Selection and Sequencing of Therapy for Patients with ER-Positive MBC

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CDK4/6 inhibitors

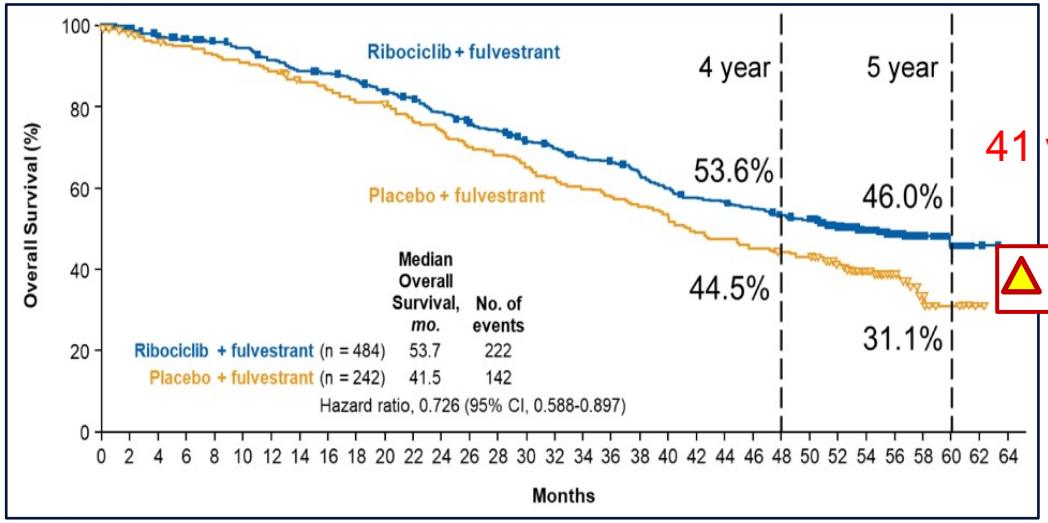
Long term follow up data

Activity in CNS

Mechanisms of resistance

Survival benefit with CDK4/6i in ET resistant MBC

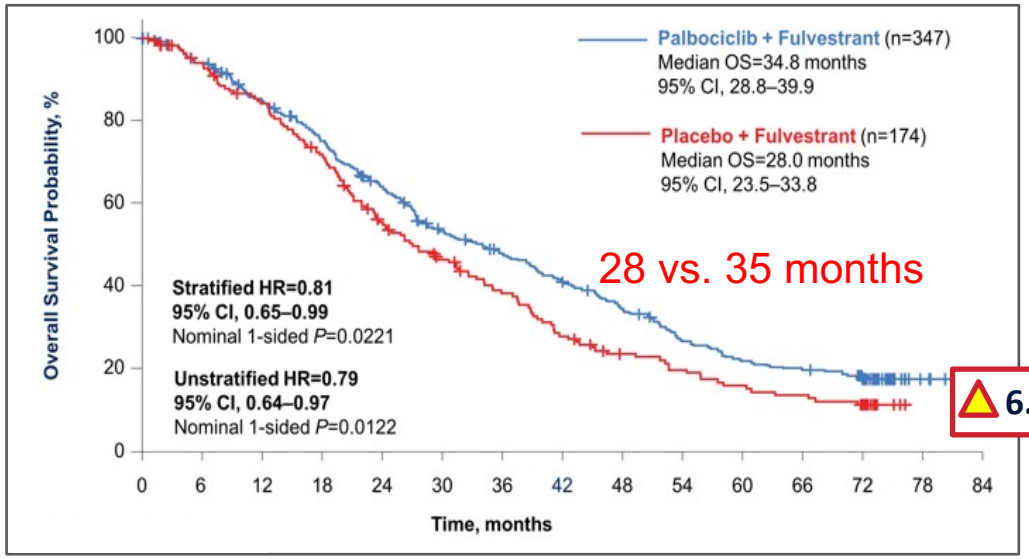
MONALEESA-3: Fulvestrant + Ribociclib/placebo



41 vs. 54 months

12.2 mo

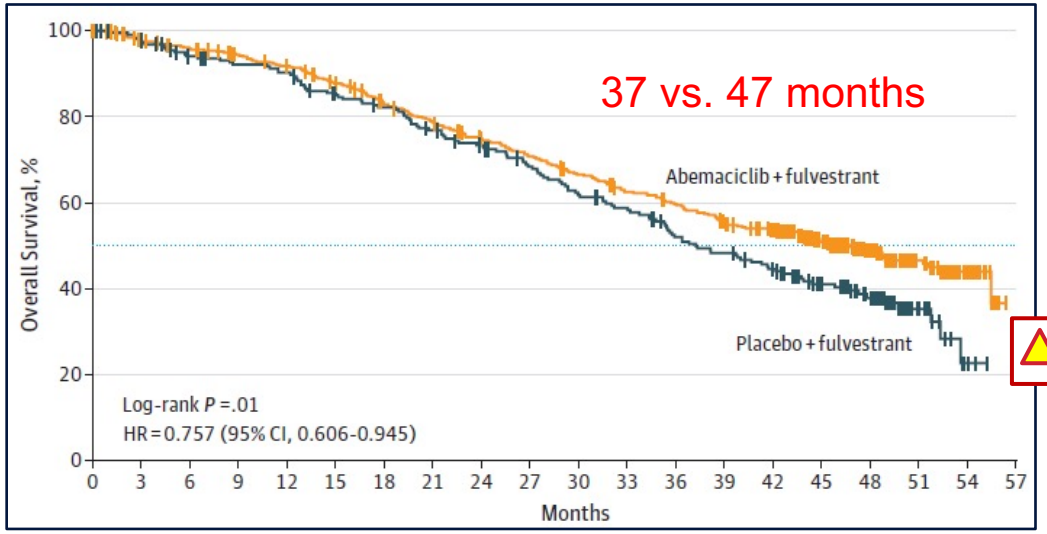
PALOMA-3: Fulvestrant + Palbociclib/placebo



