Clinical Case #1

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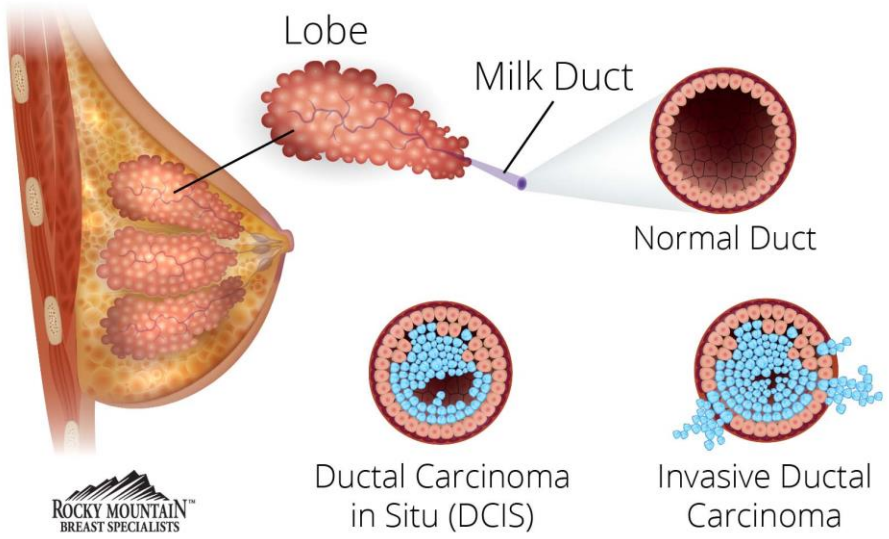
22.2.23

INTRODUCTION

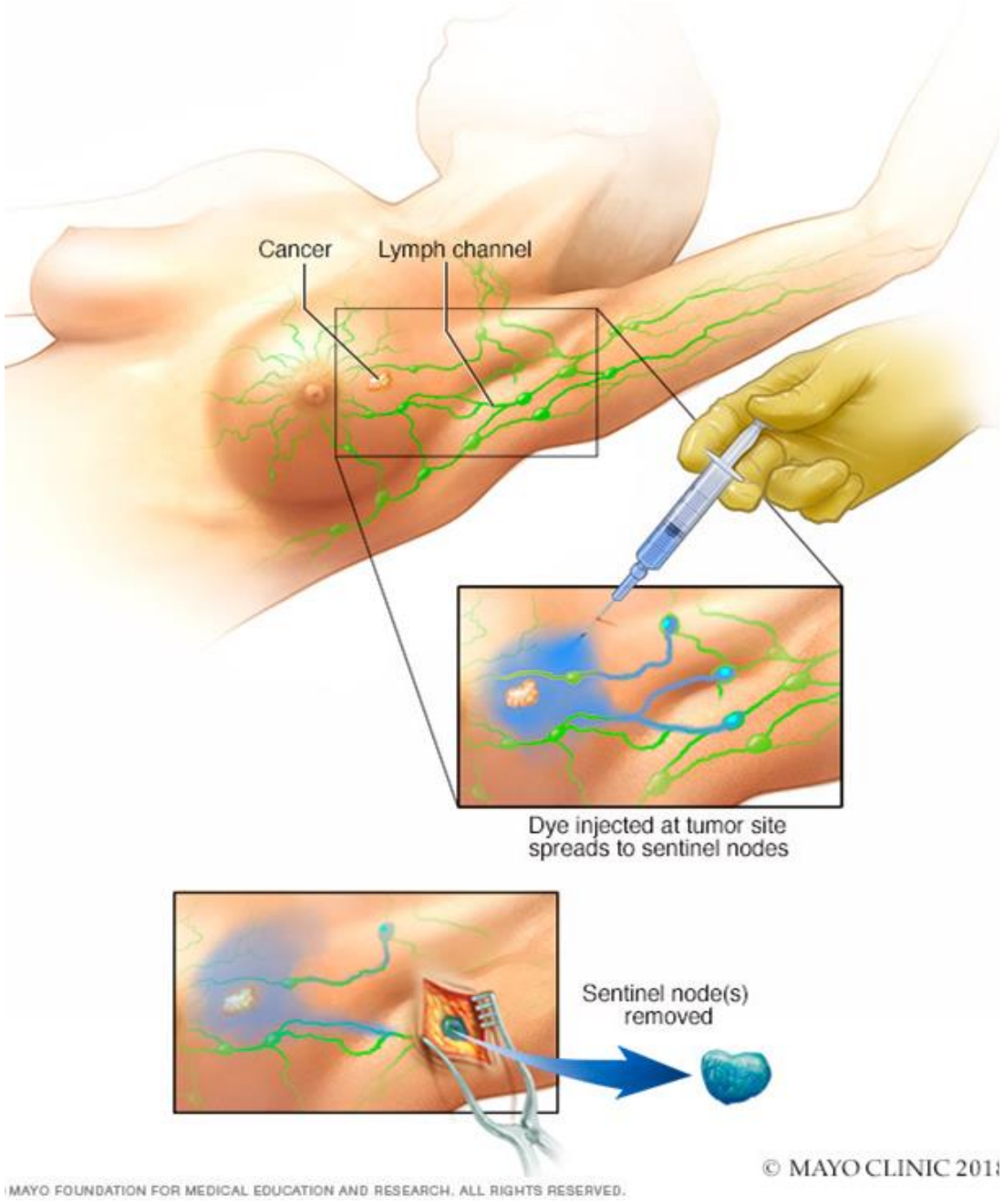
A 79-year-old woman, on 7/2015 referred to the surgical department due to carcinoma of the breast.



