Current and Future Management of ER-Positive mBC After Disease Progression on CDK4/6 Inhibition

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Disclosure

No relevant conflicts of interest to disclose.

Case Presentation: Dr Sparano

43 year old female stage IV breast cancer with liver and bone mets in July 2017, ER/PR+, HER2-, relapsed on adjuvant OFS + AI.

- Progressive disease on fulvestrant/ribociclib, capecitabine, carboplatin/gemcitabine, fulvestrant/alisertib (Aurora kinase inhibitor) on clinical trial.
- Previously found to have PIK3CA E545K mutation with allele frequency 1.6% in May 2017, same mutation in tumor from liver biopsy and MSS, intermediate TMB (10 mutations/MB) in October 2017.

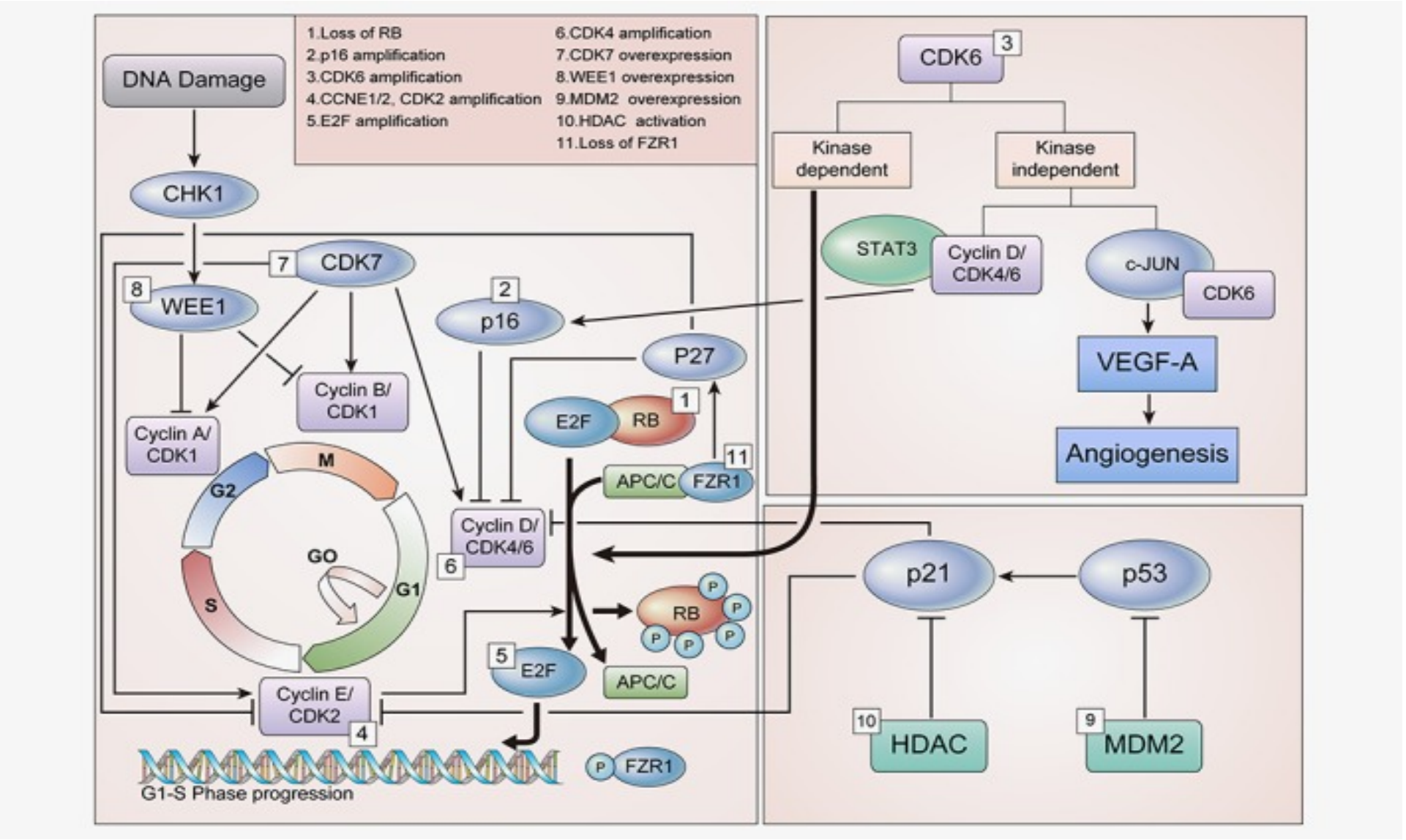
Case Presentation: Dr Goetz (continued)

Patient receives radiation therapy followed by oophorectomy and letrozole. Near the completion of the 5-year course of letrozole and at the age of 46 (2017), the patient developed abdominal pain and imaging demonstrated multiple hypodense liver lesions. A bone scan, in addition to the liver lesions, revealed an area of uptake in the right ilium as well as the left femoral head.

A biopsy of liver lesion revealed moderately differentiated adenocarcinoma, estrogen receptor-positive, PR-negative, HER2- negative.

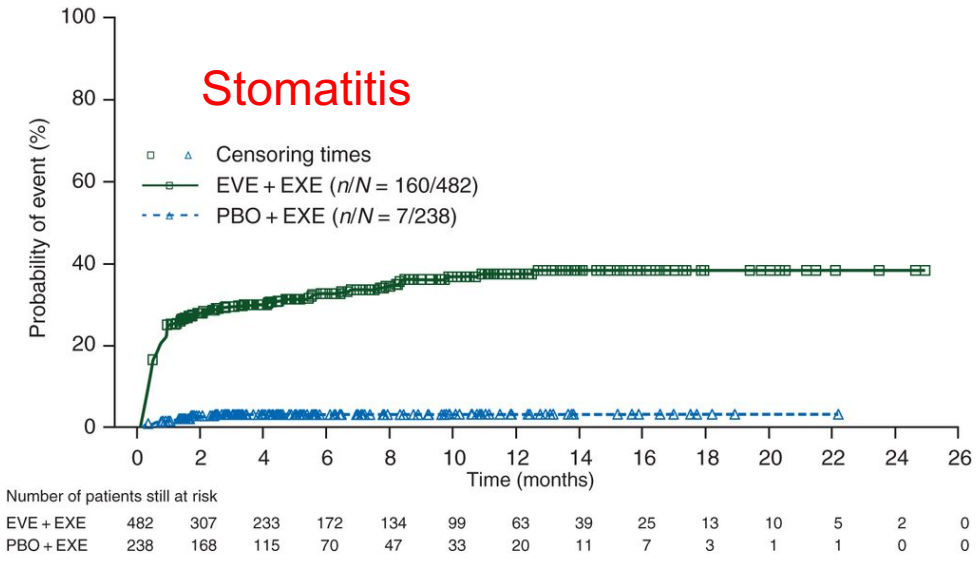
After 2 years, she exhibited progression in the liver. A liver biopsy was negative for a PIK3CA mutation.