28 vs. 35 months

6.8 mo

MONARCH-2: Fulvestrant + Abemaciclib/placebo



37 vs. 47 months

9.4 mo

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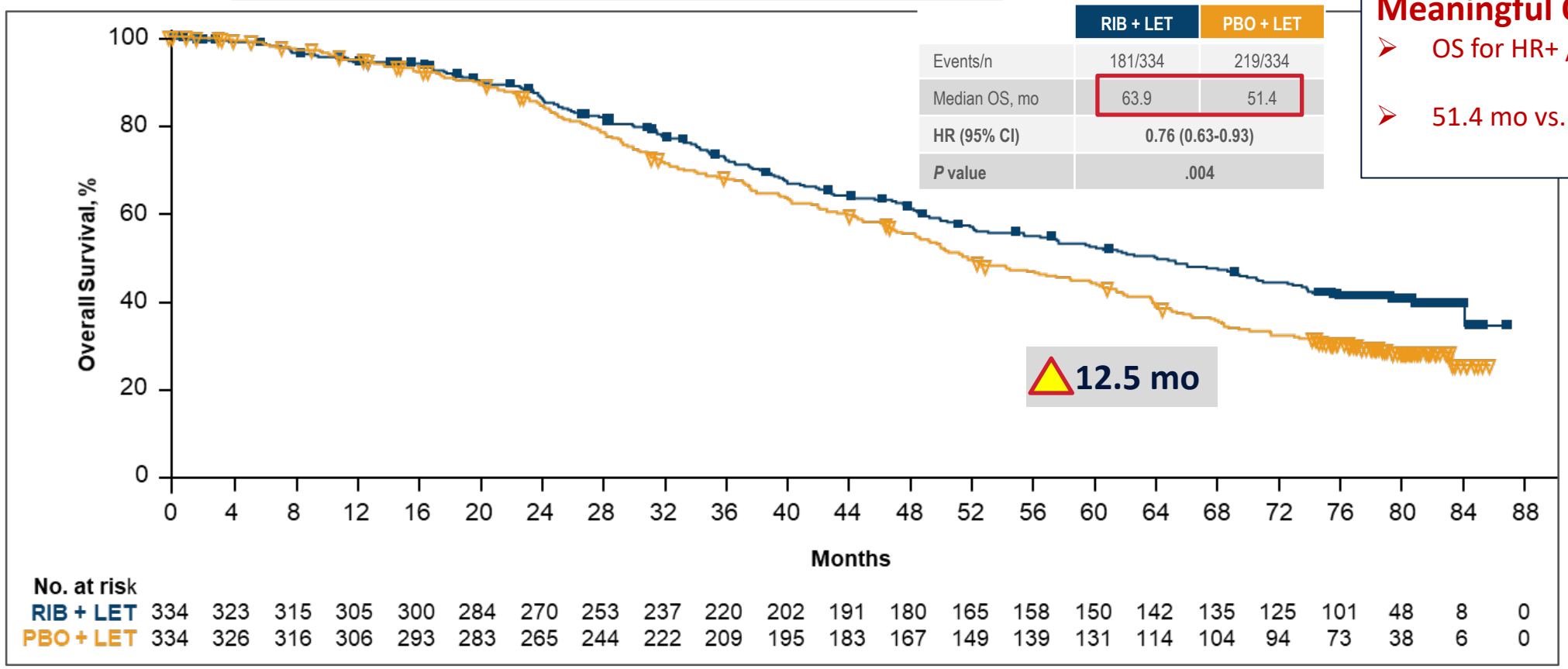
Cristofanilli M. et al ASCO 2021; Slamon DJ et al ASCO 2021; Sledge GW et al. 2019

MONALEESA-2: Ribociclib + ET in 1L ER+/HER2- MBC

Overall Survival after median follow up of 80 months



Meaningful OS benefit

- OS for HR+ /HER2- MBC is now > 5 years
- 51.4 mo vs. 63.9 mo w/ CDK

Consistent survival benefit across subgroups

- Visceral disease
- >65 years of age
- Prior chemo
- Prior endocrine
- Bone only disease
- De novo

