Dagli inibitori di CDK4/6, agli inibitori di PI3k, ai possibili scenari futuri

Dr.ssa Giulia V. Bianchi

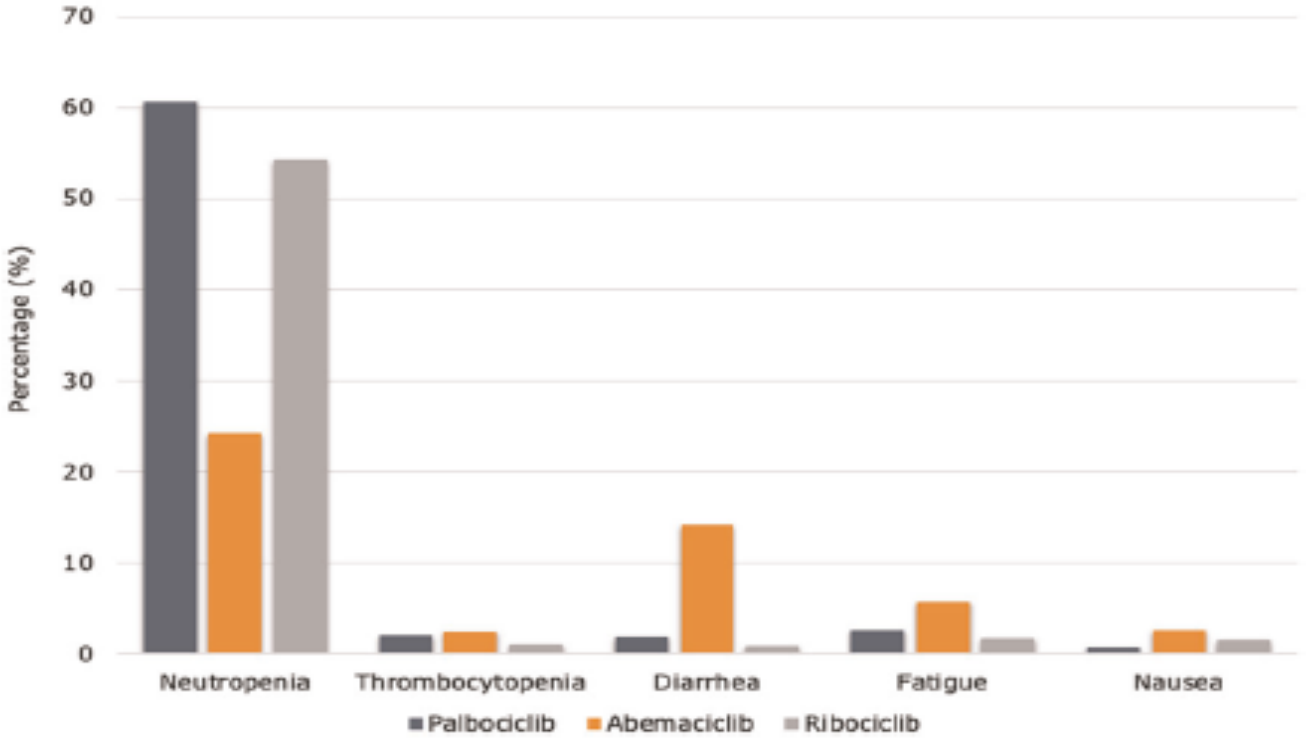
Fondazione IRCCS
ISTITUTO NAZIONALE
DEI TUMORI
DI MILANO

CDK4/6 inhibitors: clinical efficacy

	CDK4/6 inhibitor	Setting and study population	Sample size	Median progression-free survival vs placebo (months)	Median overall survival vs placebo (months)
Trials in combination with non-steroidal aromatase inhibitors					
PALOMA-2[1]	Palbociclib	Postmenopausal women with hormone receptor-positive and HER2-negative advanced breast cancer; no previous systemic treatment for advanced breast cancer; and neoadjuvant endocrine therapy permitted if disease-free interval >12 months from therapy completion	666	24·8 vs 14·5 (HR 0·58; p<0·001)	Not reported
MONALEESA-2[7]	Ribociclib	Postmenopausal women with hormone receptor-positive and HER2-negative advanced breast cancer; no previous systemic treatment for advanced breast cancer; and (neo)adjuvant endocrine therapy permitted if disease-free interval >12 months from therapy completion	668	25·3 vs 16·0 (HR 0·57; p<0·001)	Not reported
MONARCH 3[3]	Abemaciclib	Postmenopausal women with hormone receptor-positive and HER2-negative advanced breast cancer; no previous systemic treatment for advanced breast cancer; (neo)adjuvant endocrine therapy permitted if disease-free interval >12 months from therapy completion	493	Not reached vs 14·7 (HR 0·54; p<0·001)	Not reported
Trials in combination with fulvestrant					
PALOMA-3[4,60]	Palbociclib	Women with hormone receptor-positive and HER2-negative advanced breast cancer that relapsed or progressed during endocrine therapy; any menopausal status; ≤1 line of chemotherapy for advanced disease*	521	9·5 vs 4·6 (HR 0·46; p<0·001)	34·9 vs 28·0 (HR 0·81; p=0·09)
MONALEESA-3[8]	Ribociclib	Postmenopausal women and men with hormone receptor-positive and HER2-negative advanced breast cancer; 0–1 line of endocrine therapy for advanced breast cancer†	726	20·5 vs 12·8 (HR 0·60; p<0·001)	Not reached vs 40·0 (HR 0·72; p=0·005)
MONARCH 2[6]	Abemaciclib	Women with hormone receptor-positive and HER2-negative advanced breast cancer that had progressed during previous endocrine therapy; any menopausal status, ≤1 endocrine therapy; no previous chemotherapy for advanced disease‡	669	16·4 vs 9·3 (HR 0·55; p<0·001)	46·7 vs 37·3 (HR 0·76; p=0·014)
Trials in combination with tamoxifen or non-steroidal aromatase inhibitor plus goserelin					
MONALEESA-7[20]	Ribociclib	Premenopausal and perimenopausal women with hormone receptor-positive and HER2-negative advanced breast cancer; no previous endocrine therapy for advanced disease; ≤1 line of chemotherapy for advanced disease	672	23·8 vs 13·0 (HR 0·55; p<0·001)	Not reached vs 40·9 (HR 0·71; p=0·01)

