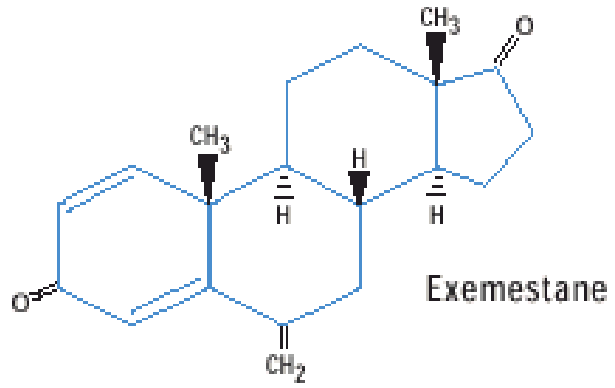
- Non-steroidal aromatase inhibitors
- First-line adjuvant therapy for the treatment of ER+ positive breast cancer in postmenopausal women
- Oral
- No established risk for endometrial cancer



Exemestane

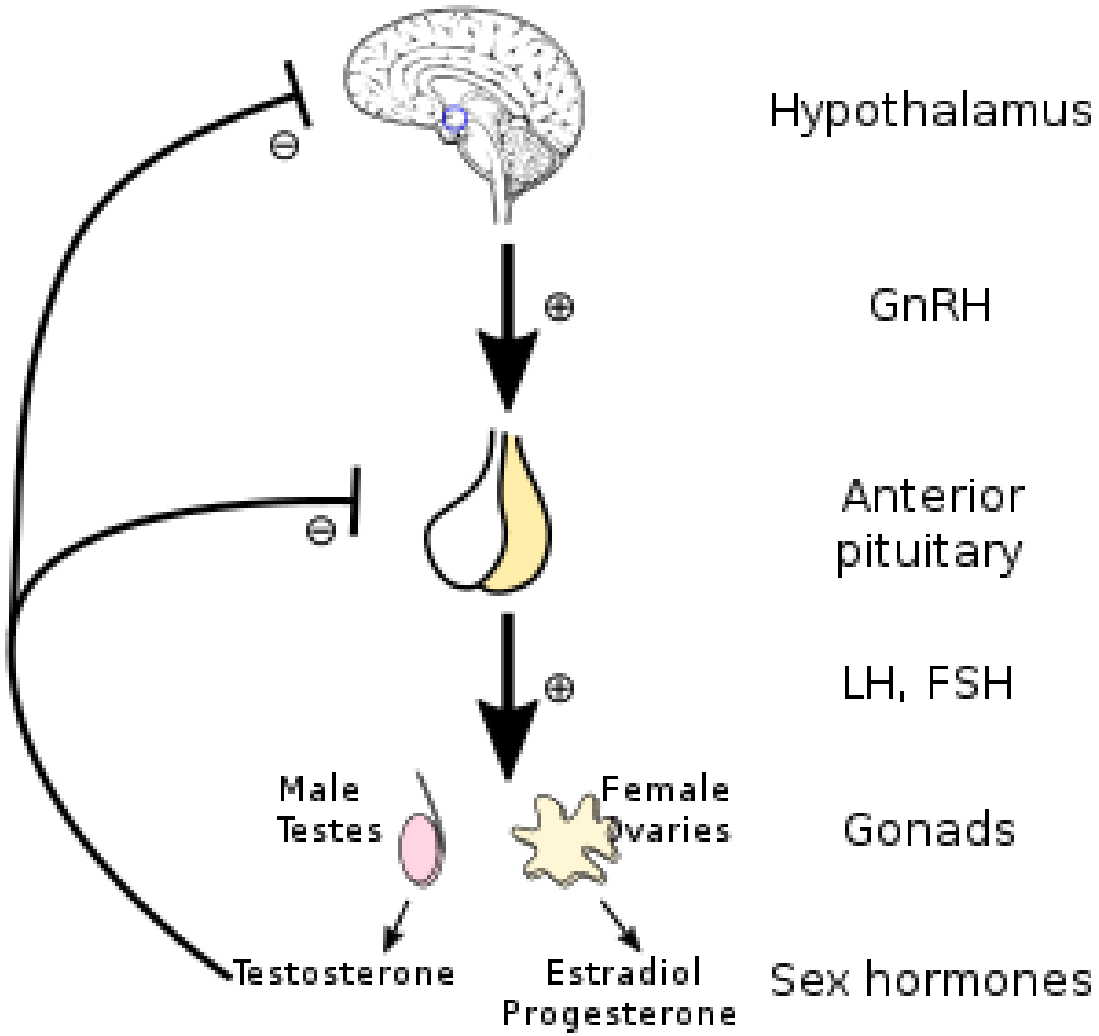
- Steroidal, irreversible aromatase inhibitor
- ASCO guidelines: alternative to tamoxifen and/or raloxifene to reduce the risk of invasive ER+ breast cancer
- Oral