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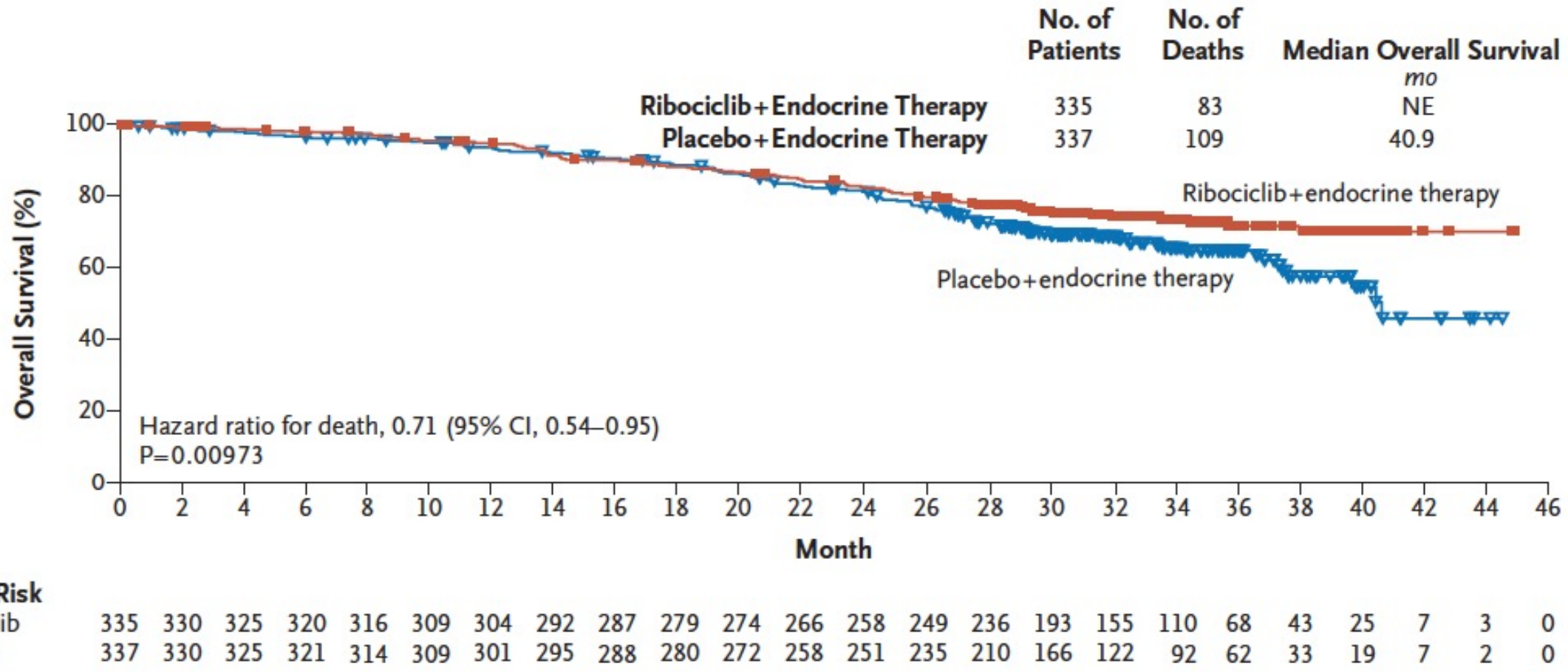
Hortobagyi GN et al ESMO 2021

MONALEESA-7: Ribociclib + ET for First-Line ER-Positive, HER2-Negative MBC



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Im SA et al. *N Engl J Med* 2019;381(4):307-16.

CDK 4/6i and breast cancer brain mets

- Although HR+ is the most common BC subtype, incidence of brain mets is the lowest in this subtype, ~14%

- Do CDK4/6i have activity within the brain?
  - Abemaciclib[1] and Ribociclib[2] do cross the BBB
  - Phase 2 trial of abemaciclib monotherapy in HR+ brain mets[3]
    - Plasma & CSF concentrations were comparable
    - Intracranial ORR = 5.2% (3/58 pts)
    - Intracranial CBR = 25%
    - Median Intracranial PFS = 4.9 months