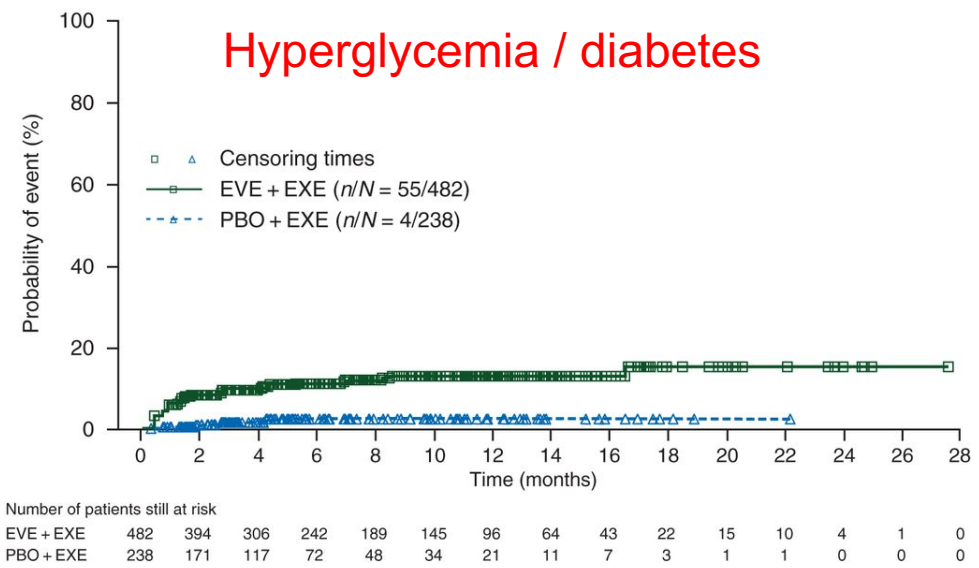
Mechanisms of Resistance to CDK4/6 Inhibitors

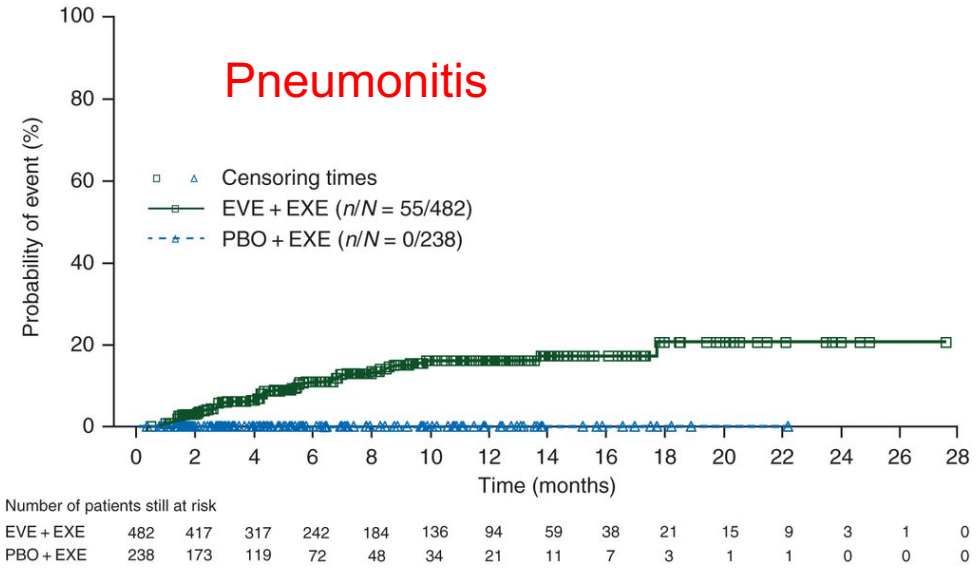


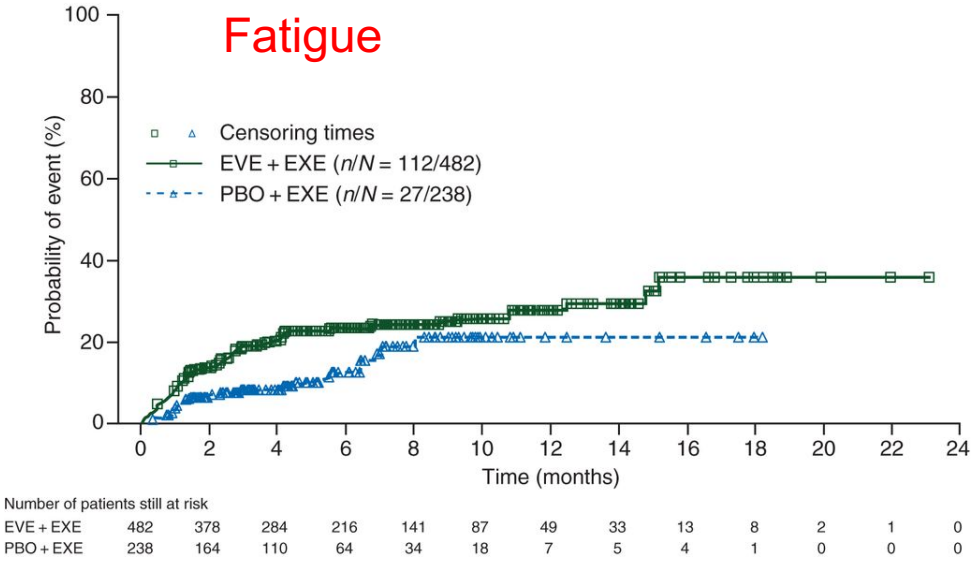
Pandey K, et al.
Int J Cancer 2019;145:1179