TREATMENT

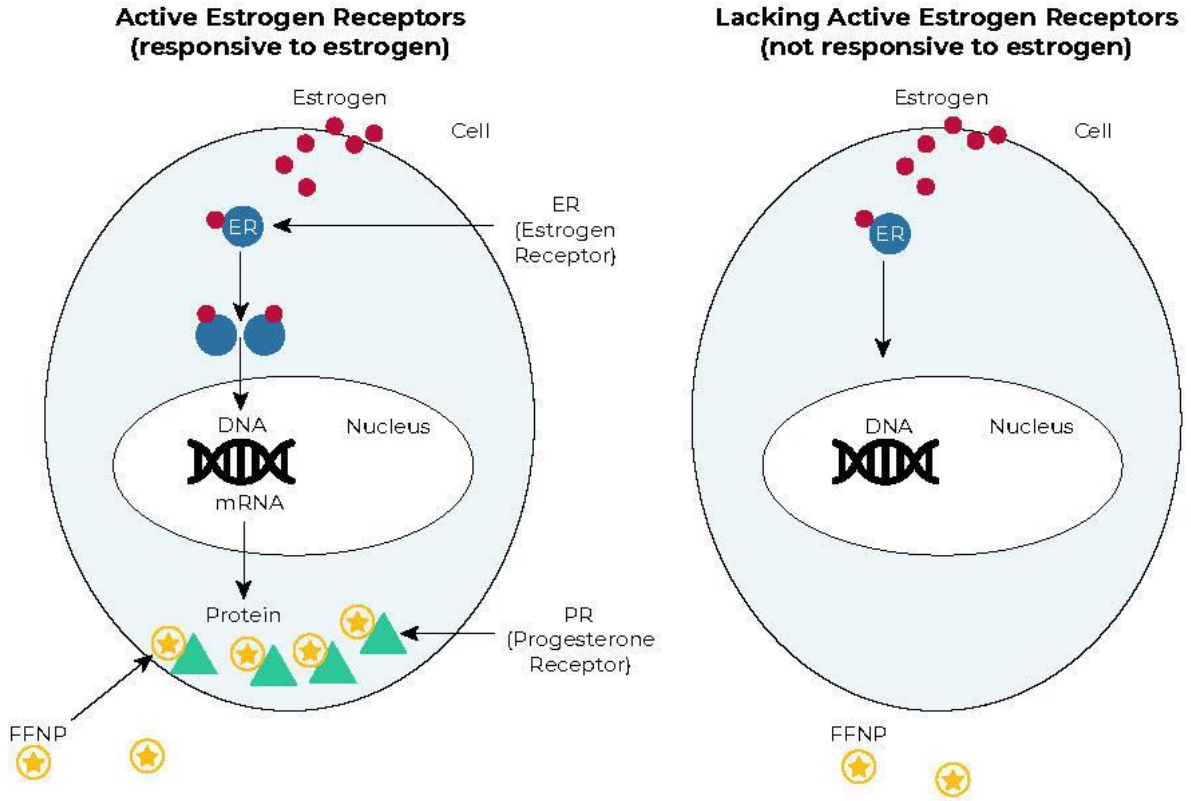
7/2015

Lumpectomy & sentinel lymph node



Pathology: Stage I, G1 ER/P positive HER2 negative

- Stage 1: Localized cancer
- Grade 1: Cells are slower-growing and look more like normal breast cells
- ER/P positive: Tumor cells contain an abundance of receptors for the hormone estrogen and the growth of these cancers is fueled by estrogen
- About 70%–80% of breast cancers in women and 90% in men are ER positive.



(Imaging Test to Guide Breast Cancer Treatment - NCI 2021)