- Area of unmet need that needs more effective options

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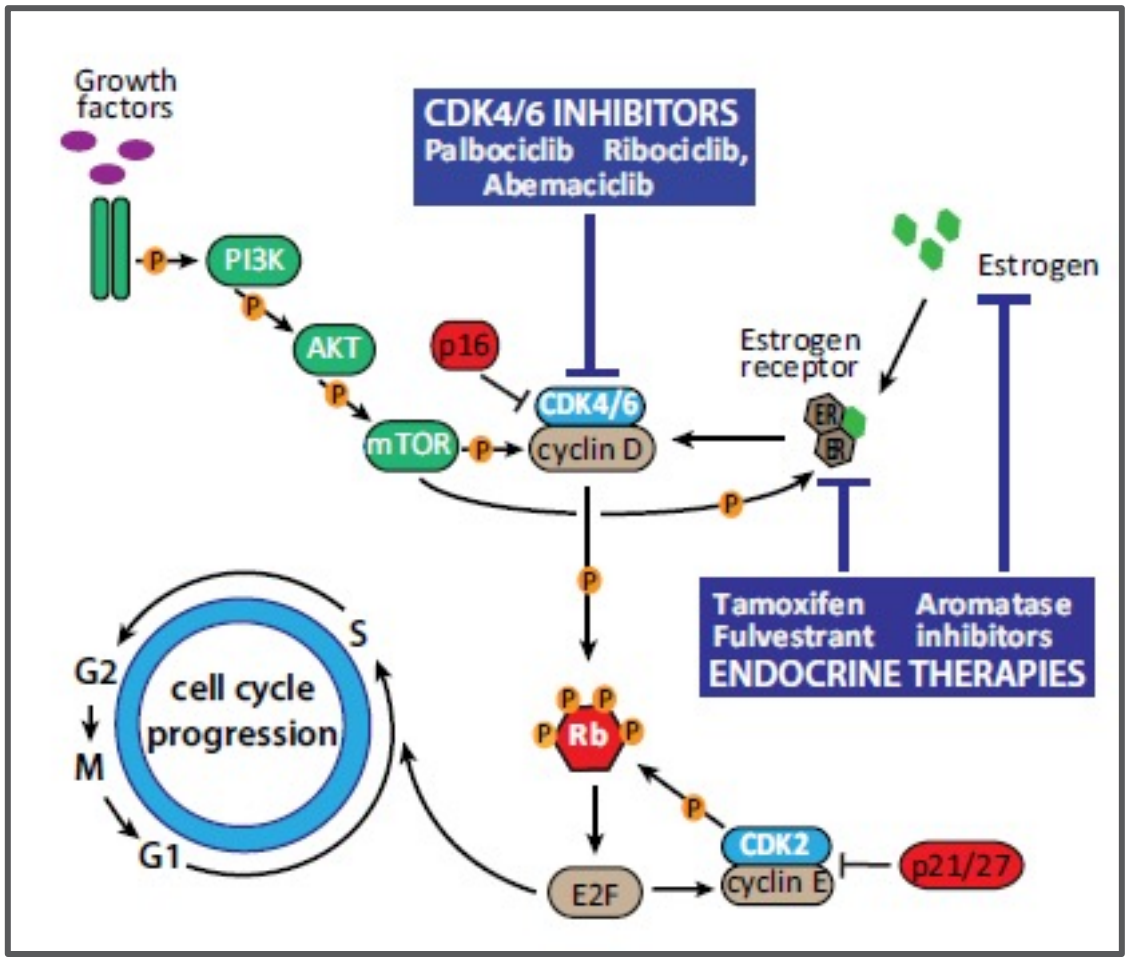
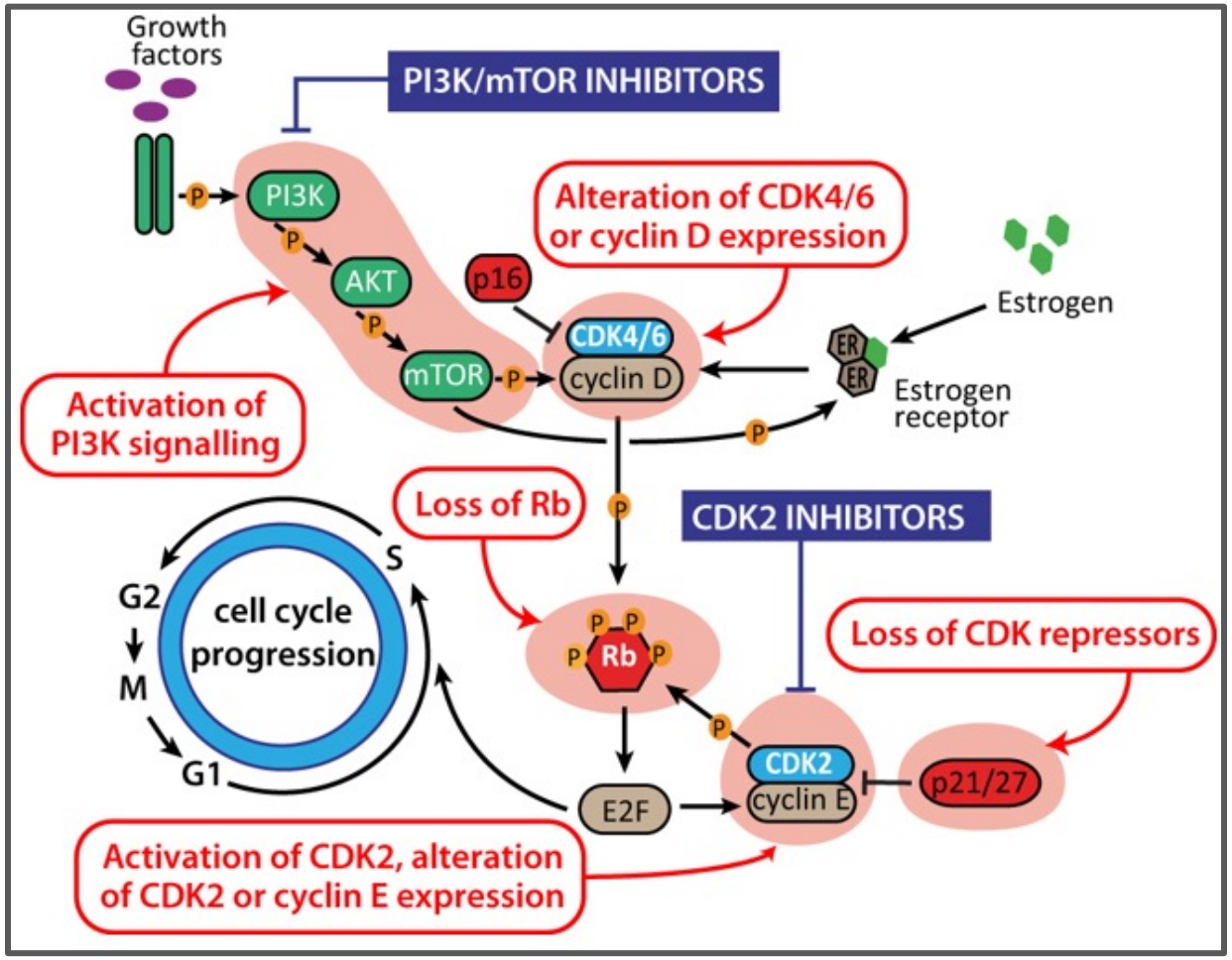
1. Schlam I. & Tolaney S. Oncotarget 2021 2. Tien A-C. et al. Clin Cancer Res 2019
3. Tolaney S. et al. Clin Cancer Res 2021

Proposed mechanisms of resistance to CDK 4/6i

Regulation of cell cycle in ER+ BC and key nodes targeted by current therapies



Key mechanisms implicated in development of resistance to CDK 4/6 inhibitors



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Figures from: N. Portman et al. *Endocrine-Related Cancer,* 2019

Mechanisms of resistance to CDK 4/6i

- Thus far, the only predictive biomarker for response to CDK4/6i is ER expression

- Mechanisms of resistance to CDK 4/6i include:
  - Alteration in components of the cell-cycle machinery
  - Aberrations in PI3K/Akt/mTOR or RTK pathways
  - FGFR signaling alterations
  - Synthetic lethality between RB1 mutations and Aurora kinase A and B inhibition[1]

- RB1 LOF alterations[2] and FAT1 truncating mutations/deep deletion[3] are the only biomarkers accepted to predict resistance to CDK4/6

RTK- receptor tyrosine kinase
LOF- loss of function
PD- pharmacodynamic

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1. Gong X et al. 2019 2. Bertucci F et al. 2019 3. Li Z et al. 2018