BOLERO-2. Cumulative risks for grade ≥ 2 adverse events



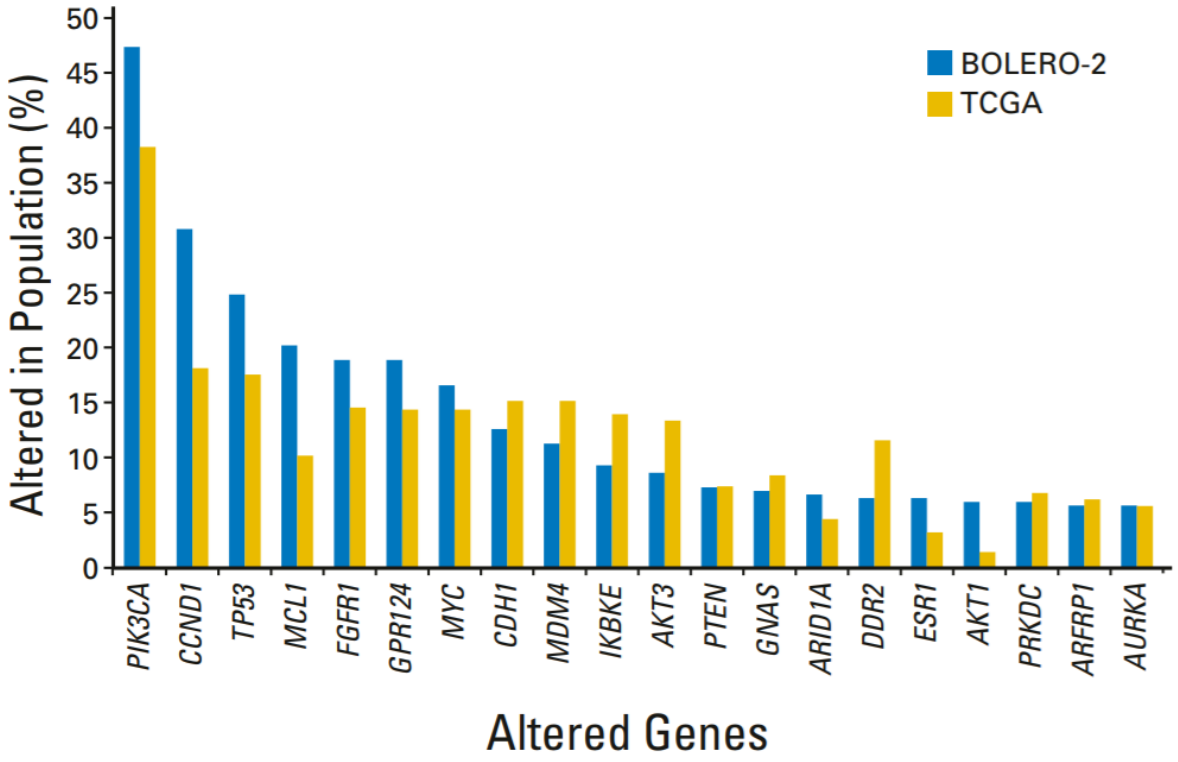


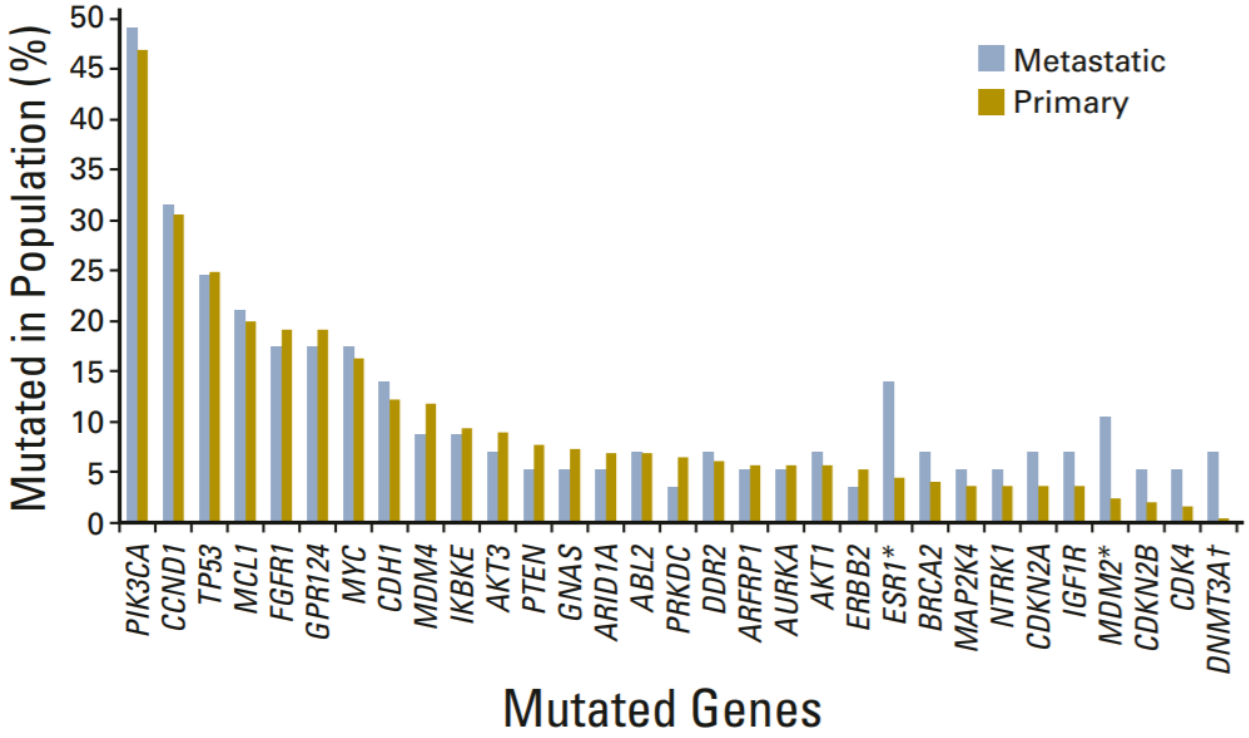




Rugo H S et al. Ann Oncol 2014;annonc.mdu009

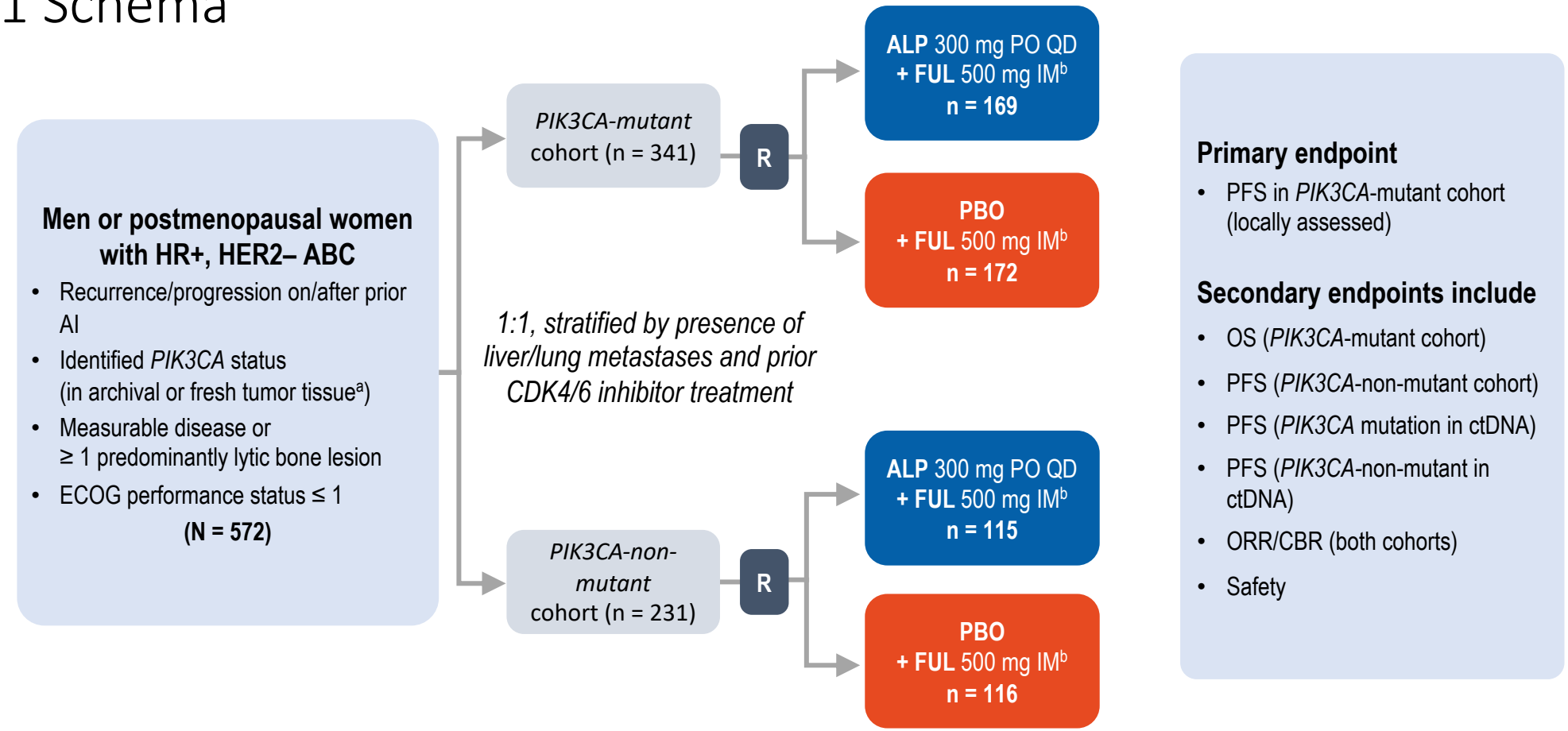
Frequency of PIK3CA mutations in ER+, HER2- breast cancers





Hortobagyi, JCO, 2016

SOLAR-1 Schema



- The primary endpoint included all randomized patients in the *PIK3CA*-mutant cohort; PFS was analyzed in the *PIK3CA*-non-mutant cohort as a proof of concept
- Safety was analyzed for all patients who received ≥ 1 dose of study treatment, in both cohorts

ABC, advanced breast cancer; AI, aromatase inhibitor; ALP, alpelisib; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; FUL, fulvestrant; HER2–, human epidermal growth factor receptor-2–negative; IM, intramuscular; ORR, overall response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, oral; QD, once daily; R, randomization.