Spring LM et al, Lancet 2020

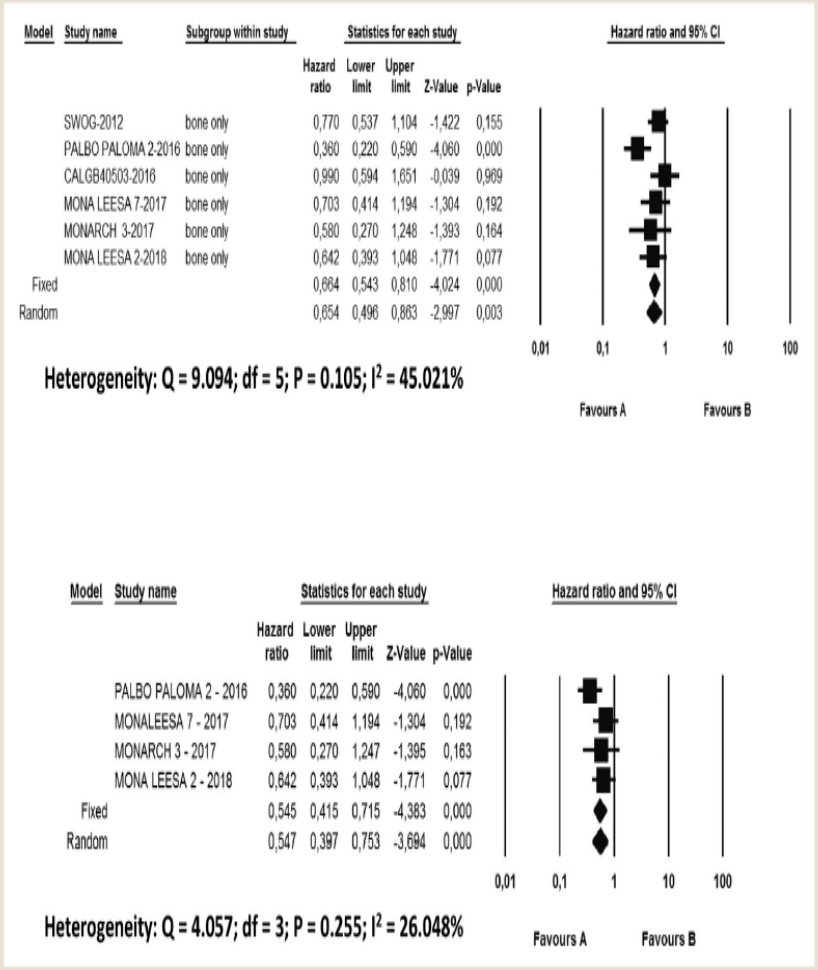
CDK4/6 inhibitors: grade 3 adverse events



Marra et al., Breast Cancer 2019

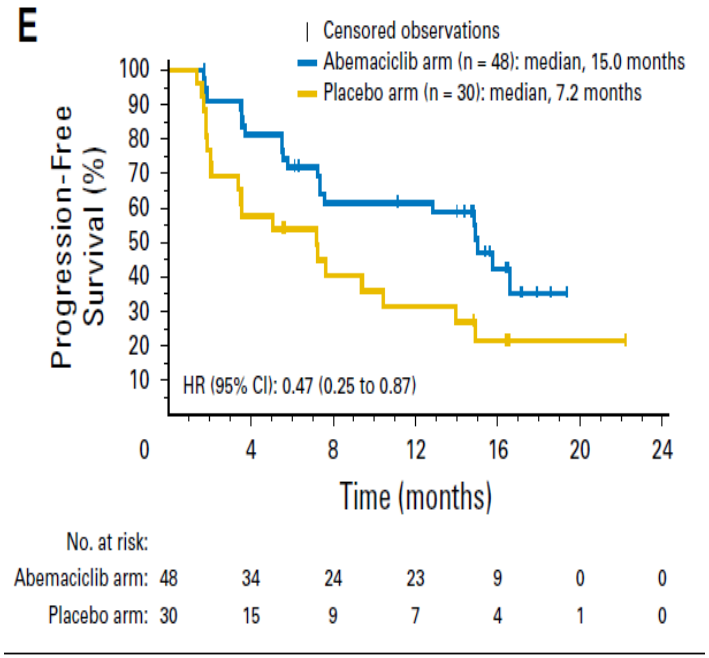
CDK4/6 inhibitors: efficacy in all subgroups

Figure 2 Meta-analysis of HR for Subgroup "Bone-Only Disease" of 6 Studies Included and in 4 Trials Investigating CDKi Combinations