PIK3CA mutations in HR+/HER2- MBC

Frequency and Prognosis

Trials with alpha-specific PI3K inhibitors

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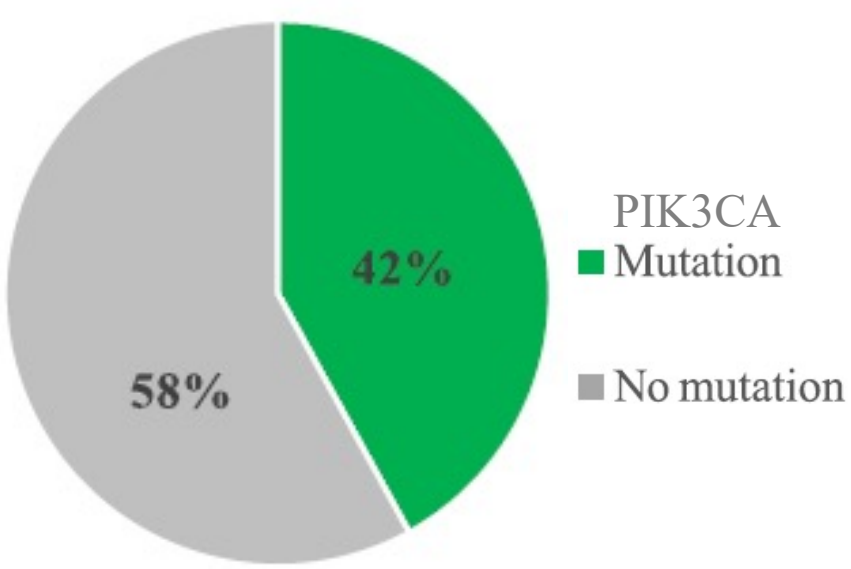
Frequency & prognostic effects of PIK3CA mutations in HR+/HER2- MBC

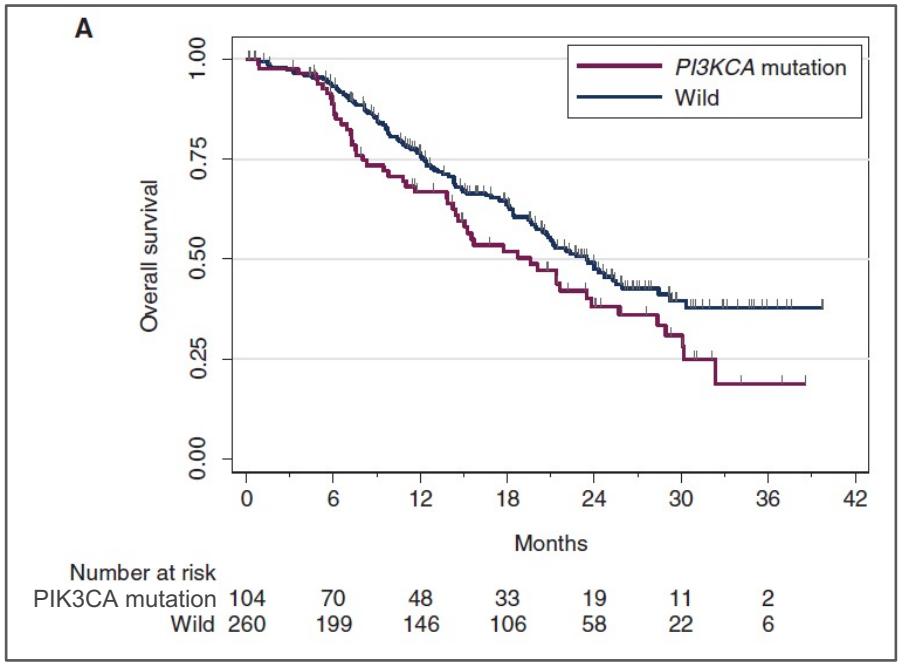
- Mutations in the PI3K pathway are very common in breast cancer, especially in HR+/HER2- MBC

Frequency of PIK3CA mutations in HR+/HER2- BC*[1]



*Combined dataset of 6338 invasive BC tı
includes METABRIC, MSKCC & TCGA datasets

SAFIR02: Overall survival in the HR+/HER2- MBC subset[2]



- ✓ Poor survival prognosis in HR+ MBC for PIK3CAm tumors (mOS19.6 mo vs 23.6 mo in WT)
- ✓ These tumors are also less responsive to chemotherapy

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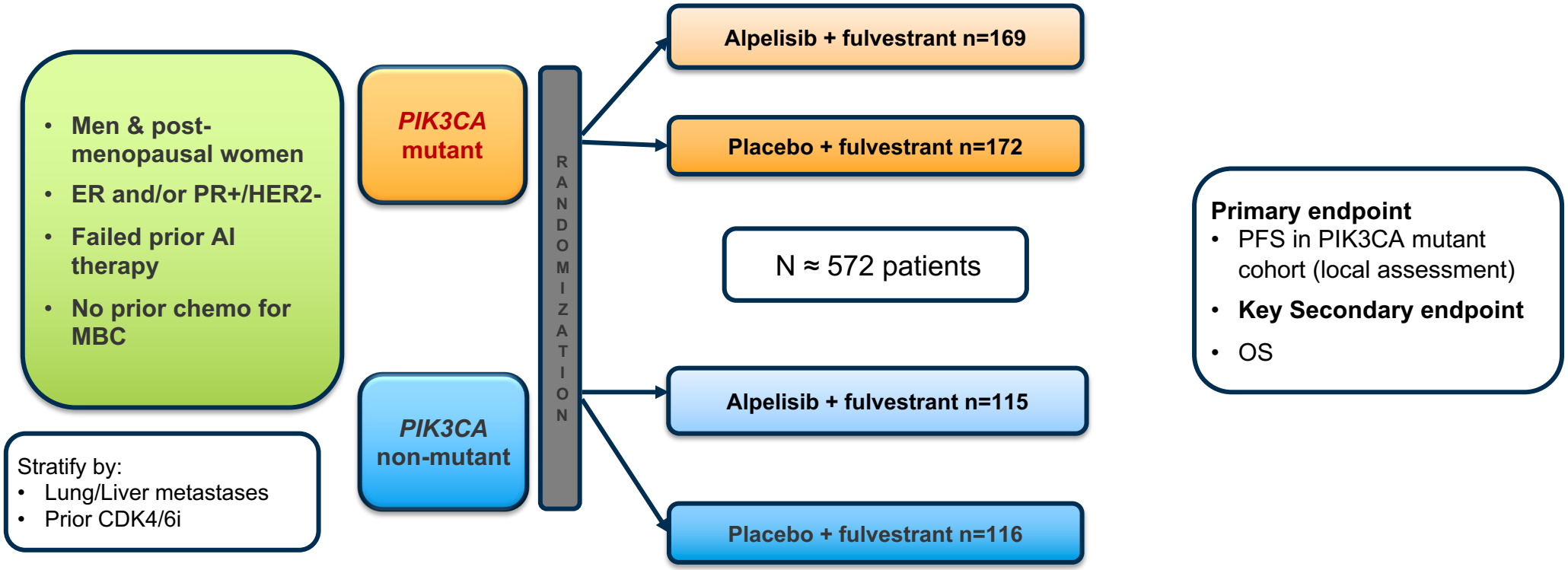
1. Martinez-Saez O et al. Breast Cancer Research 2020 2. Mosele F et al. Annals Oncology 2019