Steroidal



Exemestane

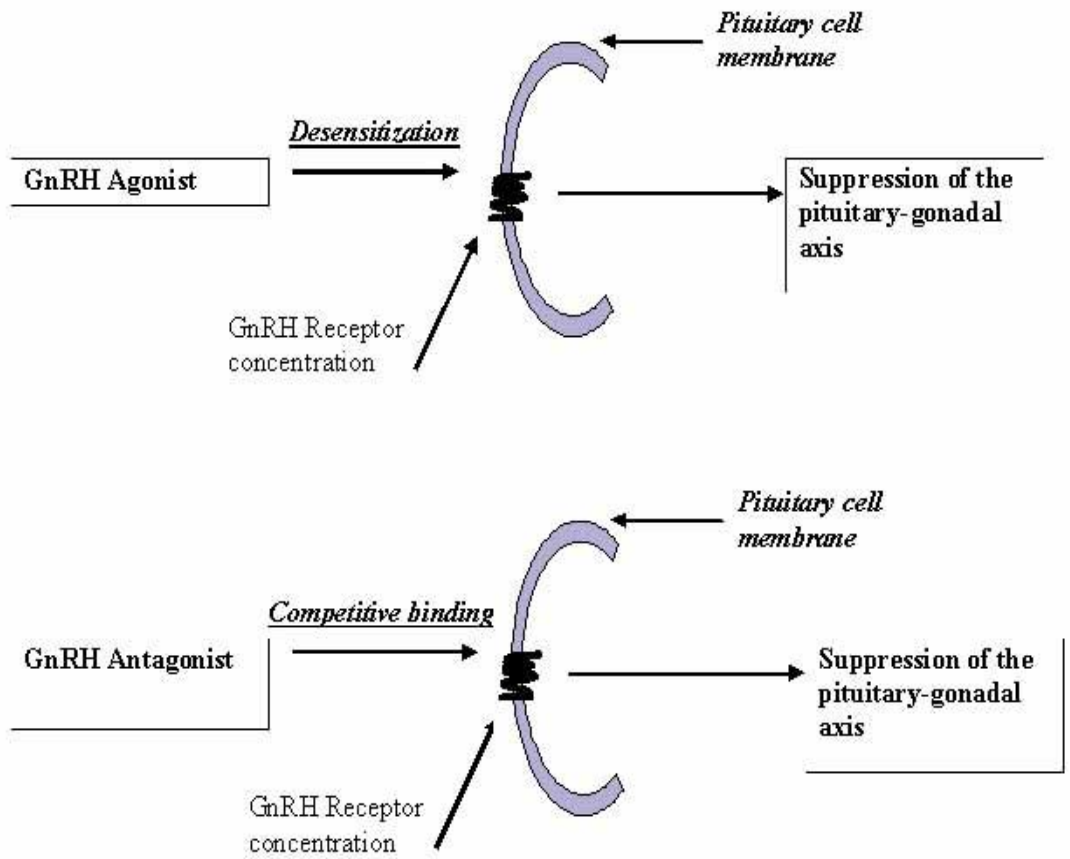
GnRH


Hypothalamus
GnRH
Anterior pituitary
LH, FSH
Male Testes
Female ovaries
Gonads
Testosterone
Estradiol
Progesterone
Sex hormones

GnRH Analogues

Mechanism of action

- Synthetic analogs of GnRH
- Occupy GnRH receptor in pituitary → receptor desensitization → inhibit FSH (and LH) release
- Used for adjuvant treatment of advanced ER+ breast cancer in combination with tamoxifen
- Drugs:
  - Leuprolide
  - Goserlin