TREATMENTS

7/2015: Radiotherapy

7/2015-9/2020: Letrozol

Lowers the levels of the female sex hormone oestrogen in the body

10/2018
another cancer is detected…

Stage IIA melanoma

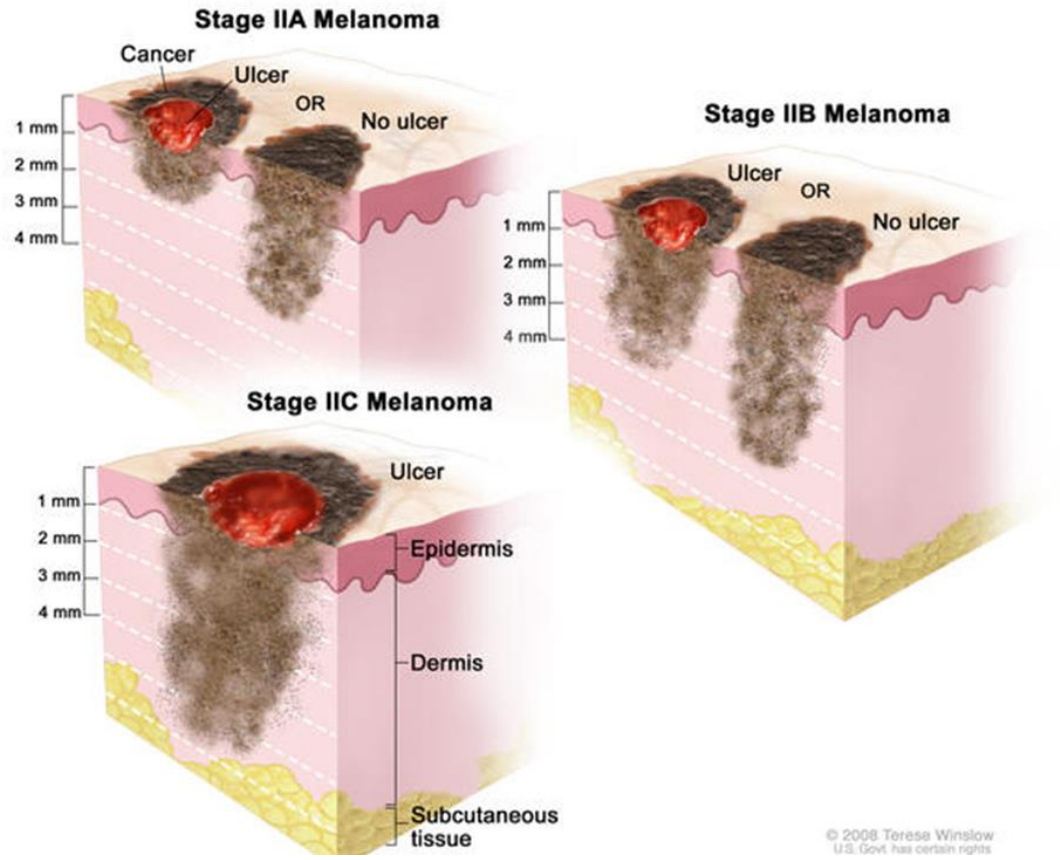
Stage IIA Melanoma

Melanoma is a type of cancer that originates in the melanocytes, which are the cells responsible for producing the pigment melanin.

1. Tumor thickness: The primary tumor is between 2-4mm thick.
2. No ulceration?
3. No lymph node involvement.
4. No distant metastasis

Treated with resection

five-year survival rates: 88%



(Understanding Melanoma n.d.)

CASE TIMELINE

2021 July

Imaging: Lymph node and bone lesions

2021 July

Pathology: Invasive duct carcinoma, ER/PR positive HER2 negative

2021 Aug.

Treatment: fulvestrant in combination with palbociclib

2021 Nov.

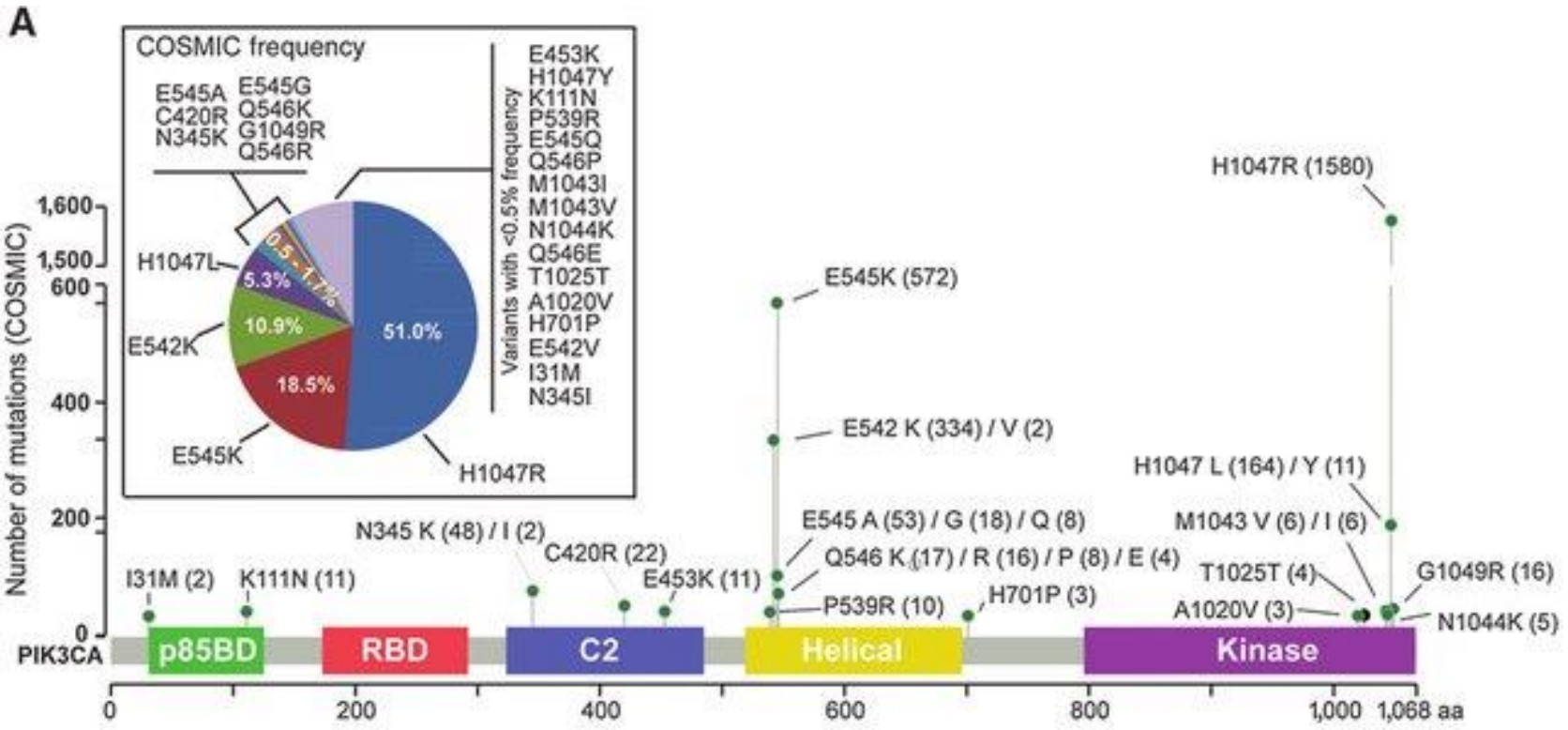
Liver biopsy: Revealed ER/PR positive HER2 negative invasive duct carcinoma