Toss A et al, Clin Breast Cancer 2019

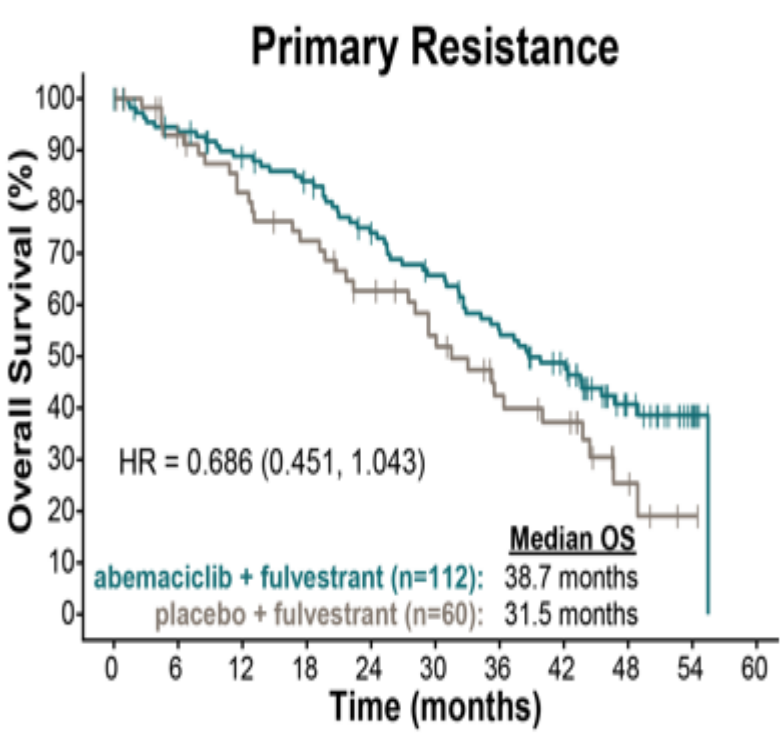
Monarch 3: liver metastases

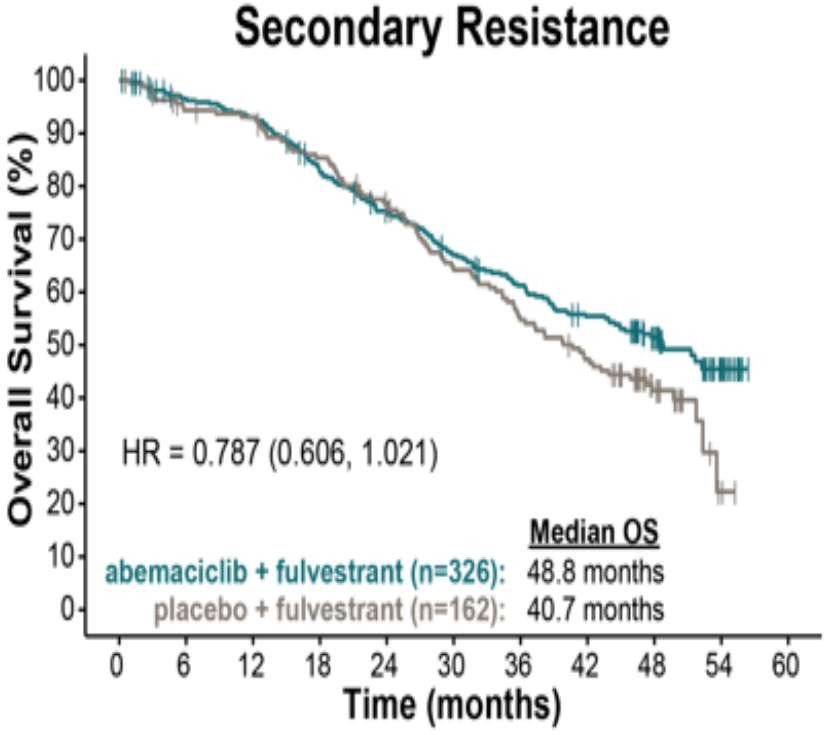


Goetz MP. J Clin oncol 2017

CDK4/6 in endocrine-resistance

Primary resistance vs secondary: MONARCH2 OS

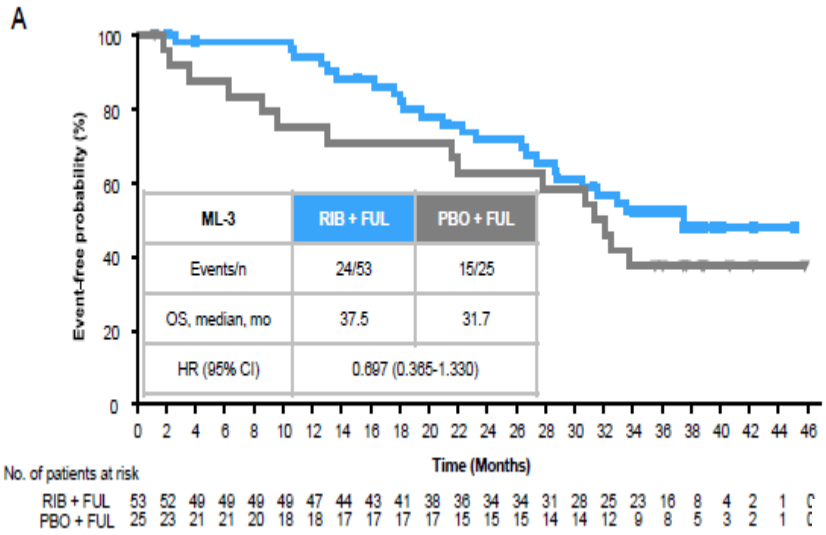




Sledge GW et al, JAMA Oncol 2019

MONALEESA 3 and 7: OS in endocrine-resistance

MONALEESA 3



MONALEESA 7

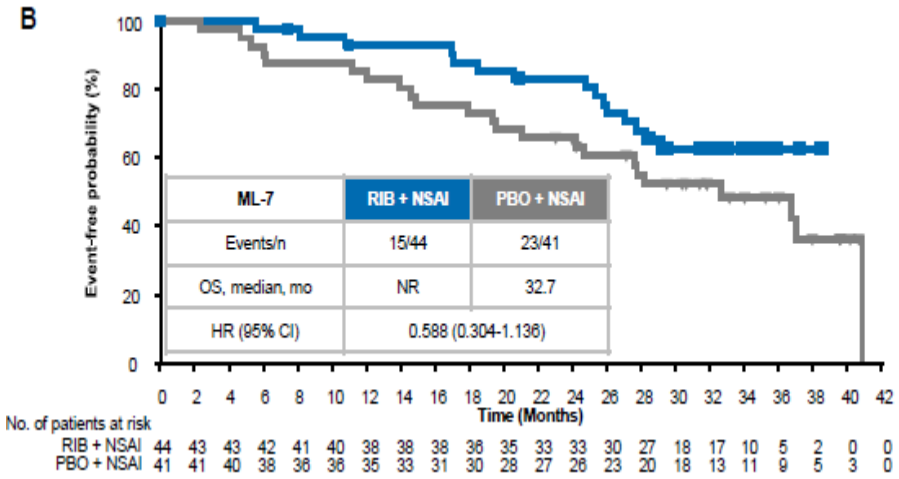
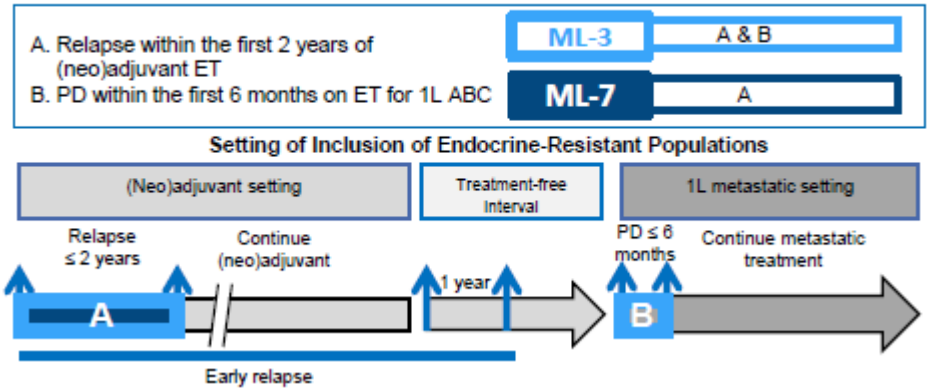