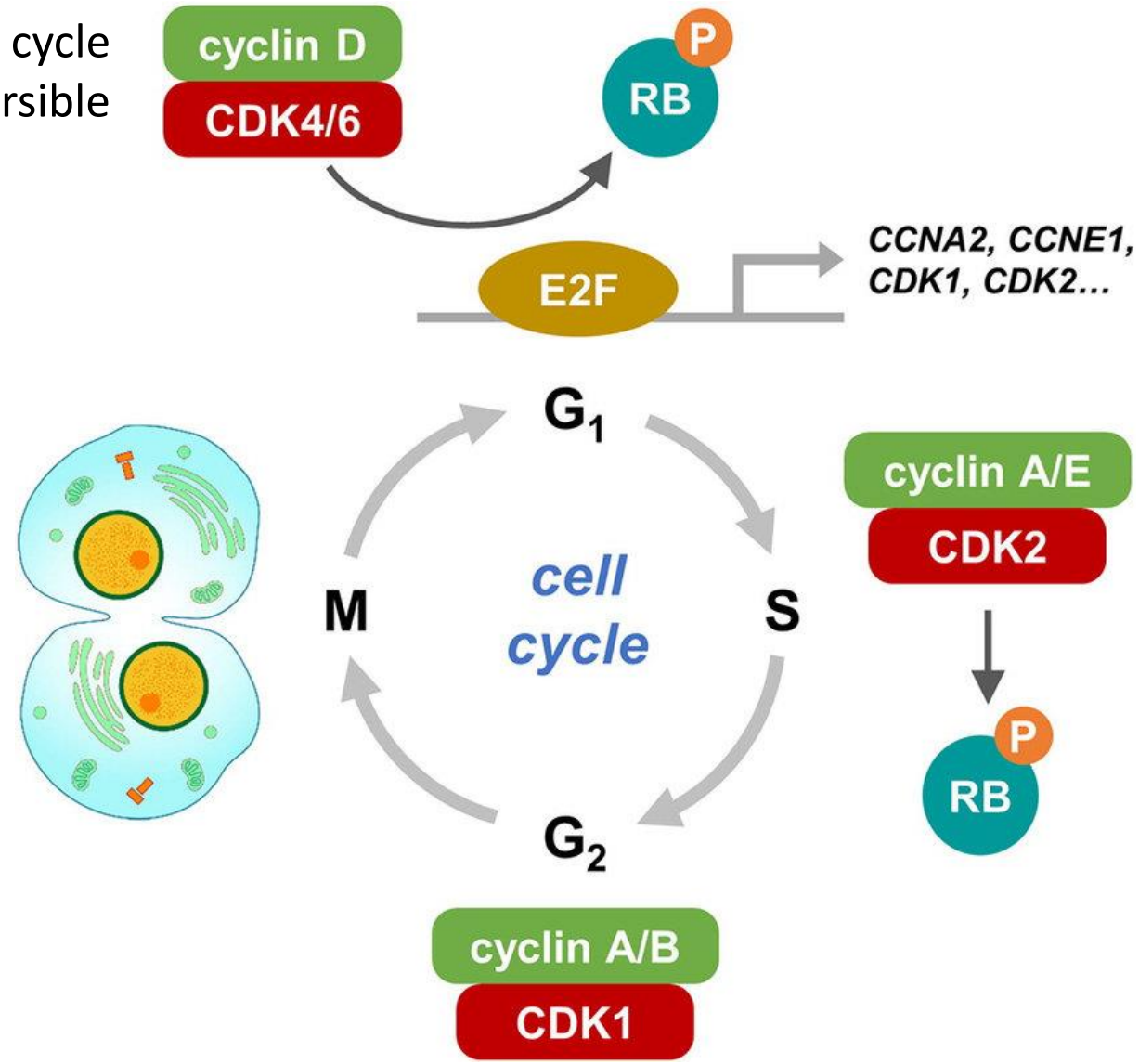
Summary of Hormonal Therapy

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Prednisone	PO	Hyperglycemia, infection, ulcers, pancreatitis, mood changes, cataract formation, osteoporosis		Glucose, CBC	Administer with food
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	
Flutamide, Nilutamide, Bicalutamide	PO	Hot flashes, N, gynecomastia, pain, constipation	*Warfarin*	Hepatic function, PSA	Combined with LHRH agonists or surgical castration

PO=oral administration; N=nausea; V=vomiting; CBC=complete blood count; Sub-Q=subcutaneous; IM=intramuscular; PSA=prostate-specific antigen; LHRH=luteinizing hormone–releasing hormone.

Cell Cycle

CDK4/6 regulate cell cycle progression by their reversible interaction with cyclin D1

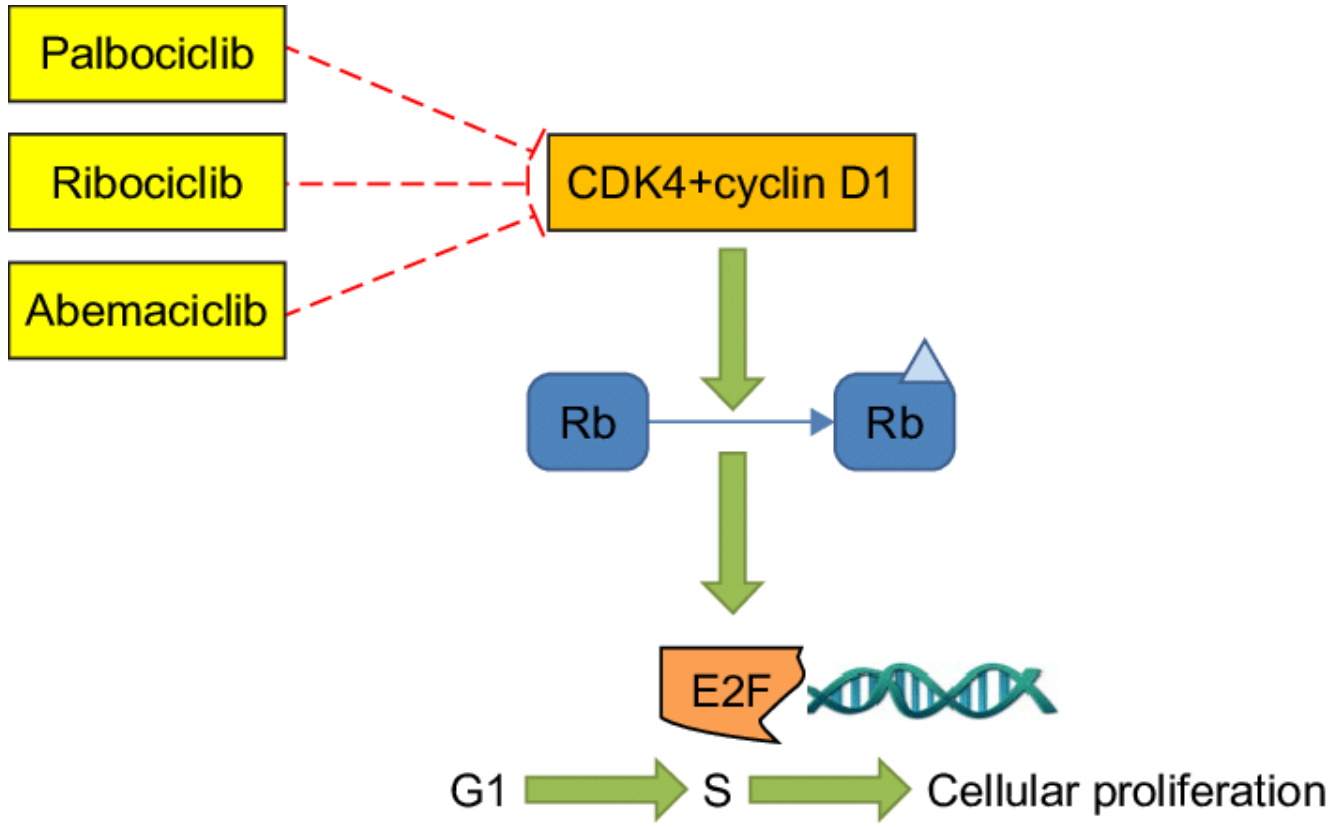


CDK4/6 Inhibitors

- Around 15-30% of ER+ have amplification of cyclin D1 and CDK4

Mechanism of action:

- Blocking the phosphorylation of retinoblastoma protein, thereby downregulating E2F-response genes to mediate G1-S arrest



CDK4/6 Inhibitors

Palbociclib

- Indicated for use (in combination with aromatase inhibitors) for postmenopausal women with metastatic ER+/HER2- breast cancer

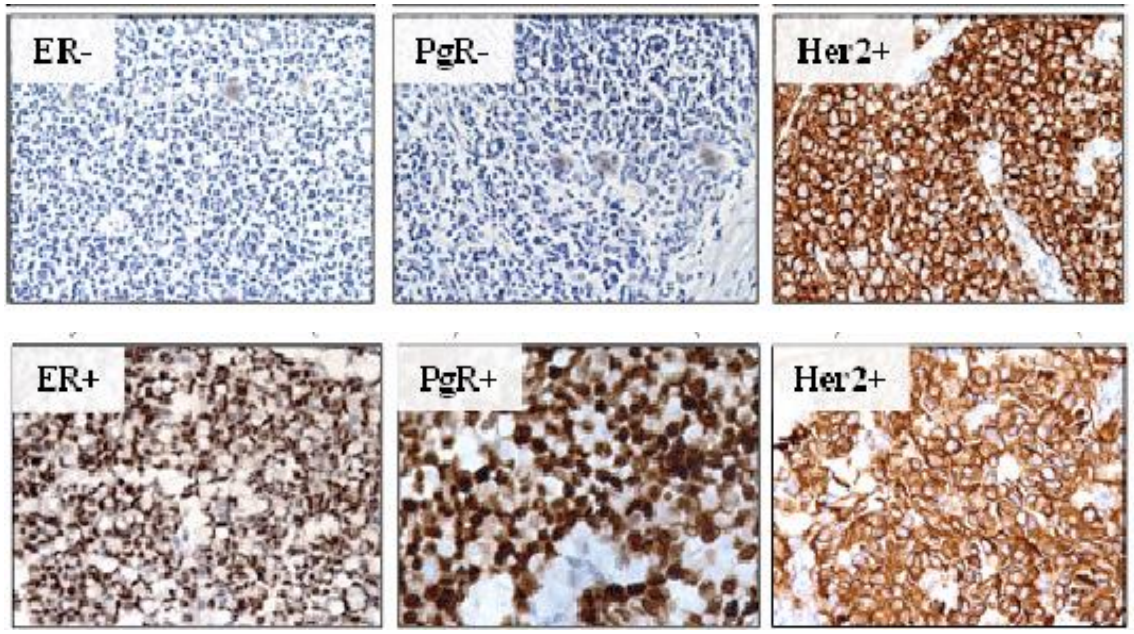
Adverse effects:

- ❑Neutropenia
- ❑Fatigue
- ❑Gastrointestinal symptoms

Treatment of HER2-positive Breast Cancer

HER2-positive Breast Cancer

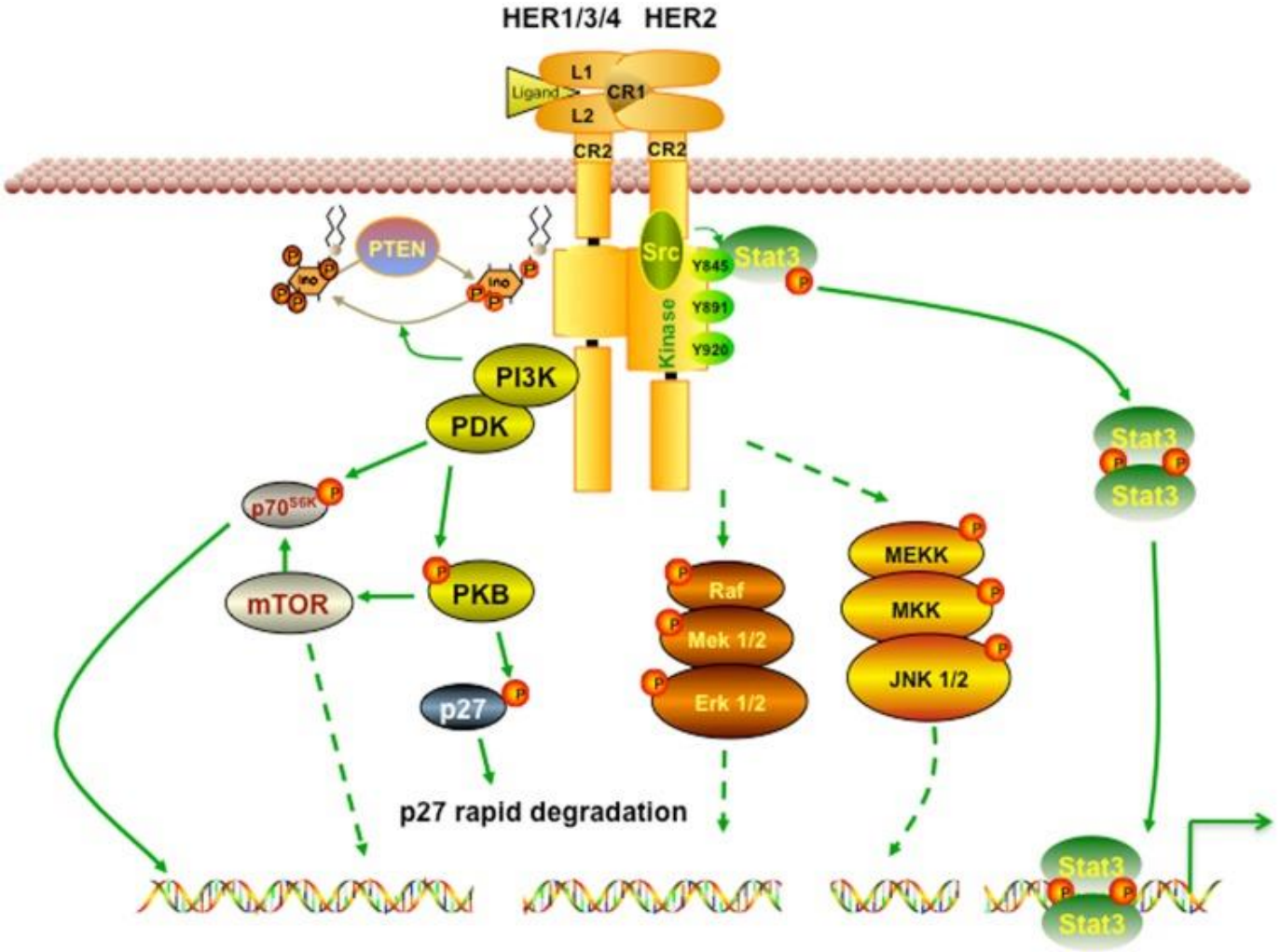
- **ERBB2, CD340, proto-oncogene Neu, HER2, HER2/Neu:** member of the human epidermal growth factor receptor (EGFR) family.
- Normally expressed at a low level on the surface of epithelial cells: breast, ovary, lung, liver, kidney, and central nervous system.
- The overexpression or gene amplification of HER2 has been found in about 20–30% of breast cancers.



Breast Cancer Samples

HER2-positive Breast Cancer

- HER2 is activated by the formation of homodimers or heterodimers with other EGFR proteins e.g., HER2/HER3 dimer
- autophosphorylation and/or transphosphorylation of specific tyrosine residues in EGFR intracellular domains
- Activation of pro-proliferation signaling pathways



Vu and Claret et al., Front Oncol., 2012

Trastuzumab (Herceptin)

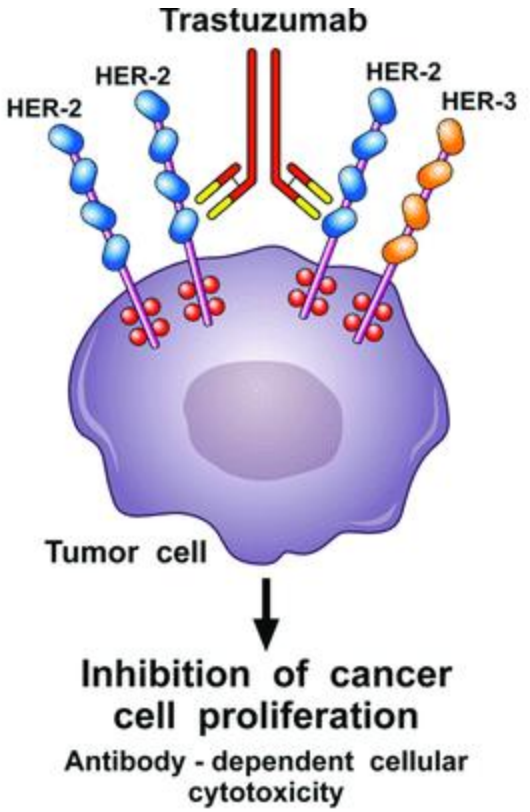
- recombinant humanized monoclonal antibody against HER2
- **Actions:**

❑triggers HER2 internalization and degradation

❑attracts immune cells to HER2-overexpressing tumor cells

❑inhibits pro-proliferation pathways e.g., MAPK and PI3K/Akt pathways

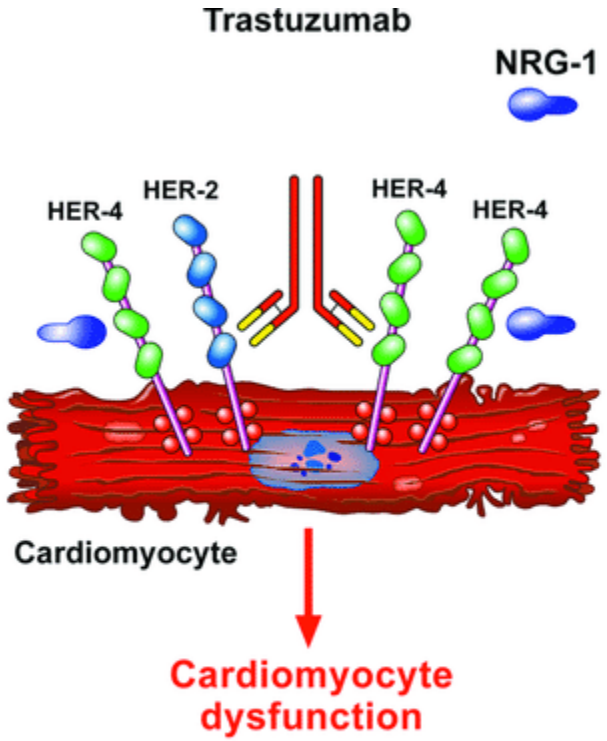
❑suppresses cell growth and proliferation