2021 Dec.

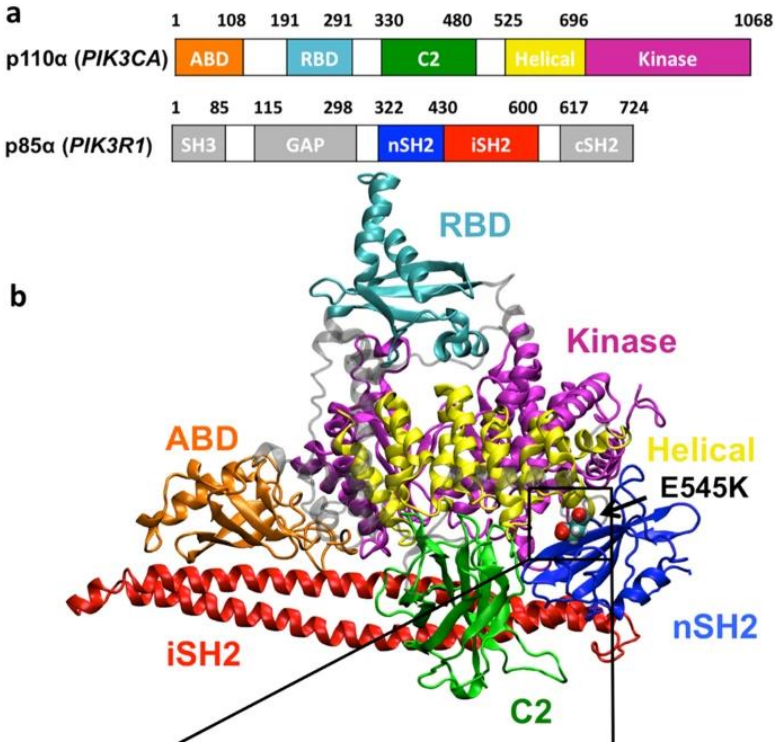
Treatment: Capecitabine

OCA Results: PIK3CA Mutations

- PIK3CA c.3140A>T p.His1047Leu
- A missense somatic mutation



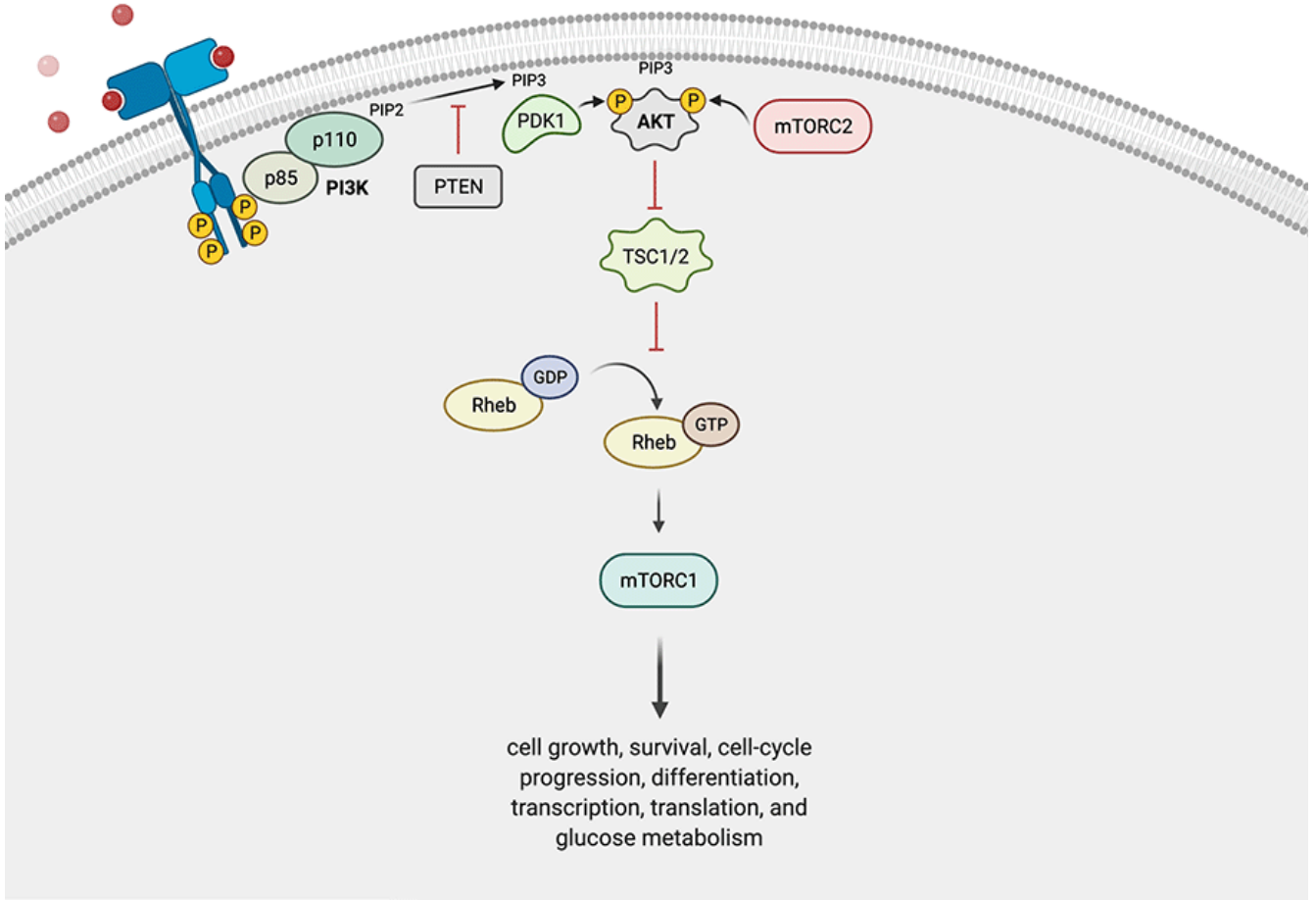
(Dogruluk et al. 2015)