Figure 2. Ad Hoc Definitions of ET Resistance



Hurvitz SA et al ESMO 2020

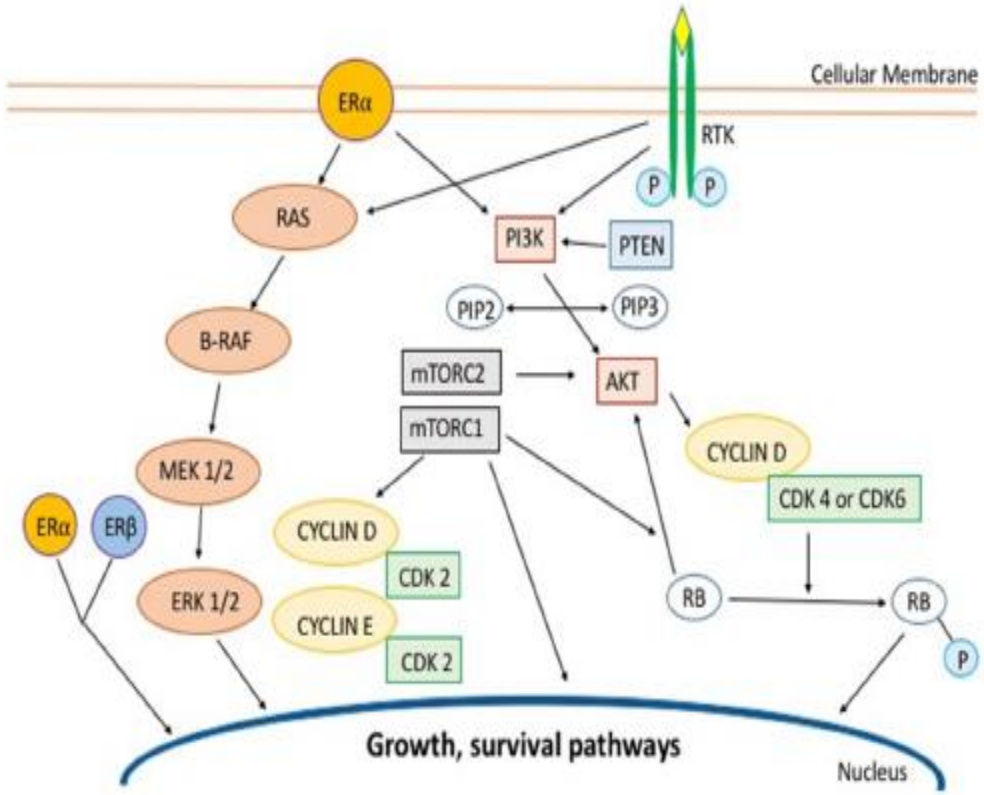
CDK4/6 in adjuvant trials

Table 1. Characteristics of the studies included in the meta-analysis

Study characteristics	PALLAS[9]		MonarchE[11,12]		PENELOPE-B[10]	
	Palbociclib + ET	ET alone	Abemaciclib + ET	ET alone	Palbociclib + ET	ET alone
N	2883	2877	2808	2829	631	619
Median follow-up (months)	23.7		19.1		42.8	
CDK4/6i duration (years)	2		2		1	
Age, years, median (range)	52 (25-90)	52 (22-85)	51 (23-89)	51 (22-86)	49 (22-76)	48 (19-79)
Stage, *n* (%)						
IA	—	—	2 (0.1)	1 (0)	—	—
IIA	504 (17.5)	509 (17.7)	323 (11.5)	353 (12.5)	—	—
IIB	968 (33.6)	951 (33.1)	389 (13.9)	387 (13.7)	—	—
III	1402 (48.6)	1408 (48.9)	2081 (74.1)	2077 (73.4)	—	—
Pathologic tumor size, *n* (%)						
T0, T1, Tx, Tis	557 (19.3)	500 (17.4)	780 (27.8)	765 (27.0)	238 (37.7)	208 (33.7)
T2	1603 (55.6)	1636 (56.9)	1369 (48.8)	1419 (50.2)	368 (58.3)	389 (62.9)
T3, T4	722 (25.0)	741 (25.8)	610 (21.7)	612 (21.6)	25 (4.0)	21 (3.4)
Nodal status, *n* (%)						
N0/1	1794 (62.2)	1798 (62.5)	—	—	310 (49.1)	310 (50.1)
N2/3	1088 (37.8)	1079 (37.5)	—	—	321 (50.9)	309 (49.9)
Grade, *n* (%)						
G1	300 (10.4)	313 (10.9)	209 (7.4)	215 (7.6)	—	—
G2	1622 (56.3)	1658 (57.6)	1373 (48.9)	1395 (49.3)	—	—
G3	836 (29.0)	767 (26.7)	1090 (38.8)	1066 (37.7)	294 (46.7)	297 (48.1)
Ki-67[a], *n* (%)						
Low	—	—	953 (33.9)	973 (34.4)	—	—
High	—	—	1262 (44.9)	1233 (43.6)	161 (25.5)	158 (25.5)
Prior CT, *n* (%)	2384 (82.7)	2370 (82.4)	2681 (95.5)	2695 (95.3)	631 (100)	619 (100)
Adjuvant ET, *n* (%)						
Tamoxifen	923 (32.0)	949 (33.0)	857 (30.7)	898 (32.1)	314 (49.8)	308 (49.8)
Tamoxifen + ovarian suppression	—	—	192 (6.9)	232 (8.3)	—	—
AI, *n* (%)	1954 (67.8)	1918 (66.7)	1928 (69.1)	1891 (67.5)	—	—
AI + ovarian suppression, *n* (%)	—	—	410 (14.7)	386 (13.8)	—	—
Ovarian suppression (any time), *n* (%)	532 (18.5)	604 (21.1)	606 (21.7)	627 (22.4)	108 (17.1)	113 (18.3)
IDFS events	351 events		395 events		308 events	