SOLAR-1: ET + Alpelisib In HR+ HER2- MBC

- PI3K: 4 isoforms; PIK3CA encodes α-isoform
- Targeting the PI3K α-isoform may decrease toxicity compared with pan-PI3K
- Alpelisib in an α-specific PI3K inhibitor



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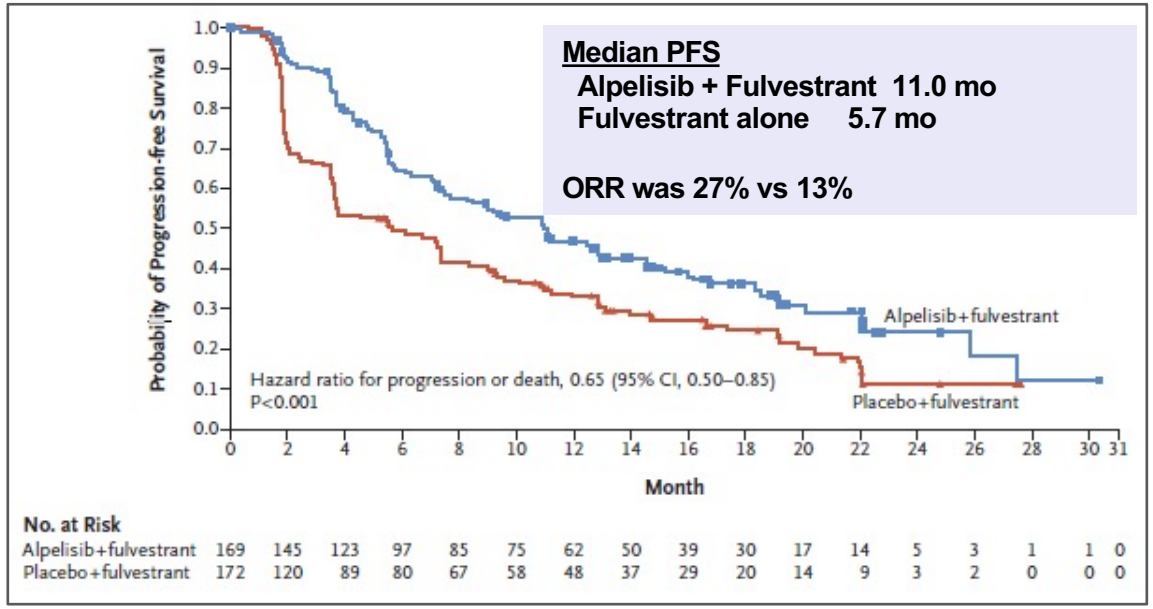
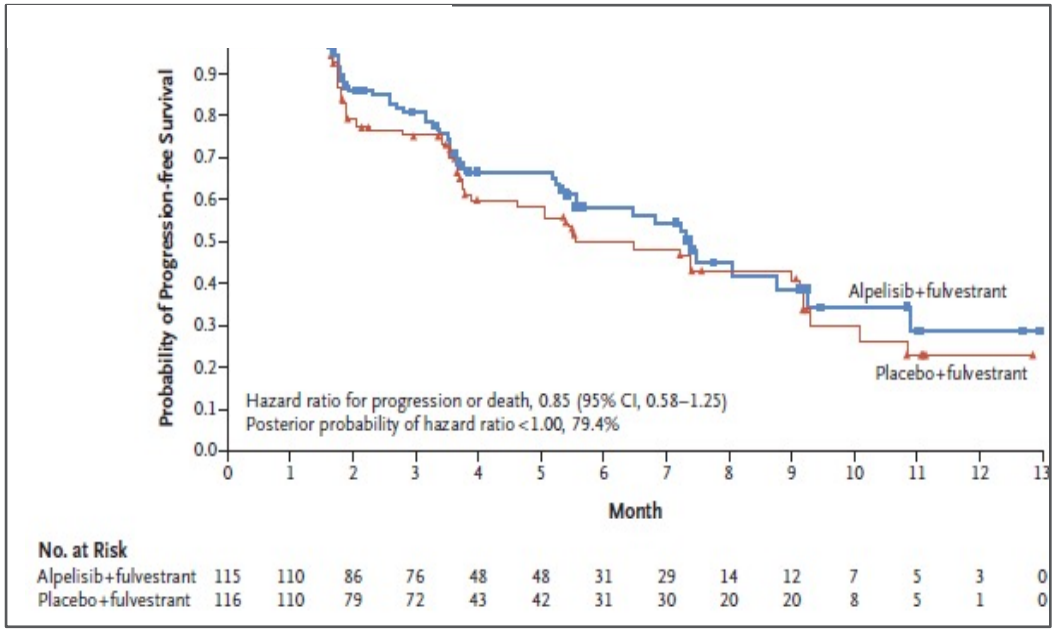
Andre F et al. NEJM 2019

SOLAR-1: Progression-free survival

Cohort with PIK3CA mutant tumors



Cohort without PIK3CA mutant tumors



On May 24, 2019, FDA approved alpelisib + fulvestrant for PIK3CA HR+/HER2- mutated MBC following progression on prior ET.