Trastuzumab (Herceptin)

Adverse effects

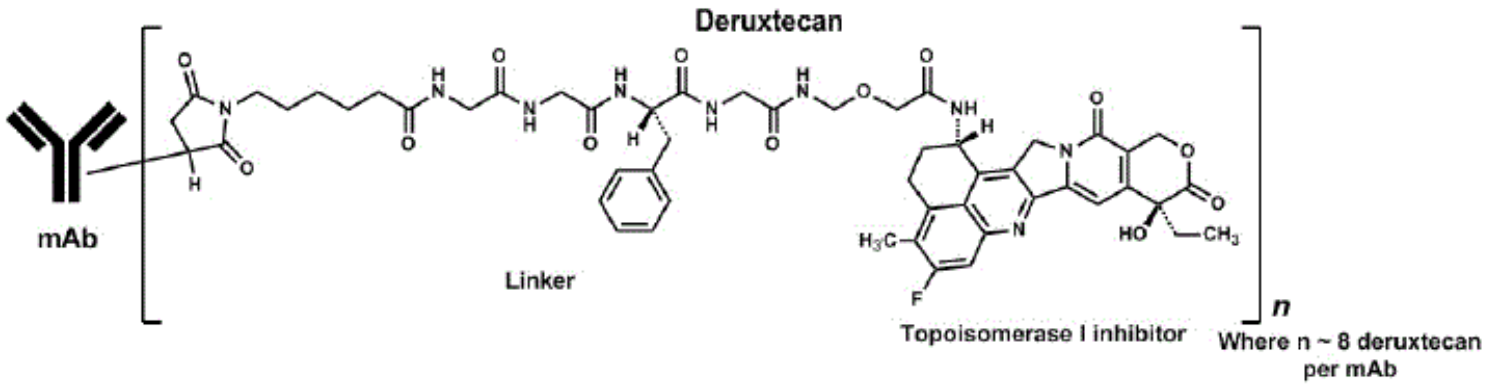
- Pain (47%)
- Asthenia (42%)
- Fever (36%)
- Nausea (33%)
- Chills (32%)
- Cough (26%)
- Headache (26%)
- Diarrhea (25%)
- Vomiting (23%)
- Cardiotoxicity (congestive heart failure)



Treatment of HER2-positive Breast Cancer

Other options:

1. Pertuzumab
2. ado-trastuzumab emtansine
3. Fam-trastuzumab deruxtecan (new, 2020)
4. Lapatinib
5. Neratinib



Treatment of Triple-Negative Breast Cancer (TNBC)

Triple-Negative Breast Cancer (TNBC)

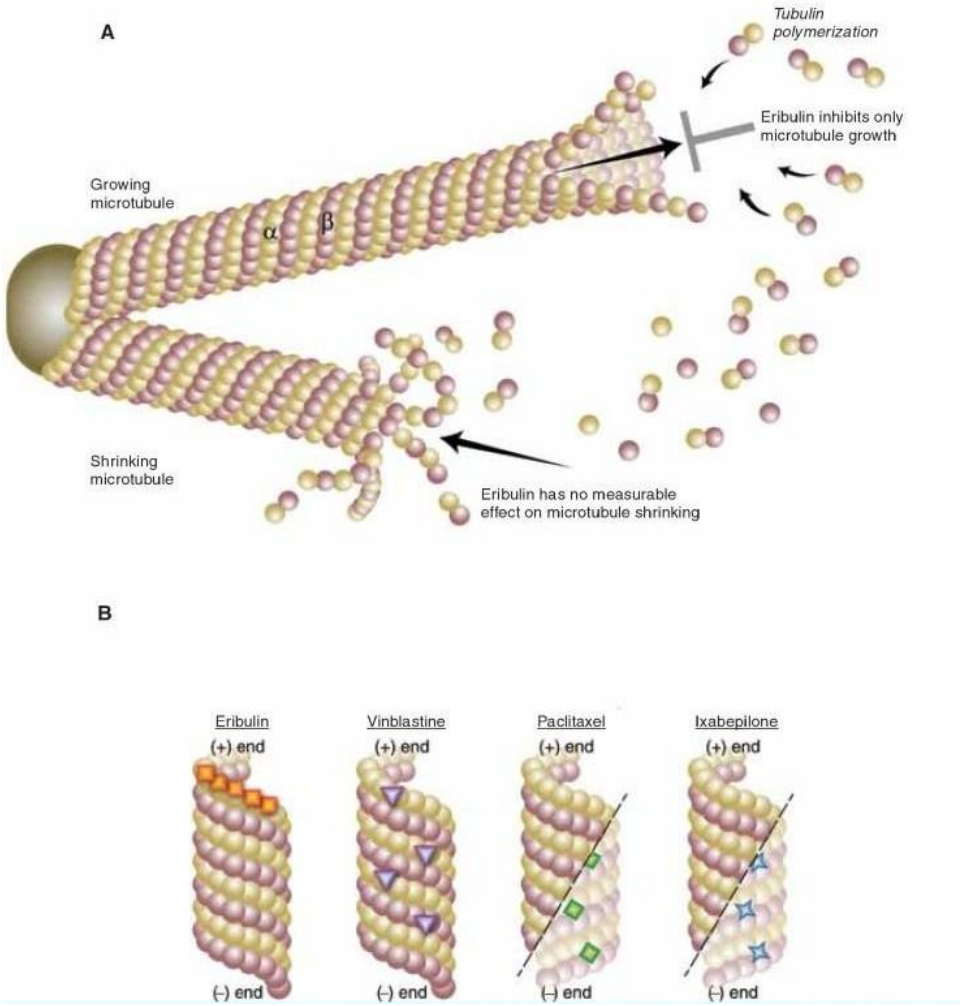
- TNBC: Breast cancer that lacks ER, PR and HER2
- 10–15% of primary breast cancers are triple negative
- Important because:

1. TNBC is a poor prognostic factor for disease-free and overall survival
2. No effective specific targeted therapy is readily available for TNBC

Treatment of Triple-Negative Breast Cancer (TNBC)

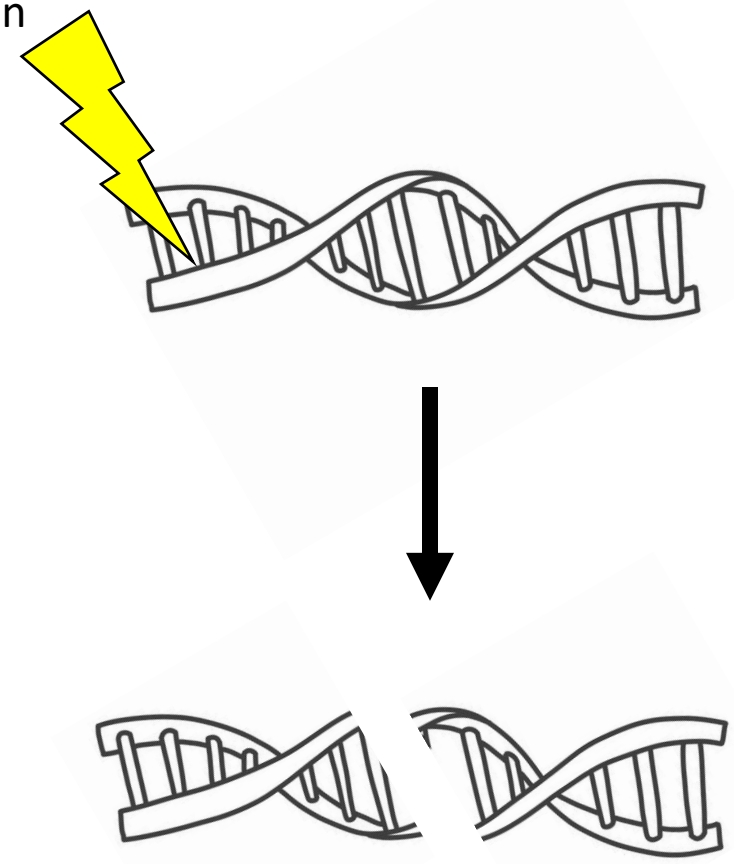
Cytotoxic chemotherapy

- Anthracyclines (doxorubicin, epirubicin)
- Taxanes (paclitaxel, docetaxel)
- Antimetabolites (gemcitabine, capecitabine)
- Platinum-coordination complexes (cisplatin or carboplatin)



DNA Damage

e.g., ionizing radiation



DNA double-stranded break

DNA Damage Repair

What happens in case of BRCA mutations?