IDFS	HR 0.93 (0.76-1.15), $P = 0.51$		HR 0.71 (0.58-0.87), $P = 0.0009$		HR 0.93 (0.74-1.17), $P = 0.525$	
DRFS events, *n*	271		324		227	
DRFS	1.00 (0.79-1.27)		0.69 (0.55-0.86)		No difference (HR not reported)	
Early CDK4/6i discontinuation, *n* (%)	1199 (42.2)		773 (27.7)		123 (19.5)	
Early CDK4/6i discontinuation due to AEs, *n* (%)	772 (26.7)		481 (17.2)		33 (5.2)	

Agostinetto E et al Esmo open 2021

PI3k Pathway/mTOR pathway



PI3k mutation and outcome

Hormone therapy ± PI3K inhibitors					
BELLE-2 (Baselga)[62]	Buparlisib + Fulvestrant	7.0 (5.0–10.0)	6.8 (4.7–8.5)	0.58 (0.41–0.82)	1.02 (0.79–1.30)
	Placebo + Fulvestrant	3.2 (2.0–5.1)	6.8 (4.7–8.6)		
BELLE-3 (Di Leo)[63]	Buparlisib + Fulvestrant	4.2 (2.8–6.7)	3.9 (4.7–8.5)	0.46 (0.29–0.73)	0.73 (0.53–1.00)
	Placebo + Fulvestrant	1.6 (1.4–2.8)	2.7 (4.7–8.6)		
FERGI (Krop)[64]	Pictilisib + Fulvestrant	6.5 (3.7–9.8)	5.8 (3.6–11.1)	0.73 (0.42–1.28)	0.72 (0.42–1.23)
	Placebo + Fulvestrant	5.1 (2.6–10.4)	3.6 (2.8–7.3)		
SOLAR-1 (André)[4]	Alpelisib + Fulvestrant	11.0 (7.5–14.5)	7.4 (5.4–9.3)	0.65 (0.50–0.85)	0.85 (0.58–1.25)
	Placebo + Fulvestrant	5.7 (3.7–7.4)	5.6 (3.9–9.1)		
SANDPIPER (Baselga)[65]	Taselisib + Fulvestrant	7.4 (7.3–9.1)	5.6 (4.1–9.1)	0.70 (0.56–0.89)	0.69 (0.44–1.08)
	Placebo + Fulvestrant	5.4 (3.7–7.3)	4.0 (1.9–6.0)		
Hormone therapy ± CDK 4/6 inhibitors					
PALOMA-3 (Cristofanilli)[66]	Palbociclib + Fulvestrant	9.5 (5.7–11.2)	9.9 (9.2–13.9)	0.48 (0.30–0.78)	0.45 (0.31–0.64)
	Placebo+ Fulvestrant	3.6 (1.9–5.6)	4.6 (3.4–7.3)		
Hormone therapy ± mTOR inhibitors					
BOLERO-2 (Moynahan)[67]	Everolimus + Exemestane	6.9 (5.6–8.3)	7.4 (6.8–9.7)	0.37 (0.27–0.51)	0.43 (0.34–0.56)
	Placebo + Exemestane	2.7 (1.5–4.1)	3.0 (2.8–4.2)		

Abbreviations: PFS, progression-free survival; CI, confidence interval; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; CDK, cyclin-dependent kinase; NSAI, non-steroidal aromatase inhibitor; PI3K, phosphoinositide 3 kinase; mTOR, mammalian target of rapamycin.