[a] More than 90% of patients had mutational status identified from archival tissue.

[b] Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.

1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

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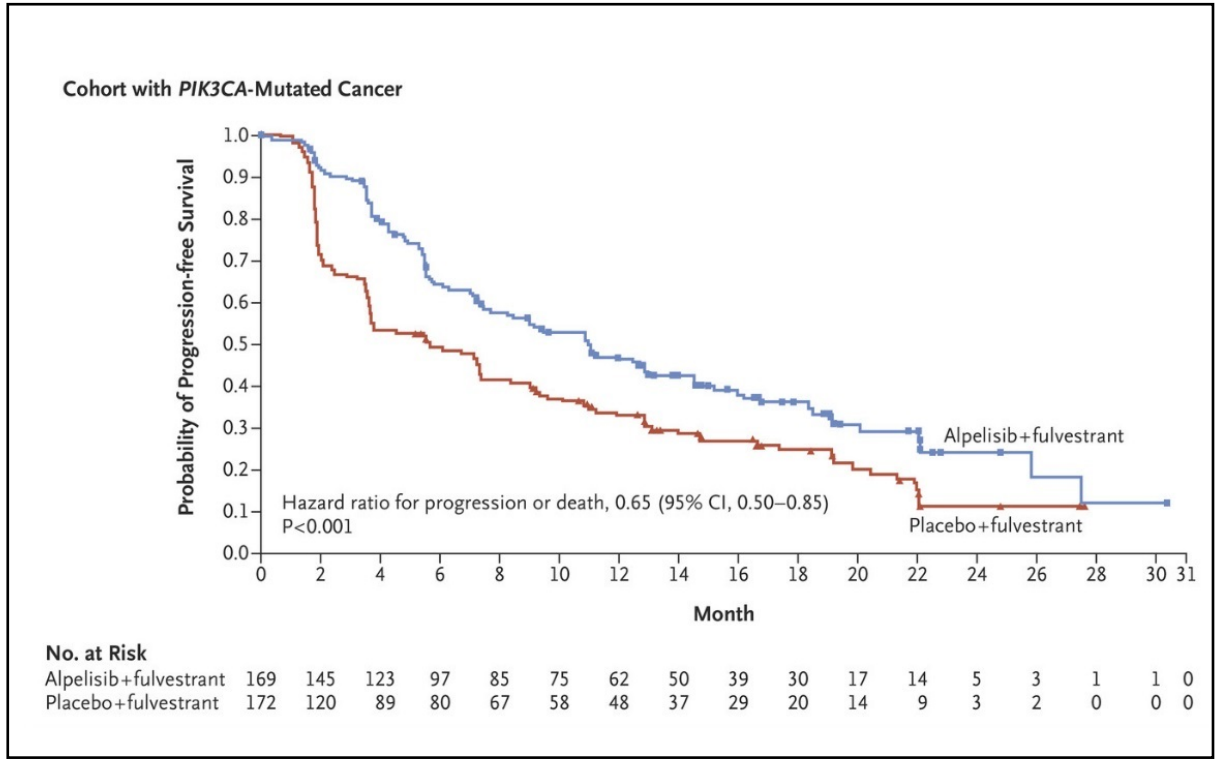
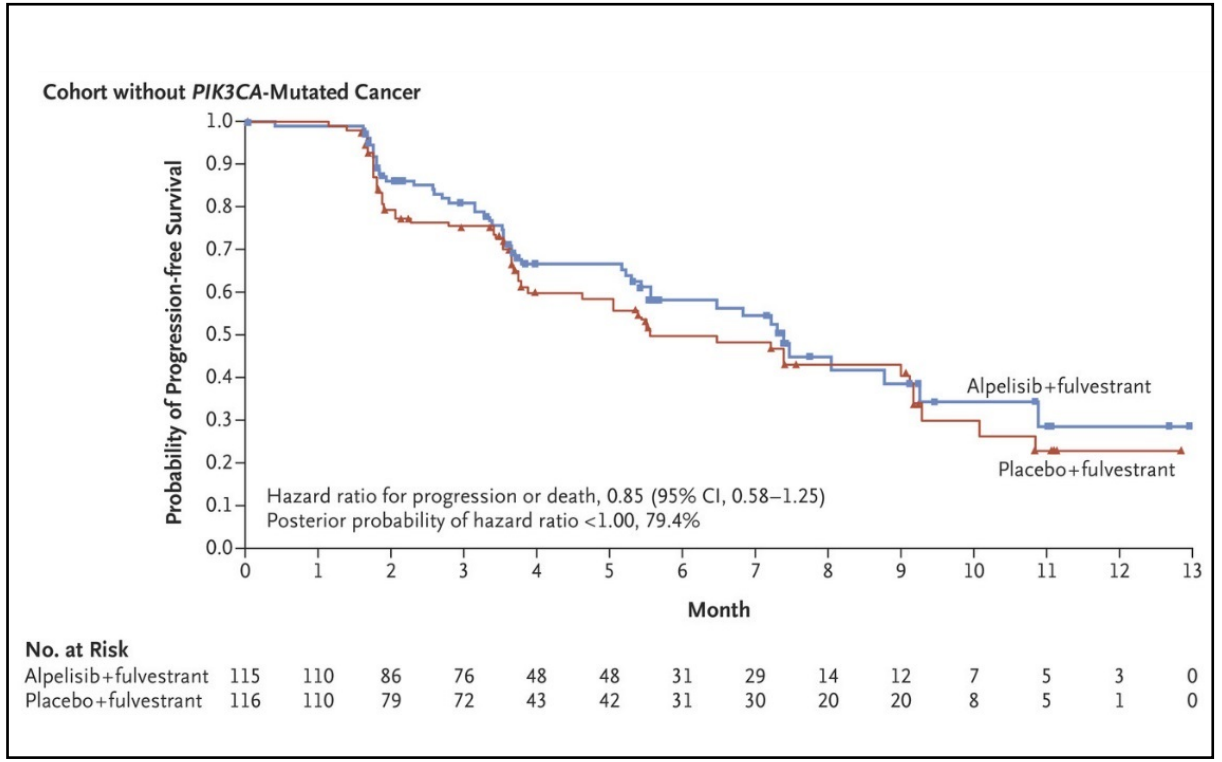
SOLAR-1: Progression-Free Survival Outcomes





F André et al. N Engl J Med 2019;380:1929-1940.

Alpelisib: Toxicity Management

Most Frequent Adverse Events, According to Single Preferred Term and Regardless of Relationship to Intervention, in the Overall Patient Population.*

Adverse Event	Alpelisib–Fulvestrant Group (N=284)			Placebo–Fulvestrant Group (N=287)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia†	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea‡	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea‡	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash§	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting‡	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Weight loss	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0
Alopecia	56 (19.7)	0	0	7 (2.4)	0	0
Mucosal inflammation	52 (18.3)	6 (2.1)	0	3 (1.0)	0	0
Pruritus	51 (18.0)	2 (0.7)	0	16 (5.6)	0	0
Headache	50 (17.6)	2 (0.7)	0	38 (13.2)	0	0
Dysgeusia	47 (16.5)	0	0	10 (3.5)	0	0
Arthralgia	32 (11.3)	1 (0.4)	0	47 (16.4)	3 (1.0)	0

F André et al. N Engl J Med 2019;380:1929-40.