(Leontiadou et al. 2018)

The Healthy Pathway of PIK3CA

1. Activation of receptor tyrosine kinases (RTKs) by Growth factors
2. Recruitment and activation of PI3K
3. Conversion of PIP2 to PIP3 by activated PI3K
4. Activation of downstream signaling: PIP3 serves as a second messenger that recruits and activates several proteins, including AKT
5. Modulation of downstream pathways



Castel *et al.*, 2014

Mutations in PIK3CA: p.His1047Leu

Result in constitutive activation of the PI3K pathway, leading to increased cell survival, proliferation, and tumor growth.

Gene Variant Detail

Gene	PIK3CA
Variant	H1047L
Impact List	missense
Protein Effect	gain of function
Gene Variant Descriptions	PIK3CA H1047L is a hotspot mutation that lies within the PI3K/PI4K domain of the Pik3ca protein (UniProt.org). H1047L results in increased phosphorylation of Akt and Mek1/2, growth factor-independent cell survival, and transformation in cell culture (PMID: 26627007, PMID: 29533785).

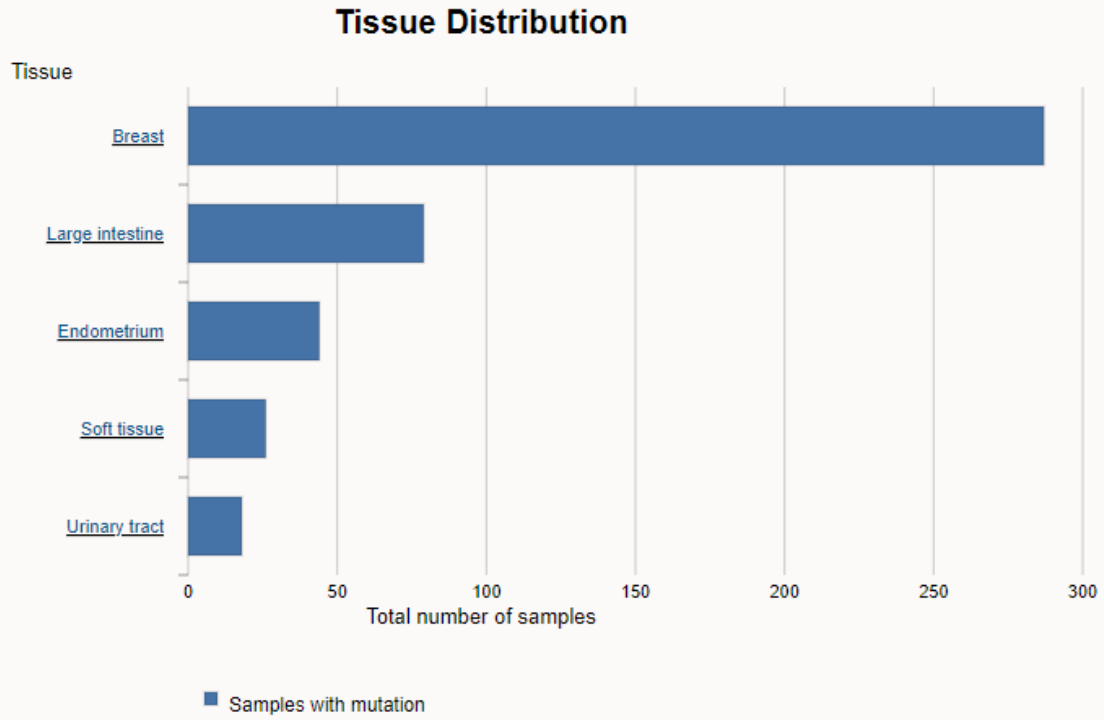
The Predictive Role of the Mutation in Breast Cancer