Chang DY et al Ther And Clin Risk Man 2021

Ongoing Clinical Trials Investigating Therapies Targeting the PI3K/AKT/mTOR Pathway

Therapy	PI3K-α	PI3K-β	PI3K-δ	PI3K-γ	AKT	mTOR	Trial ID	Study Phase
MEN1611 + Trastuzumab ±faslodex	x						NCT03767335	Ib
AZD8186 + docetaxel		x					NCT03218826	I
Alpelisib + faslodex or letrozole	x						NCT03056755	II
Alpelisib + nab-paclitaxel	x						NCT04216472	II
Gedatolisib + palbociclib + faslodex	x	x	x	x		x	NCT02626507	Ib
Gedatolisib + palbociclib/letrozole or palbociclib/faslodex	x	x	x	x		x	NCT02684032	Ib
Ipatasertib + faslodex					x		NCT03959891	I
Ipatasertib + aromatase inhibitor (AI)								
Ipatasertib + faslodex + palbociclib								
Ipatasertib + trastuzumab + pertuzumab + endocrine therapy (if HR+)					x		NCT04253561	Ib
Gedatolisib + PTK7-ADC	x	x	x	x		x	NCT03243331	I
PDR001 (PD1 monoclonal antibody) + everolimus, LCL161 or panobinostat						x	NCT02890069	Ib
AZD5363 + paclitaxel					x		NCT02423603	II
AZD2014 + olaparib						x	NCT02208375	Ib
AZD 5363 + olaparib					x		NCT02208375	Ib
AZD2014 + selumetinib (MEK inhibitor)						x	NCT02583542	Ib/II
Taselisib +enzalutamide	x		x	x			NCT02457910	Ib/II

Breast Cancer: Targets and Therapy 2020

SOLAR-1

Prospective evaluation of an α-selective PI3K inhibitor in HR+, HER2– ABC

NCT02437318

- **Men or postmenopausal women with HR+, HER2–ABC**
- Recurrence/progression on/after prior AI-based therapy
- Identified *PIK3CA* status (in archival or fresh tumour tissue)
- Measurable disease or ≥1 predominantly lytic bone lesion
- ECOG PS ≤1

(N=572)

***PIK3CA*-mutant cohort** (n=341) → **R 1:1**

- **Alpelisib** 300 mg QD PO **+ Fulvestrant** 500 mg IM[a] **n=169**
- **Placebo + Fulvestrant** 500 mg IM[a] **n=172**

Stratified by presence of liver/lung metastases and prior CDK4/6 inhibitor treatment

***PIK3CA*-non-mutant cohort** (n=231) → **R 1:1**

- **Alpelisib** 300 mg QD PO **+ Fulvestrant** 500 mg IM[a] **n=115**
- **Placebo + Fulvestrant** 500 mg IM[a] **n=116**

Primary endpoint

- PFS in *PIK3CA*-mutant cohort (locally assessed)

Key secondary endpoint

- OS (*PIK3CA*-mutant cohort)

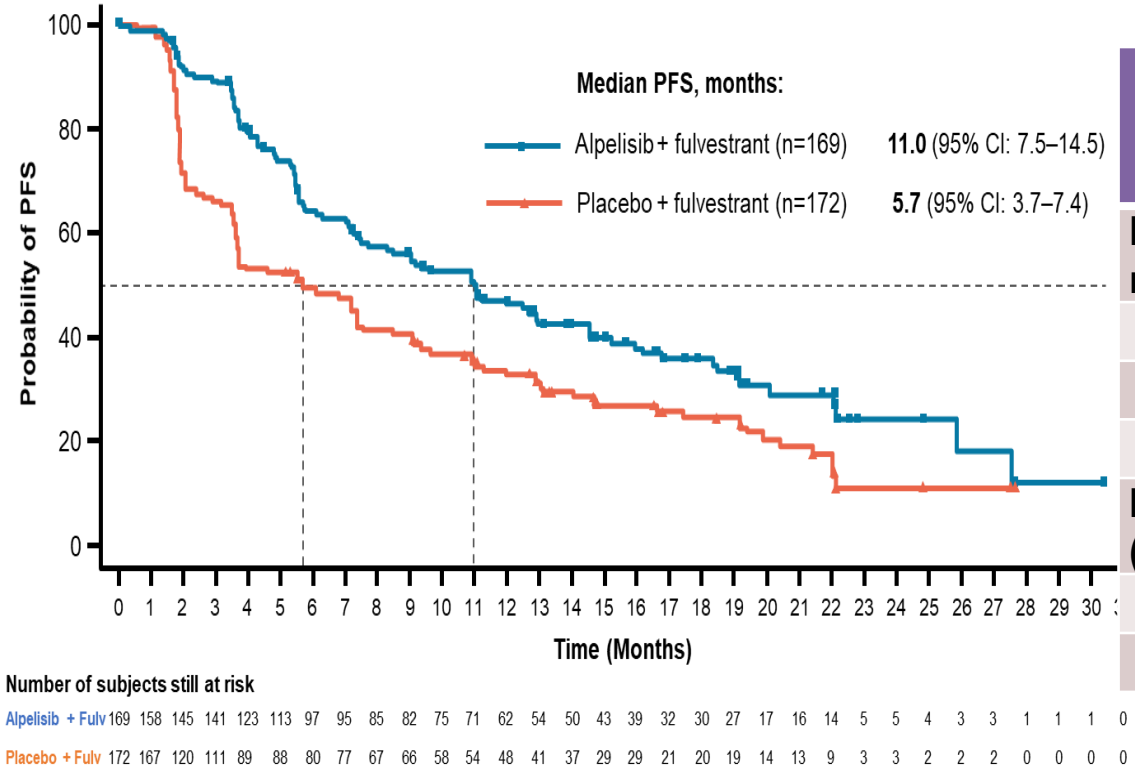
Secondary endpoints include

- ORR/CBR
- Safety
- Global health status/quality of life

AI, aromatase inhibitor; CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinases 4 and 6; ctDNA, circulating tumour DNA; ECOG, Eastern Cooperative Oncology Group; IM, intramuscular; ORR, overall response rate; PO, orally; PS, performance status; QD, daily; R, randomisation.
[a]Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.