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Andre F et al. NEJM 2019

BYLieve: Alpelisib+ET in PIK3CA mutated HR+ MBC post CDK 4/6i

Goal: In the post-CDKi setting, assess the efficacy and safety of alpelisib + ET (fulvestrant or letrozole) in patients with *PIK3CA*-mutated HR+, HER2– ABC

- **Pts with HR+/HER2- MBC with a PIK3CA mutation**
- **Last prior line of tx: CDK 4/6i + ET for A and B**

Patients who received CDKi + AI as immediate prior treatment (N=112)[b]
(Cohort A)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Patients who received CDKi + fulvestrant as immediate prior treatment (N=112)
(Cohort B)
Alpelisib 300 mg oral QD + letrozole 2.5 mg[d]

Patients who progressed on/after AI and received chemotherapy or ET as immediate prior treatment (N=112)
(Cohort C)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Treatment crossover between cohorts is not permitted

Primary endpoint
- Proportion of patients alive without PD at 6 months (RECIST v1.1) in each cohort
- **Secondary endpoints include**

(assessed in each cohort)
- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

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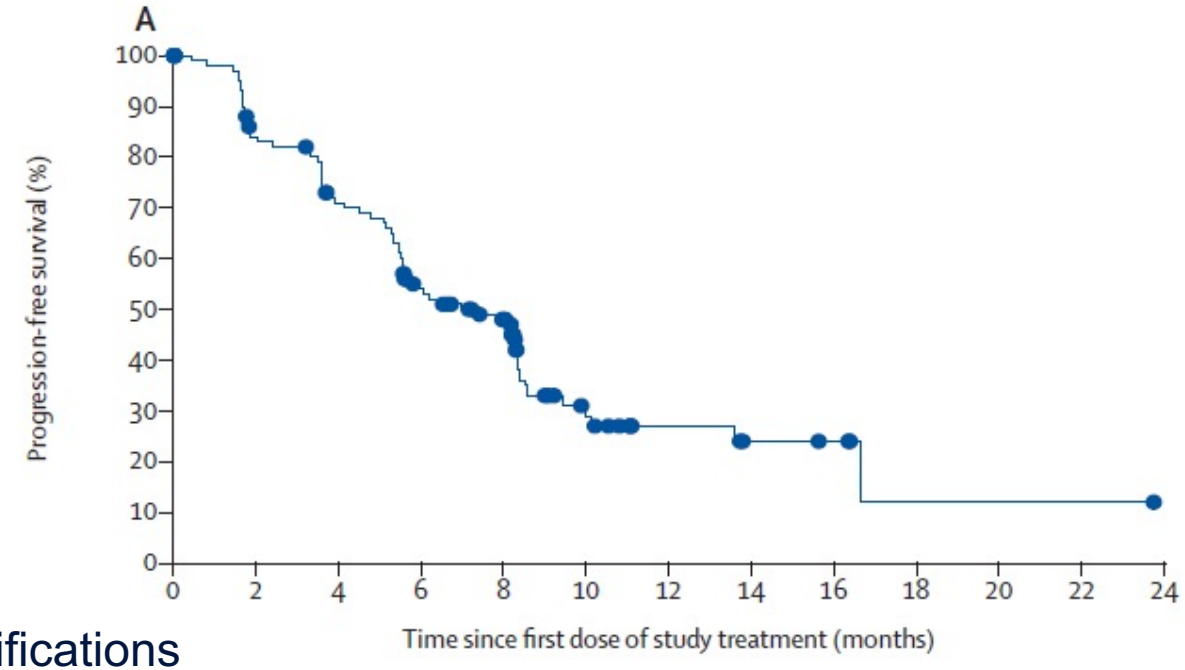
Rugo HS et al. ASCO 2020

BYLieve: Alpelisib+ET in PIK3CA mutated HR+ MBC post CDK 4/6i

Endpoint	BYLieve (Cohort A) n=121	SOLAR 1 (CDK 4/6i pre tx pts) n=20
Primary Endpoint: Patients who were alive without PD	**54%**	**44.4%**
Secondary Endpoints		
Median PFS	**7.3 months**	**5.5 months**
Median OS	**17.3 months**	**NR**
Median DOR	**6.6 months**	**NR**

BYLieve: PIK3CA mutant & post CDKi
Median PFS: 7.3 months



Adverse events

- Hyperglycemia ≥G3 in 25% of pts leading to dose modifications
- Rash ≥G3 in 8% of pts leading to dose modifications

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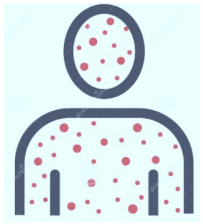
Rugo HS et al. Lancet Oncol 2021

SOLAR-1: Most common side effects with alpelisib

	Adverse event (AE)	% of patients with AE
	**Hyperglycemia**	**32.7% (G3); 3.9% (G4)**
	**Diarrhea**	**6.7% (G3)**
	**Rash**	**9.9% (G3)**

Hyperglycemia and rash occurred early during alpelisib treatment, while diarrhea occurred at a later time point.

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Rugo HS et al. Ann Oncol 2020

Monitoring Hyperglycemia: Recommended schedule

Hyperglycemia appears with a median time to onset of 15 days from starting alpelisib

Monitoring to check for hyperglycemia

FPG*
(Fasting Plasma Glucose)
Measures glucose levels.

- 1X once before starting Alpelisib
- 1X at least once a week for the first 2 weeks of taking Alpelisib
- 1X after the first 2 weeks, at least once every 4 weeks while taking Alpelisib and as your doctor feels is necessary

HbA1c
(Hemoglobin A1c)
Measures glycosylated hemoglobin levels.