COSMIC
Catalogue Of Somatic Mutations In Cancer

Genomic Mutation ID	COSV55873401
Legacy Identifier	COSM776
Gene name	PIK3CA
AA mutation	p.H1047L (Substitution - Missense, position 1047, H→L)
CDS mutation	c.3140A>T (Substitution, position 3140, A→T)
Nucleotides inserted	n/a
Genomic coordinates	GRCh38, 3:179234297..179234297, view Ensembl contig
CDD	n/a
HomoloGene	n/a
Ever confirmed somatic?	Yes
Remark	n/a
Recurrent	n/a
Drug resistance	n/a
Alternative Ids	175394114{PIK3CA_ENST00000643187}

Tissue distribution

This section displays the distribution of mutated samples and tissue types (top 5). You can see more information on our help pages.



Prognostic Impact of PIK3CA Mutation in HR+/HER2- Metastatic Breast Cancer

- Metastatic breast cancer (mBC) has a low 5-year survival rate of 27%.
- In HR+/HER2- mBC patients without PIK3CA-targeted therapies, PIK3CA mutation is a negative prognostic factor, associated with shorter PFS (approximately 2 months) and OS (approximately 8 months).
- Effective therapies targeting PIK3CA-mutated mBC are crucial to address this clinical burden.

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Invasive Breast Cancer

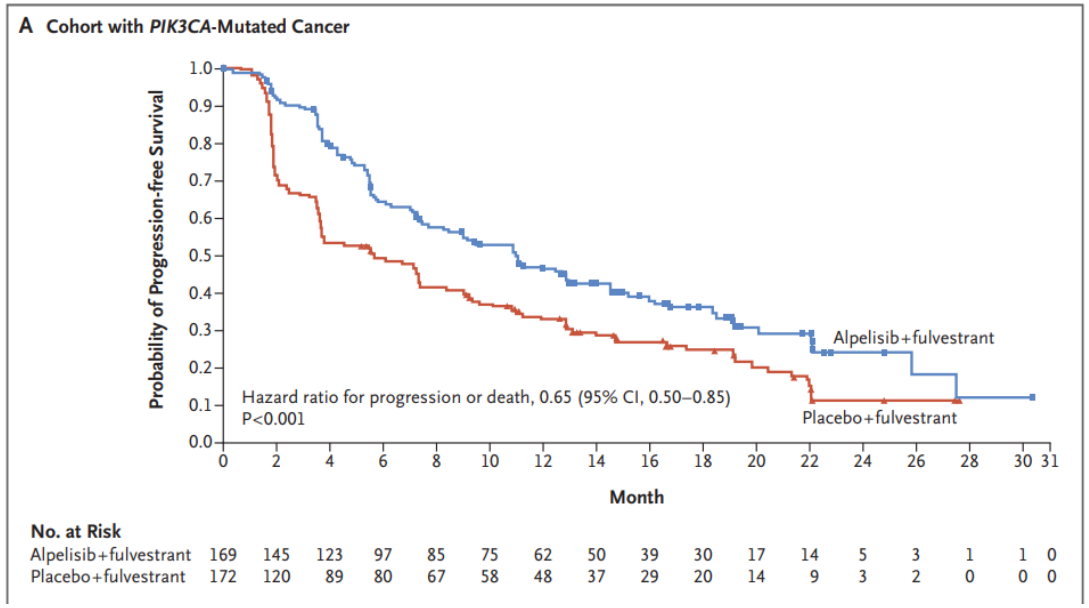
NCCN Guidelines Index
Table of Contents
Discussion

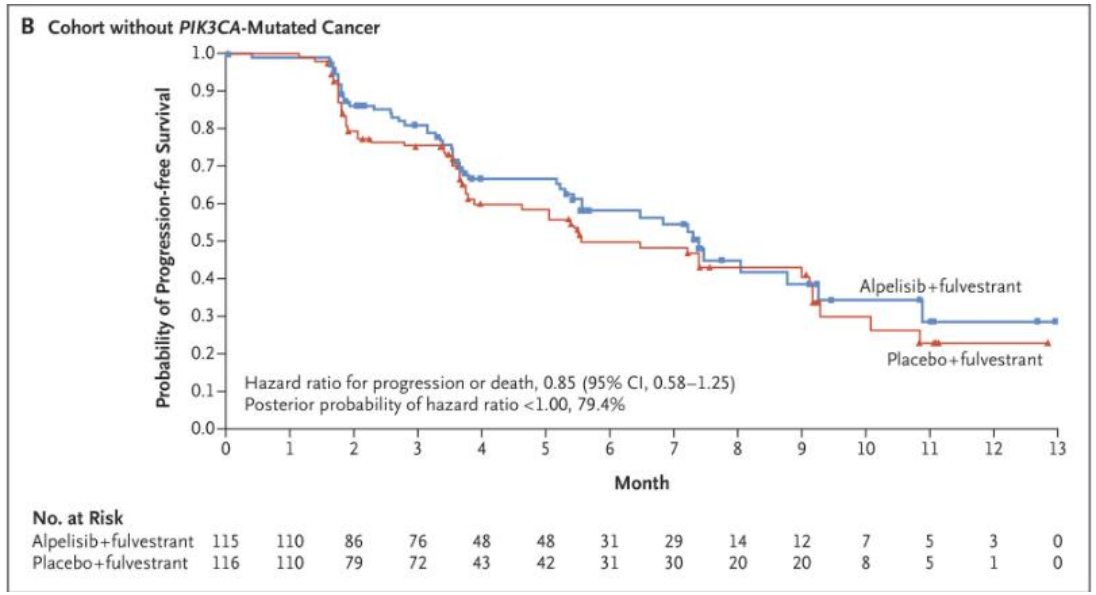
ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2-negative[v]	*PIK3CA* activating mutation	PCR (blood or tissue block if blood negative)	Alpelisib + fulvestrant[w]	Category 1	Preferred second- or subsequent-line therapy