Andre F, et al. N Engl J Med. 2019

SOLAR 1: PFS in the *PIK3CA*-mutant cohort



Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=169)	Placebo + fulvestrant (N=172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5–14.5)	5.7 (3.7–7.4)
HR (95% CI)	0.65 (0.50–0.85)	
p-value	0.00065	

– The primary endpoint crossed the prespecified Haybittle–Peto boundary (one-sided p≤0.0199)

André F et al 2018- ESMO 2018, Presidential Symposium

SOLAR-1: OS in Patients in *PIK3CA*-mutant Cohort

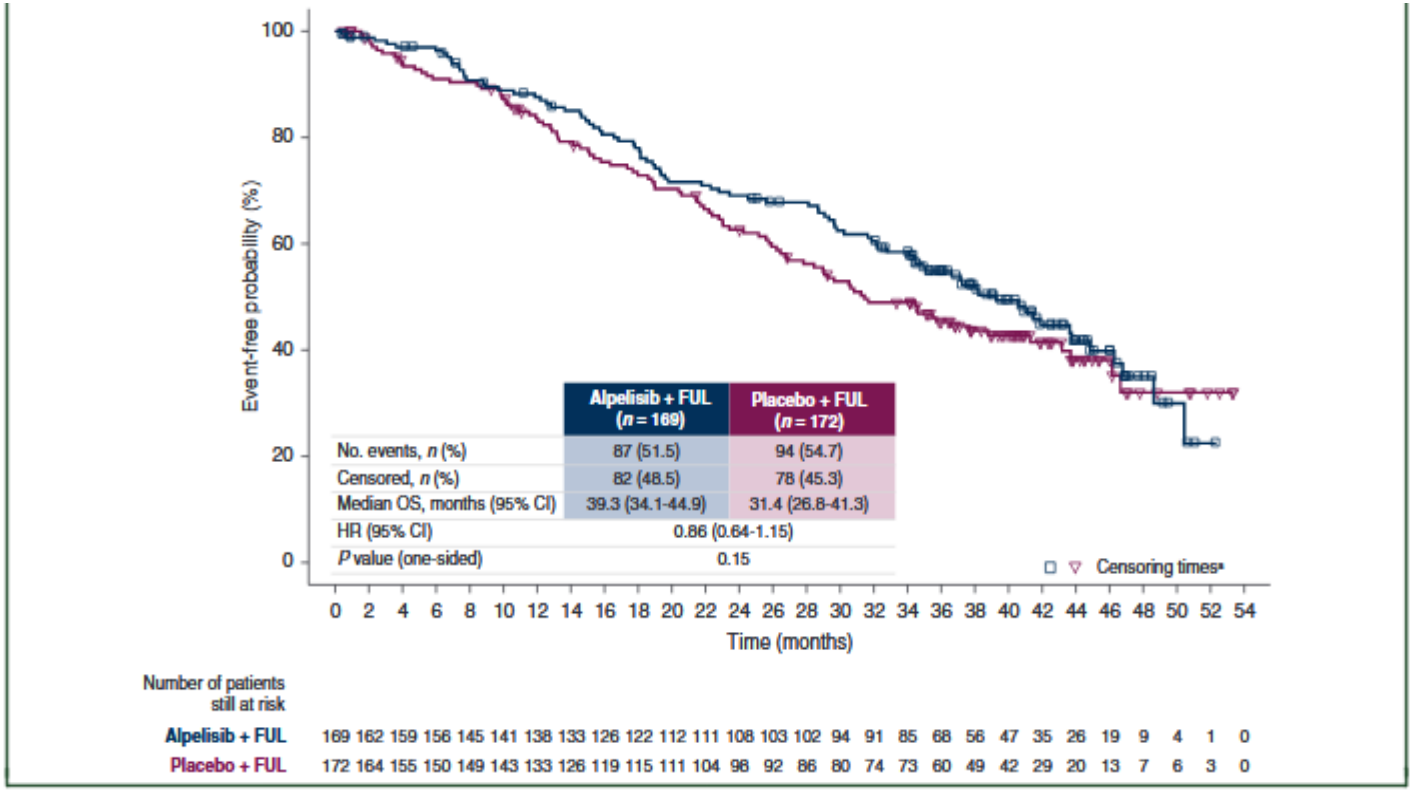


Figure 1. Overall survival in *PIK3CA*-mutant cohort of patients comparing alpelisib plus fulvestrant and placebo plus fulvestrant treatment arms using one-sided stratified log-rank test.

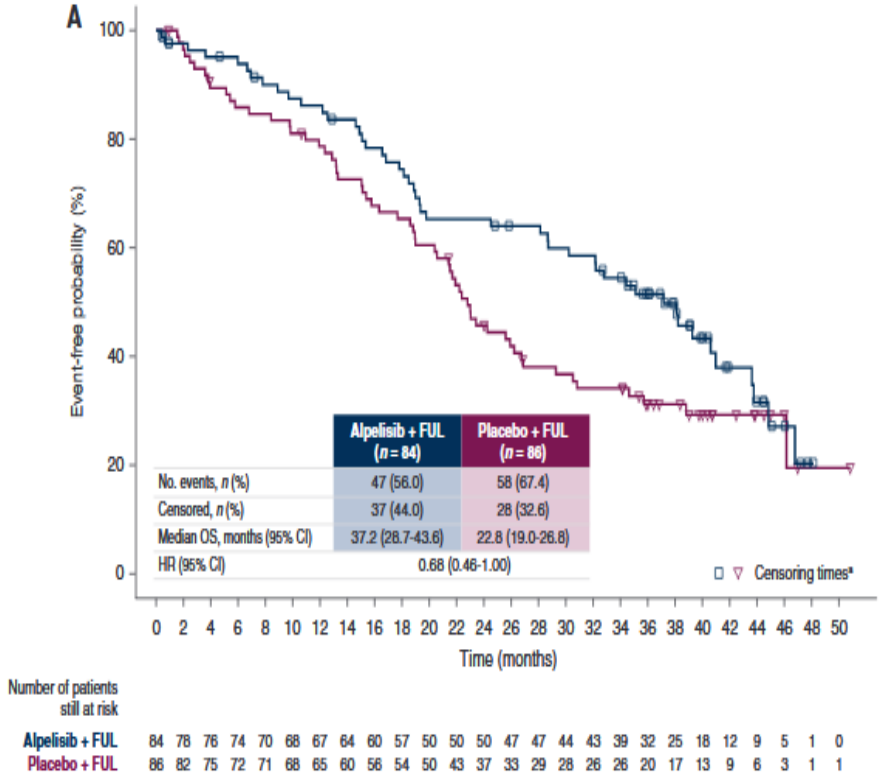
CI, confidence interval; FUL, fulvestrant; HR, hazard ratio; OS, overall survival.