Protocol Guidance for Treatment of Hyperglycemia in SOLAR-1

Hyperglycemia	

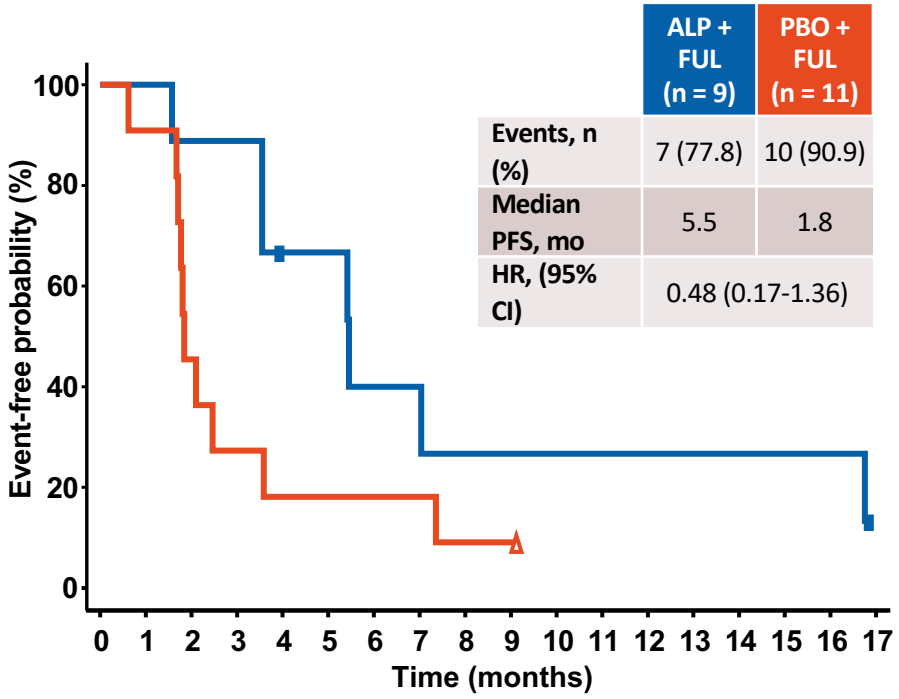
Grade 1	• **Maintain dose level** and remind patient of lifestyle changes.
	  ○ If FPG <140 mg/dL, consider adding metformin*
	  ○ If FPG 140–60 mg/dL, start or intensify metformin*
	• Initiate metformin 500 mg once daily with dinner.
	  ○ If no GI intolerance after several days, increase to 500 mg twice daily with breakfast and dinner
	  ○ If tolerated, 1 g twice daily with breakfast and dinner
	  ○ If not tolerated, reduce to prior tolerated dose
	• Monitor FPG as clinically indicated and at least weekly for 8 weeks, then every 2 weeks until FPG is within baseline values.

Grade 2	• **Maintain dose level** and remind patient of lifestyle changes.
	  ○ Metformin 500 mg twice daily with breakfast and dinner
	  ○ If no GI intolerance, increase to 500 mg with breakfast, 1000 mg with dinner
	  ○ If tolerated, 1000 mg bid with breakfast and dinner
	  ○ If not tolerated, reduce to prior tolerated dose
	  ○ Titrate to the maximum tolerated dose over a period of 3 weeks
	• Exclude confounding factors such as UTI and consider consultation with a diabetologist.
	• If FPG continues to rise, or is persistently >160 mg/dL (>8.9 mmol/L), on MTD of metformin, add an insulin-sensitizer, e.g. pioglitazone 30 mg.
	• Monitor FPG as clinically indicated, and at least weekly, until FPG resolves to ≤Grade 1.
	  ○ If FPG does not resolve to ≤Grade 1 within 21 days after initiation of appropriate antidiabetic treatment, reduce alpelisib/placebo by one dose level.
	  ○ Continue with antidiabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks.
	  ○ Alert treating physician if FPG >250 mg/dL.

Grade 3	• **Interrupt treatment with alpelisib/placebo** and confirm fasting status of the assessment. If non-fasting, re-check within 24 hours.
	• Exclude confounding factors such as UTI and consider consultation with a diabetologist.
	• Administer IV hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate.
	• Start metformin and titrate as outlined for Grade 2, add pioglitazone as outlined for Grade 2.
	• Insulin may be used for 1–2 days until hyperglycemia resolves; however this may not be necessary in the majority of cases of alpelisib-induced hyperglycemia, given the short half-life of alpelisib.
	• Monitor FPG as clinically indicated and at least twice weekly until FPG resolves to ≤Grade 1.
	  ○ If FPG resolves to ≤Grade 1 within 3–5 days, while off study treatment and on metformin, re-start alpelisib/placebo and reduce one dose level, continue with antidiabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG >250 mg/dL.
	  ○ If FPG does not resolve to Grade 1 within 3–5 days while off study treatment and on metformin, consultation with a diabetologist for management of diabetes is strongly recommended.
	  ○ If FPG does not resolve to ≤Grade 1 within 21 days after initiation of appropriate antidiabetic treatment in cooperation with a diabetologist, and exclusion of confounding factors e.g. urinary tract infection, permanently discontinue patient from alpelisib/placebo treatment.

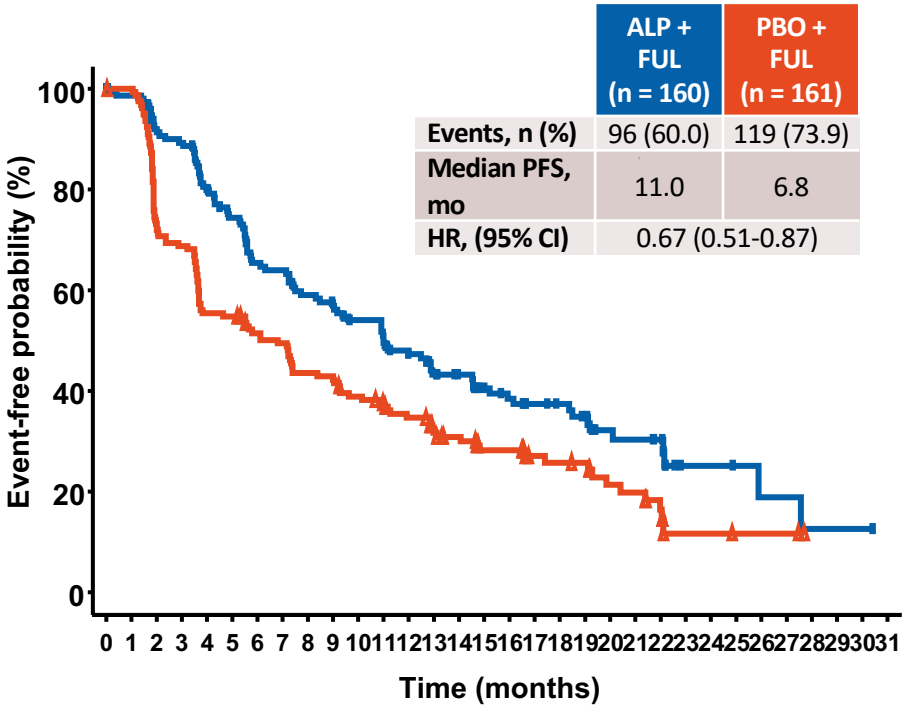
SOLAR-1: PFS by Prior CDK4/6 Inhibitor Treatment in the *PIK3CA*-mutant Cohort

With prior CDK4/6 inhibitor therapy



	ALP + FUL (n = 9)	PBO + FUL (n = 11)
Events, n (%)	7 (77.8)	10 (90.9)
Median PFS, mo	5.5	1.8
HR, (95% CI)	0.48 (0.17-1.36)	