Effect of Alpelisib on Progression-Free Survival in PIK3CA-Mutated Cancer: Clinical Trial Results

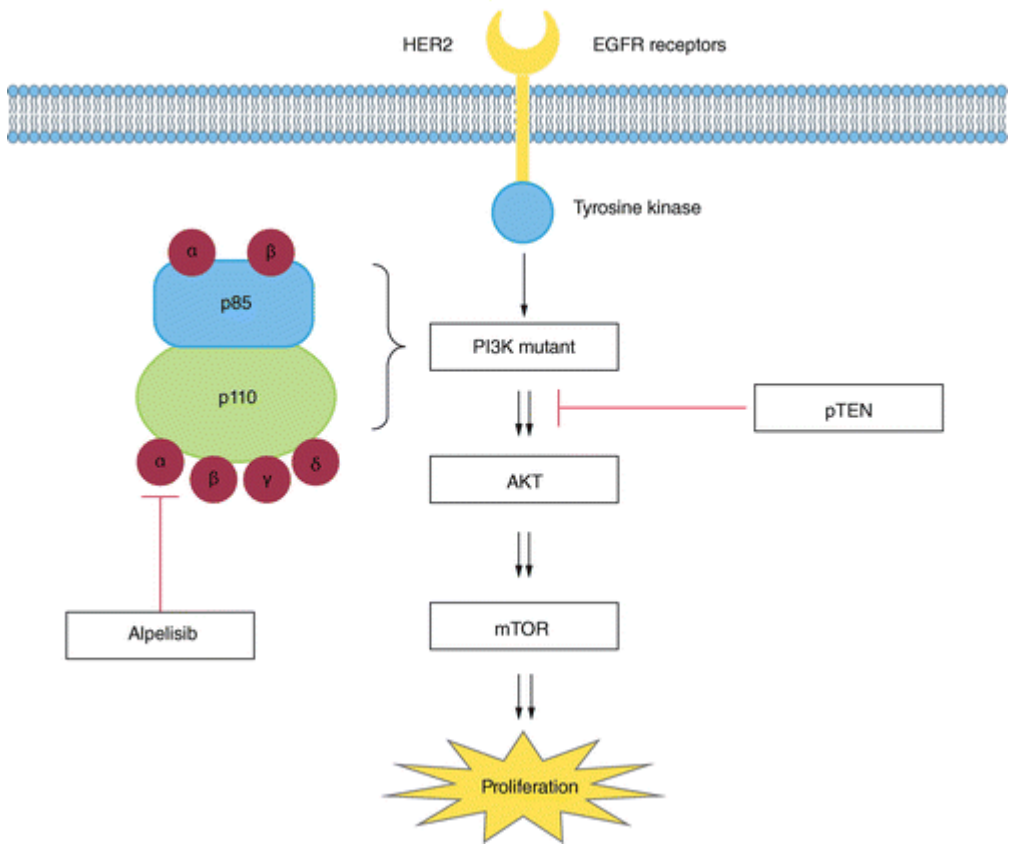




(André et al. 2019)

Alpelisib Mechanism of Action

- Alpelisib is a targeted therapy known as a PI3K inhibitor.
- It selectively inhibits the alpha isoform of the PI3K enzyme, which is encoded by the PIK3CA gene.
- By blocking PI3K, alpelisib helps restore normal regulation of the PI3K signaling pathway.



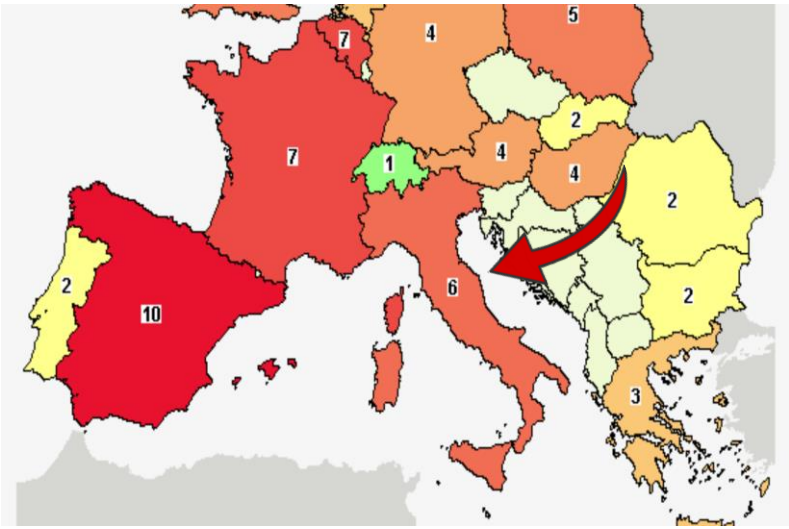
(Pérez-Fidalgo et al. 2022)

Future Treatment Options

- NCCN recommends alpelisib and fulvestrant combination.