- 1X once before starting Alpelisib
- 1X once every 3 months while taking Alpelisib and as your doctor feels is necessary

Monitoring if you develop hyperglycemia

Fasting glucose
(FPG or fasting blood glucose)
Measures glucose levels.

- 2X as your doctor feels is necessary and at least twice a week until levels return to normal

While taking anti-hyperglycemia medication

- 1X at least once a week for 8 weeks
- 1X after 8 weeks, once every two weeks and as your doctor feels is necessary

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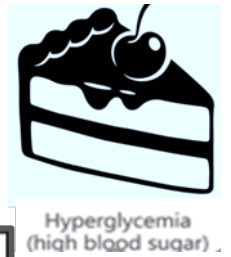
Management of Hyperglycemia



Grade	Criteria	Recommendation for alpelisib dosing	Recommendation for management
Hyperglycemia			
1	FPG > ULN to 160 mg/dl or FPG > ULN to 8.9 mmol/l	• No alpelisib dose adjustment required	• If FPG is <140 mg/dl, consider metformin • If FPG is 140–160 mg/dl, start or intensify metformin
2	FPG >160 to 250 mg/dl or FPG >8.9 to 13.9 mmol/l	• No alpelisib dose adjustment required • If FPG does not resolve to grade ≤1 within 21 days after antidiabetic treatment, reduce alpelisib by one dose level[a]	• Start oral antidiabetic treatment (e.g. metformin) • If FPG keeps rising beyond MTD of metformin, add an insulin sensitizer (e.g. pioglitazone)
3	FPG >250 to 500 mg/dl or FPG >13.9 to 27.8 mmol/l	• Discontinue alpelisib • If FPG resolves to grade ≤1 within 3 to 5 days while off alpelisib and on metformin, restart alpelisib and reduce by one dose level[a] • If FPG does not resolve to grade ≤1 within 21 days after antidiabetic treatment, permanently discontinue alpelisib	• Consider consultation with endocrinologist • Start metformin and add pioglitazone • Insulin may be used as rescue medication for 1 to 2 days
4	FPG >500 mg/dl or FPG ≥27.8 mmol/l	• Discontinue alpelisib for 24 H, then: – If grade ≤3, follow specific grade recommendations – If grade 4 persists (with no confounding factors), permanently discontinue alpelisib	• Consult with endocrinologist • See grade 3 recommendations; recheck in 24 H

AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
ADL, activities of daily living; AE, adverse event; AESI, adverse event of special interest; FPG, fasting plasma glucose; MTD, maximum tolerated dose; ULN, upper limit of normal.

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Rugo HS et al. Ann Oncol 2020

Management of Diarrhea

Grade	Criteria	Recommendation for alpelisib dosing	Recommendation for management
Diarrhea			
1	Increase of fewer than four stools per day over baseline; mild increase in ostomy output compared with baseline	• No alpelisib dose adjustment required	• Initiate appropriate medical therapy and monitor as clinically indicated • Medically manage patients according to local practice guidelines for diarrhea[a]
2	Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline; limiting instrumental ADL	• Interrupt alpelisib dose until grade ≤1 and resume at lower dose level[a] • Only one dose reduction is permitted; if toxicity reoccurs, permanently discontinue alpelisib treatment	
3	Increase of seven or more stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care ADL		
4	Life-threatening consequences; urgent intervention indicated		

[a] Management generally consists of hydration and loperamide. Further interventions may be required for higher-grade diarrhea, persistent low-grade diarrhea, or diarrhea with complications such as fever, sepsis, neutropenia, bleeding, or dehydration.

AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
ADL, activities of daily living; AE, adverse event; AESI, adverse event of special interest; FPG, fasting plasma glucose; MTD, maximum tolerated dose; ULN, upper limit of normal.

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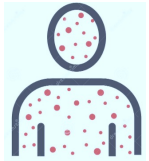
Rugo HS et al. Ann Oncol 2020

Monitoring & Management of Rash



- Rash can appear within 2 weeks of taking Alpelisib
- Prophylactic antihistamines may be prescribed to decrease the chances and severity of rash
- If rash occurs, it can be managed by use of
  - ✓ topical corticosteroids
  - ✓ oral antihistamines
  - ✓ systemic corticosteroids

SOLAR-1	Preventive anti-rash medication	
	✓	X
Incidence of rash (any grade)	26.7%	64.1%
Severity of rash (grade 3)	11.6%	22.1%

Grade	Criteria	Recommendation for alpelisib dosing	Recommendation for management
Rash			
1	<10% body surface area with active skin toxicity	• No alpelisib dose adjustment required	• Initiate topical corticosteroid treatment • Consider adding oral antihistamine to manage symptoms
2	10%–30% body surface area with active skin toxicity		
3	>30% body surface area with active skin toxicity	• Interrupt alpelisib • Once grade ≤1, resume alpelisib at the same dose level for first occurrence of rash or at lower dose level[b] in case of second occurrence	• Initiate or intensify topical corticosteroid and oral antihistamine treatment • Consider low-dose systemic corticosteroid treatment
4	Any % body surface area associated with extensive superinfection, with i.v. antibiotics indicated	• Permanently discontinue alpelisib	• Treat as medically indicated

[b] Starting dose: 300 mg/day continuously. Dose level −1: 250 mg/day continuously. Dose level −2: 200 mg/day continuously.

AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
ADL, activities of daily living; AE, adverse event; AESI, adverse event of special interest; FPG, fasting plasma glucose; MTD, maximum tolerated dose; ULN, upper limit of normal.

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Rugo HS et al. Ann Oncol 2020

What's Coming

Oral SERD, SERCA, CERAN, PROTACs

PI3 mutant selective inhibitors

Novel CDKs

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Thank You

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