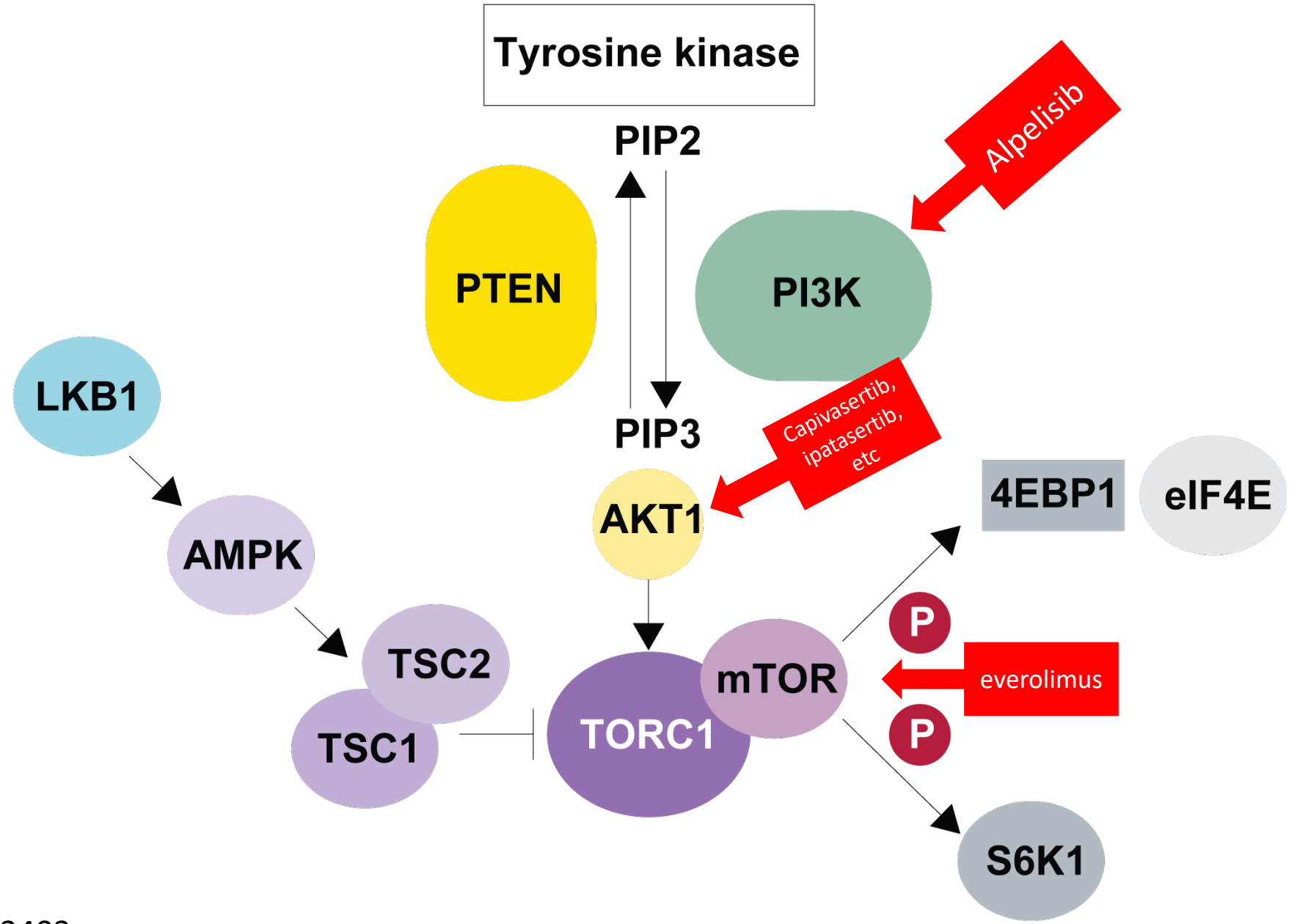
Without prior CDK4/6 inhibitor therapy



	ALP + FUL (n = 160)	PBO + FUL (n = 161)
Events, n (%)	96 (60.0)	119 (73.9)
Median PFS, mo	11.0	6.8
HR, (95% CI)	0.67 (0.51-0.87)	

- Previous treatment with any CDK4/6 inhibitor was a stratification factor, but the number of patients enrolled who had received prior CDK4/6 inhibitor therapy was small
- Treatment benefit with alpelisib was observed regardless of prior use with a CDK4/6 inhibitor

Juric D et al. San Antonio Breast Cancer Symposium 2018;Abstract GS3-08.



Turner NC, et al.
Lancet 2017;389:2403

AKT Inhibition:
FAKTION: Capivasertib (AZD5363) plus fulvestrant versus placebo plus fulvestrant in ER+ MBC

Phase 1b

3+3 design N=9 participants - Capivasertib Starting dose with fulvestrant 500mg: 400mg bd 4 days on / 3 days off

No DLT but 2 withdrawals in 9 participants - Dose not increased to the established single agent dose 480mg bd 4/7

Eligibility

- Post-menopausal women
- ER+/HER2- Metastatic or unresectable LABC
- Prior AI therapy for MBC/LABC with PD **or** relapse on adjuvant AI
- Maximum 1 line chemotherapy for MBC
- Maximum 3 lines ET for MBC
- Measurable or non-measurable disease
- Controlled type II diabetes allowed

N = 140

R

1:1

Fulvestrant 500mg q4weeks + loading dose
Placebo bd 4 days on/3 off from C1D15 N=69

Fulvestrant 500mg q4weeks + loading dose
Capivasertib bd 4 days on/3 off from C1D15 N=71

Primary endpoint:

PFS in overall population

Secondary endpoints:

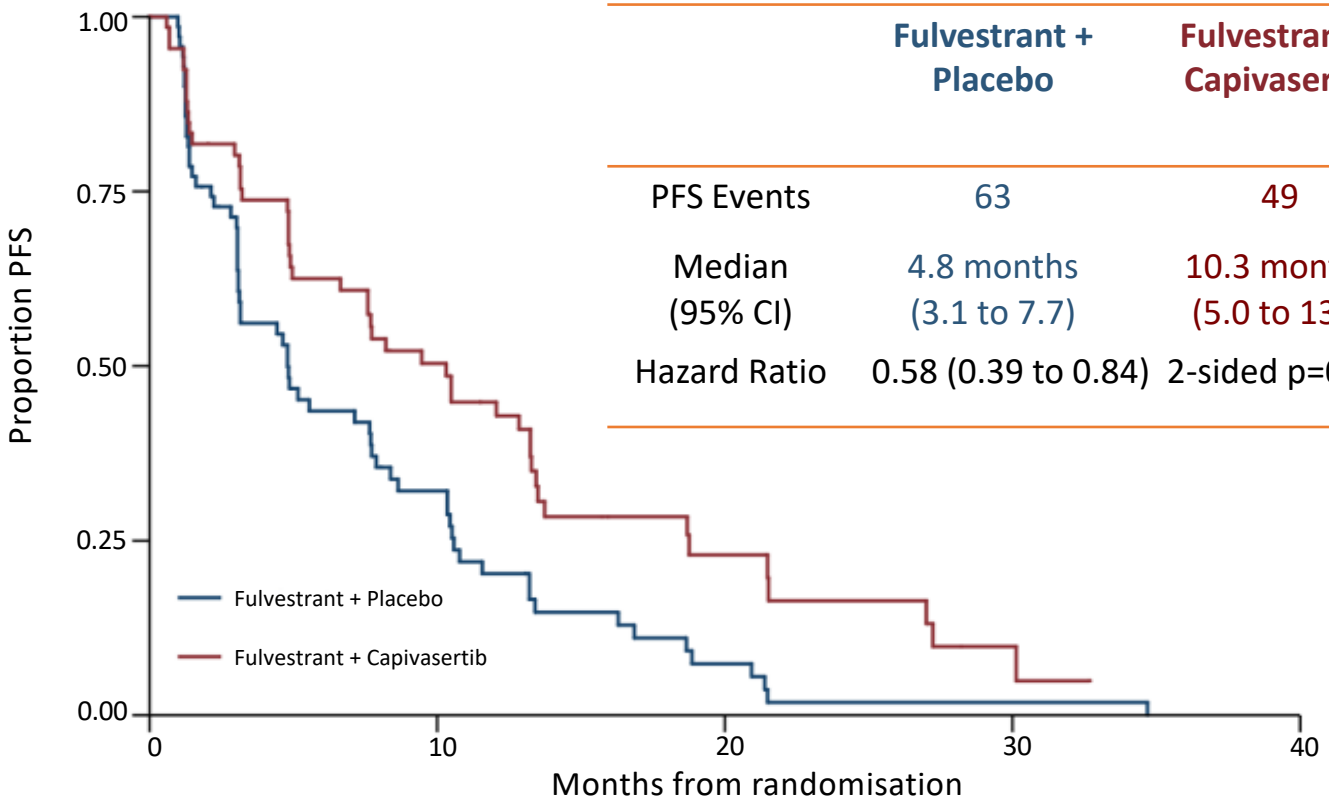
Safety and toxicity

Objective Response rates, CBR and OS: in overall population and pathway activated

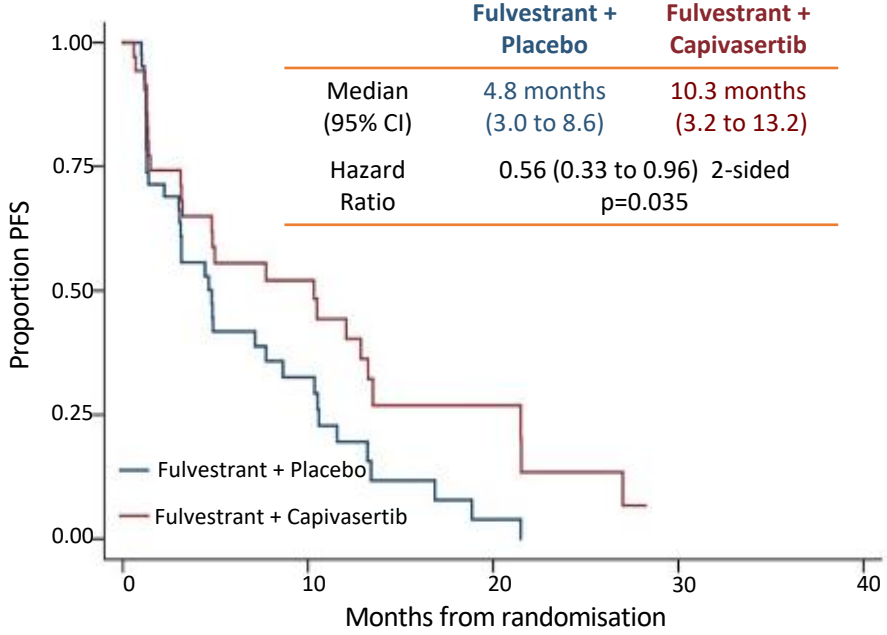
Effects of Capivasertib on the PK of fulvestrant

Jones et al, ASCO 2019

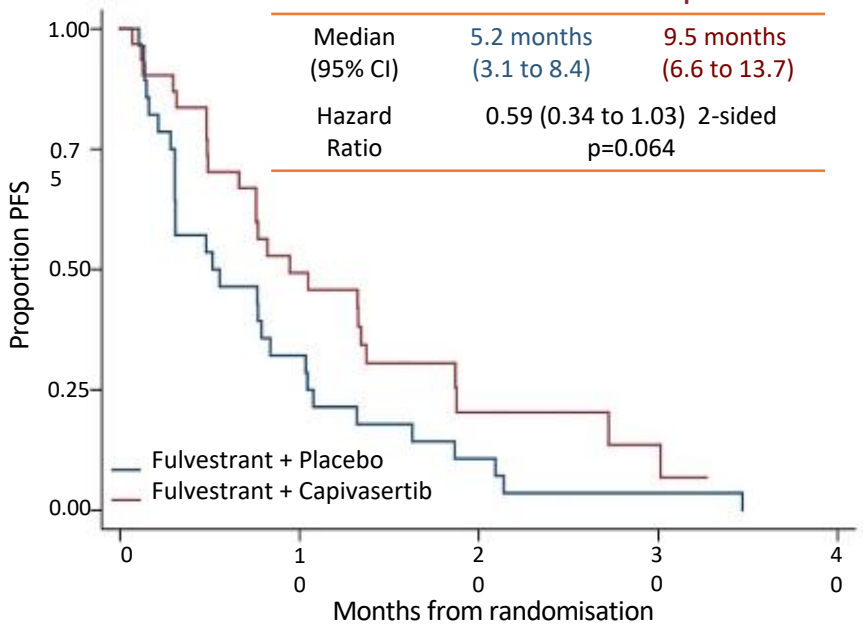
FAKTION: PFS ITT and by PI3K/AKT/mTOR pathway activation status



	Fulvestrant + Placebo	Fulvestrant + Capivasertib
PFS Events	63	49
Median (95% CI)	4.8 months (3.1 to 7.7)	10.3 months (5.0 to 13.2)
Hazard Ratio	0.58 (0.39 to 0.84) 2-sided p=0.004	



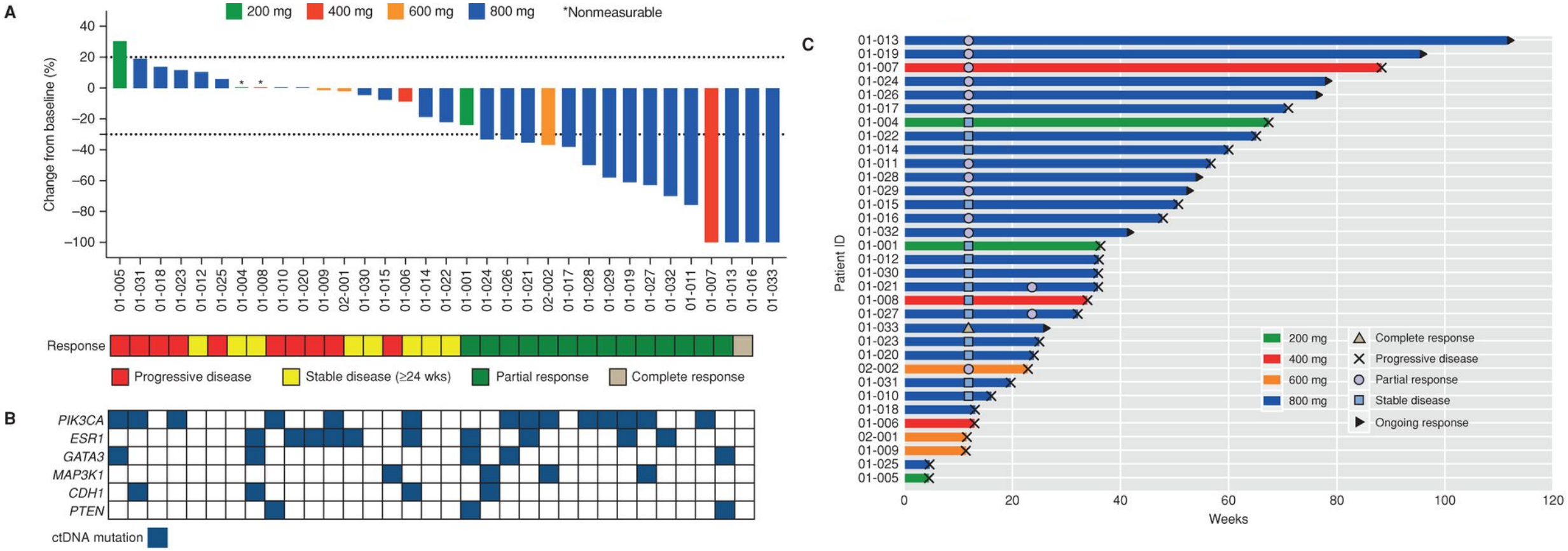
	Fulvestrant + Placebo	Fulvestrant + Capivasertib
Median (95% CI)	4.8 months (3.0 to 8.6)	10.3 months (3.2 to 13.2)
Hazard Ratio	0.56 (0.33 to 0.96) 2-sided p=0.035	