If not effective?

- Not eligible for Israeli clinical trials.
- Promising Italian clinical trial matches.



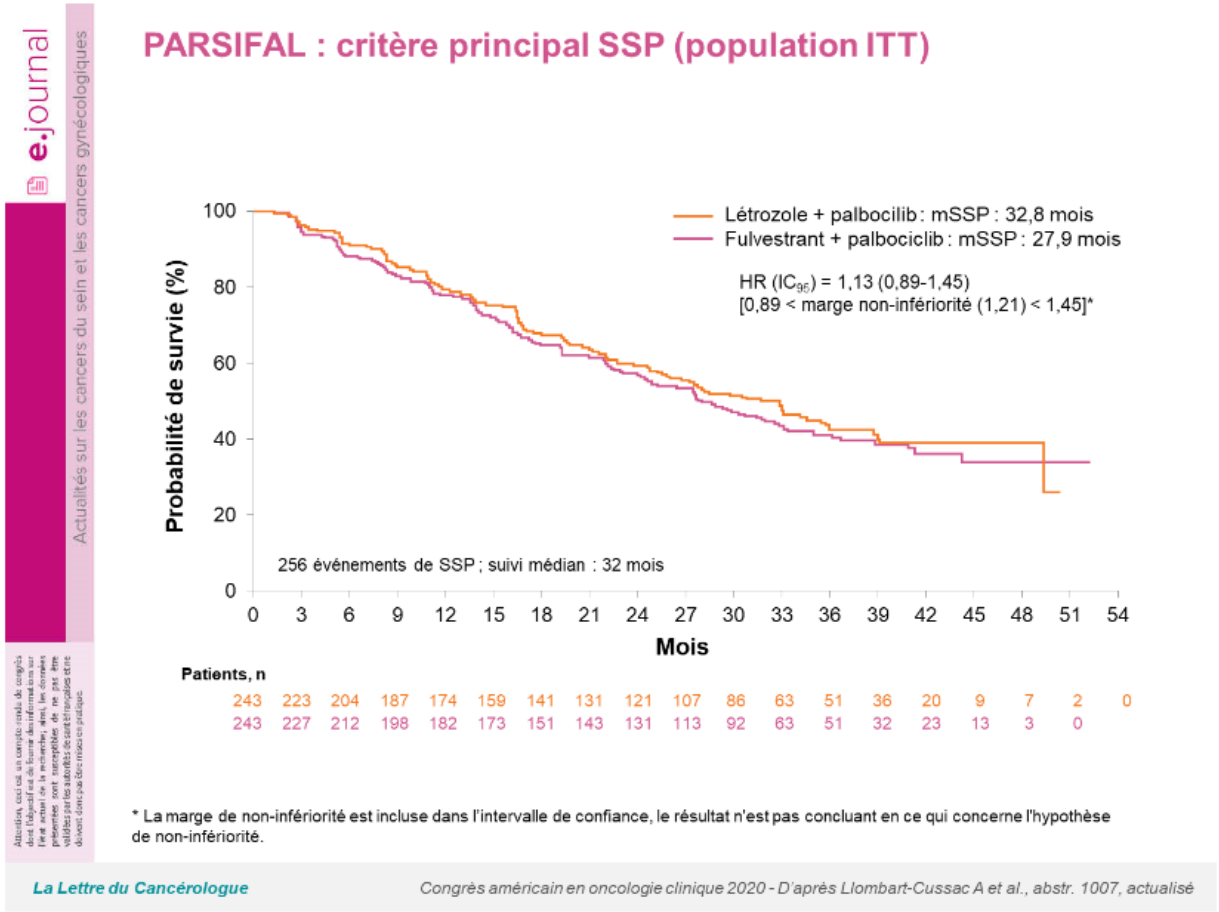
Row	Saved	Status	Study Title	Conditions	Interventions	NCT Number	Locations
4	☐	Recruiting	A NIS of Alpelisib in Combination With Fulvestrant in Postmenopausal Women, and Men, With HR+,HER2-, Locally Advanced or Metastatic **Breast Cancer** With a **PIK3CA** Mutation, After Disease Progression Following Endocrine Therapy as Monotherapy, in the Real-world Setting	• Hormone Receptor Positive HER2 Negative **Breast Cancer** With a **PIK3CA** Mutation	• Other: Alpelisib • Other: Fulvestrant	NCT04967248	• Novartis Investigative Site Vienna, Austria • Novartis Investigative Site Verduno, Chieti, Italy • Novartis Investigative Site Cremona, CR, Italy • (and 5 more...)

Questions?

I have a question for me…

What is the difference between letrozole and fulvestrant?

Fulvestrant vs. Letrozole on Equal Ground as First-Line Treatment in Combination with CDK4/6 Inhibitor



(PARSIFAL : fulvestrant-ou létrozole à égalité en première ligne en association avec un anti-CDK4 /6 CHICAGO 2020 - E-journal | Edimark.fr n.d.)

Quebec Breast Cancer Foundation

Thank You

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