Homologous Recombination

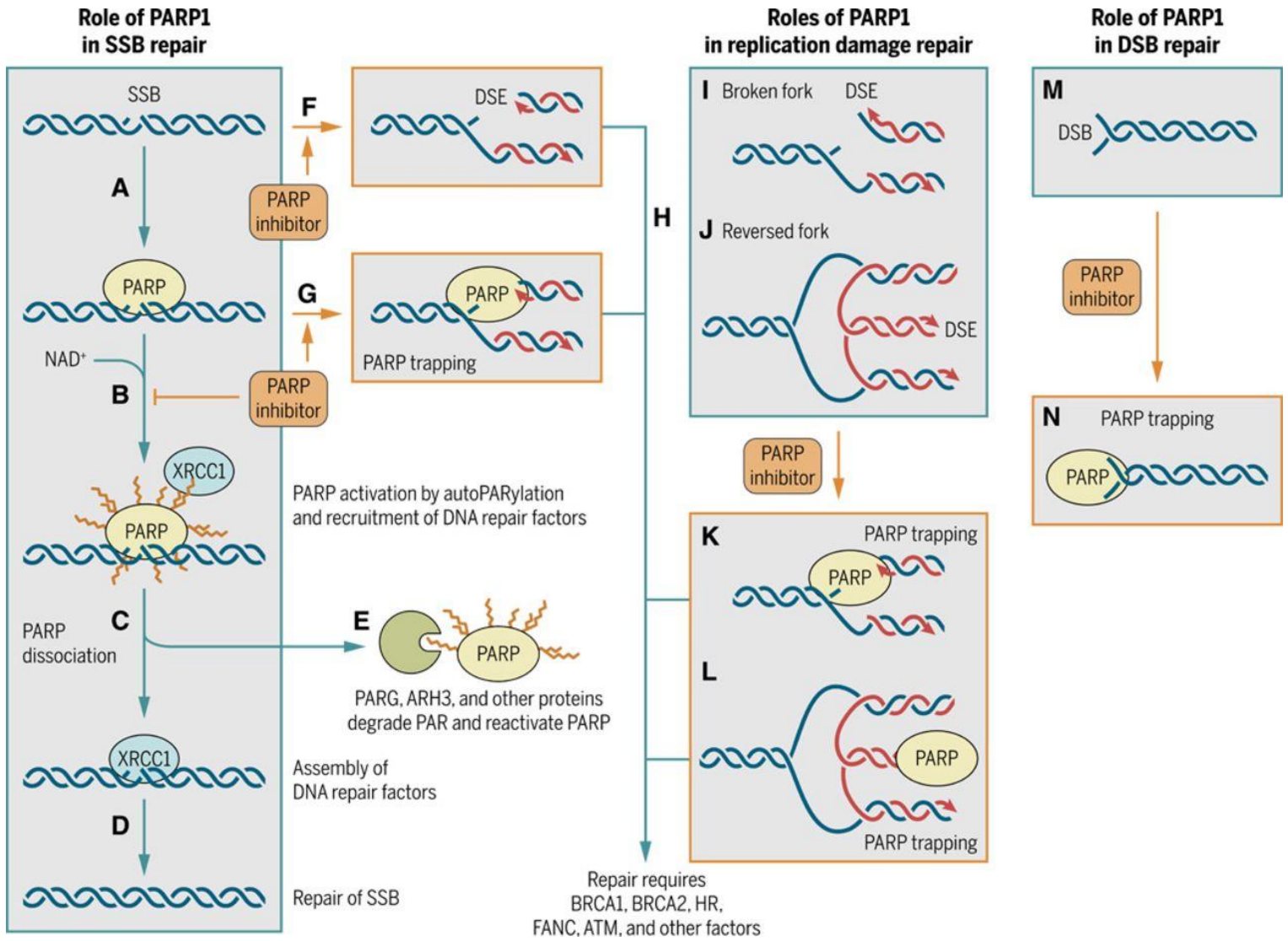
Uses sister chromatid as template
G2/M, after DNA replication
High fidelity, error-free
BRCA1 and BRCA2 dependent

Non-Homologous End Joining

No template
DNA trimmed and ligated
Error-prone
Leads to genetic instability

Remember: patients with deleterious BRCA1 mutations more commonly develop TNBCs

PARP Function



PARP Inhibitors

Olaparib

- Approved for use in women and men with deleterious germline BRCA1 or BRCA2 (gBRCA1/2+) mutations and metastatic HER2− breast cancer

Treatment of Triple-Negative Breast Cancer (TNBC)

Other potential approaches

- PIK3 Inhibitors
- CDK4/6 Inhibitors
- Immunotherapy

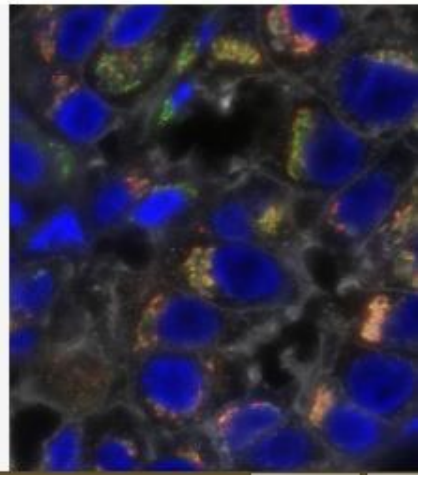
Atezolizumab Approved for Some Patients with Triple-Negative Breast Cancer

Subscribe

March 28, 2019, by NCI Staff

UPDATE: Updated findings from the IMpassion130 trial–published November 27, 2019, in *The Lancet Oncology*–showed that there was no improvement in how long patients who received atezolizumab in combination with nab-paclitaxel lived compared with those who received a placebo and nab-paclitaxel.

However, in patients whose tumors tested positive for expression of the PD-L1 protein, the median overall survival of atezolizumab-treated patients was 25 months compared with 18 months for those who received nab-paclitaxel and a placebo. But, because



What About Neoadjuvant Chemotherapy

Preoperative chemotherapy should be considered in these patients if they have any of the following:

- T3-T4 disease
- Node-positive disease
- ER-negative disease
- HER2-positive disease
- Tumors that need downsizing for surgery

Examples On Commonly Used Neoadjuvant Chemotherapy Combinations

Regimen	Dose and Schedule	Frequency	Cycles
TAC			
T - Docetaxel (Taxotere)	75 mg/m^2 IV day 1	Every 21 days	6
A – Doxorubicin	50 mg/m^2 IV day 1		
C - Cyclophosphamide	500 mg/m^2 IV day 1		

Examples On Commonly Used Neoadjuvant Chemotherapy Combinations

Regimen	Dose and Schedule	Frequency	Cycles
FEC100			
5-Fluorouracil (5-FU)	500 mg/m^2 IV day 1	Every 21 days	
Epirubicin	100 mg/m^2 IV day 1		
Cyclophosphamide	500 mg/m^2 IV day 1		