	Fulvestrant + Placebo	Fulvestrant + Capivasertib
Median (95% CI)	5.2 months (3.1 to 8.4)	9.5 months (6.6 to 13.7)
Hazard Ratio	0.59 (0.34 to 1.03) 2-sided p=0.064	

Jones et al, ASCO 2019

Venetoclax plus tamoxifen in ER+, Bcl-2+ advanced breast cancer



Sheau W. Lok et al. Cancer Discov 2019;9:354-369

Select adverse events with venetoclax plus tamoxifen in ER+, Bcl-2+ advanced breast cancer

Adverse event	<800 mg *n* = 9 *n* (%)	800 mg *n* = 24 *n* (%)	Total *n* = 33 *n* (%)
Decreased white cell count	8 (89)	21 (88)	29 (88)
Lymphopenia	9 (100)	20 (83)	29 (88)
Neutropenia	5 (56)	19 (79)	24 (73)
Nausea	6 (67)	16 (67)	22 (67)
Anemia	5 (56)	8 (33)	13 (39)
Thrombocytopenia	4 (44)	7 (29)	11 (33)
Vomiting	3 (33)	8 (33)	11 (33)
Diarrhea	2 (22)	7 (29)	9 (27)
Infection (any)	0 (0)	9 (38)	9 (27)
Fatigue	1 (33)	5 (21)	6 (18)
Lethargy	0 (0)	4 (17)	4 (12)
Pruritus	0 (0)	4 (17)	4 (12)
Rash	1 (33)	3 (13)	4 (12)

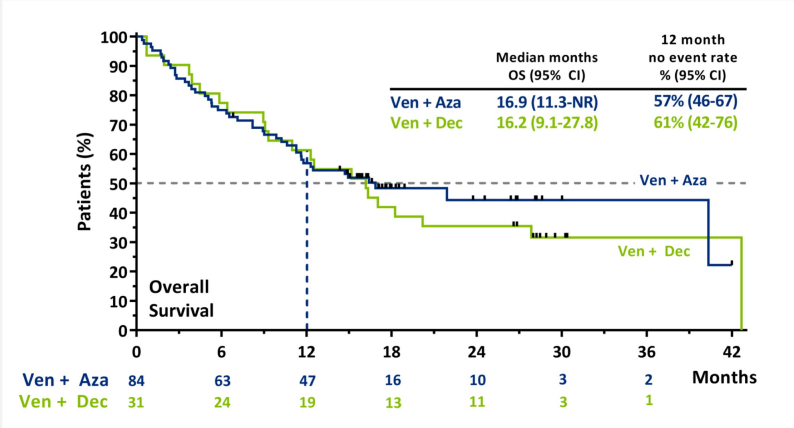
Sheau W. Lok et al. Cancer Discov 2019;9:354-369

A Phase II Study Comparing The Efficacy Of Venetoclax + Fulvestrant Versus Fulvestrant In Women With Estrogen Receptor-Positive, HER2-Negative Locally Advanced Or Metastatic Breast Cancer Who Experienced Disease Recurrence Or Progression During Or After CDK4/6 Inhibitor Therapy

- Primary endpoint: Complete Response (CR), Partial Response (PR) or Stable Disease (SD).
- Secondary endpoints: Progression Free Survival (PFS)

ASH 2019

Venetoclax + HMA: Overall Survival



Pollyea et al, ASH 2018;Abstract 285

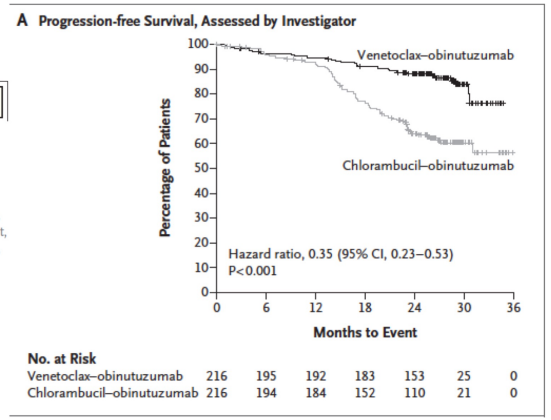
SITEMAN CANCER CENTER

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions

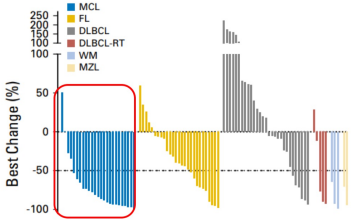
K. Fischer, O. Al-Sawaf, J. Bahlo, A.-M. Fink, M. Tandon, M. Dixon, S. Robrecht, S. Warburton, K. Humphrey, O. Samoylova, A.M. Liberati, J. Pinilla-Ibarz, S. Opat, L. Sivcheva, K. Le Dû, L.M. Fogliatto, C.U. Niemann, R. Weinkove, S. Robinson, T.J. Kipps, S. Boettcher, E. Tausch, R. Humerickhouse, B. Eichhorst, C.-M. Wendtner, A.W. Langerak, K.-A. Kreuzer, M. Ritgen, V. Goede, S. Stilgenbauer, M. Mobasher, and M. Hallek



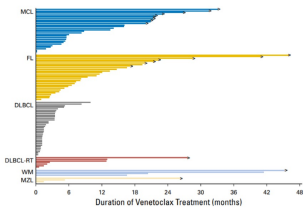
N Engl J Med 2019;380(23):2225-36.

Barnes-Jewish Hospital • Washington University School of Medicine • National Cancer Institute • National Comprehensive Cancer Network

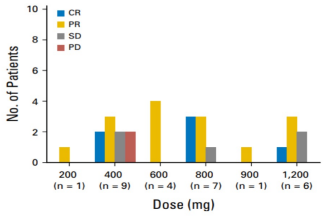
Venetoclax in Relapsed/Refractory MCL

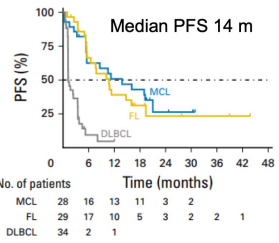


Response	
ORR	21 (75%)
CRR	6 (21%)
PRR	15 (54%)
SD	5 (18%)



Mantle cell lymphoma cohort (N=28)	
Age	72 (35-85)
Prior therapies	3 (1-10)
Bulky >5cm/>10cm	14/3
LDH > ULN	7





Davids, et al. JCO 2017

Venetoclax activity in MM: Early studies