[a] Date of censoring is defined as the last contact date.

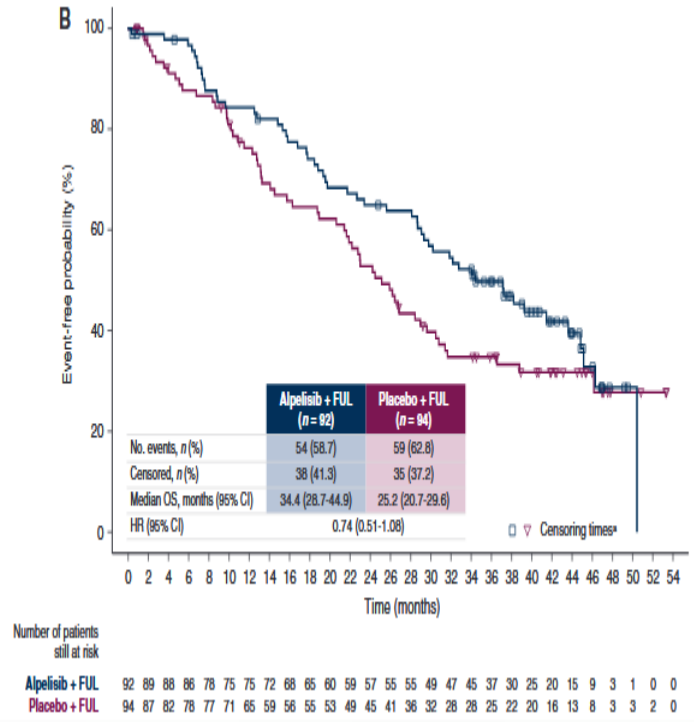
Andre' F et al, Ann Oncol 2021

SOLAR-1

OS in Patients With Lung and/or Liver Metastases



OS in Patients With *PIK3CA* Mutation in Plasma ctDNA



Andre' F et al, Ann Oncol 2021

BYLieve: A Phase 2, Open-Label, 3-Cohort, Noncomparative Trial (NCT03056755)

BYLieve
Alpelisib (BYL719) in patients with PIK3CA mutant, HR+, HER2- advanced breast cancer

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

Men or pre-/postmenopausal[a] women with HR+, HER2– ABC with a *PIK3CA* mutation

- Last line of prior therapy: CDKi + ET, systemic chemotherapy or ET
- ECOG PS ≤2
- Measurable disease (per RECIST v1.1) or ≥1 predominantly lytic bone lesion

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]

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

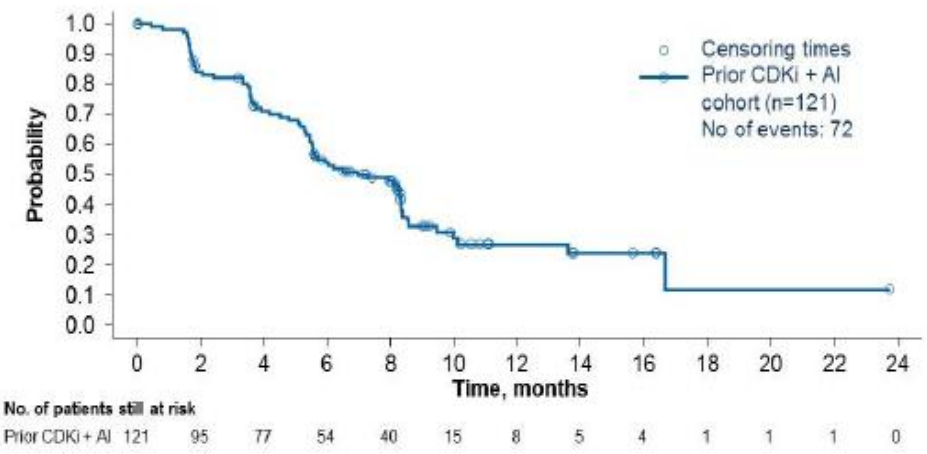
Treatment crossover between cohorts is not permitted

[a]Men in the letrozole cohort and premenopausal women also received goserelin 3.6 mg SC every 28 days or leuprolide 7.5 mg IM every 28 days for adequate gonadal suppression. [b]Enrollment in each cohort continued until at least 112 patients with a centrally confirmed *PIK3CA* mutation was reached. [c]IM on D1 and D15 of Cycle 1 and D1 for all other cycles thereafter. [d]Oral QD.

ABC, advanced breast cancer; AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; CBR, clinical benefit rate; D, day; DOR, duration of response; IM, intramuscularly; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, PFS on next-line treatment; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RECIST, Response Evaluation Criteria in Solid Tumors; SC, subcutaneously; QD, once daily.

Efficacy: Primary Endpoint and PFS Results

Endpoint	Prior CDKi + AI (Cohort A) (n=121)
Primary endpoint: Patients who were alive without disease progression at 6 mo	**50.4%** (n=61; 95% CI, 41.2-59.6)
Secondary endpoint: Median PFS	**7.3 mo** [n=72 (59.5%) with event]; 95% CI, 5.6-8.3)



The primary endpoint for the prior CDKi + AI cohort was met (lower bound of 95% CI was > 30%), with 50.4% of patients alive without disease progression at 6 months

- In SOLAR-1, 44.4% of patients in the *PIK3CA*-mutant cohort with prior CDKi treated with alpelisib plus fulvestrant were alive without disease progression at 6 months

AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; CI, confidence interval; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Everolimus and exemestane

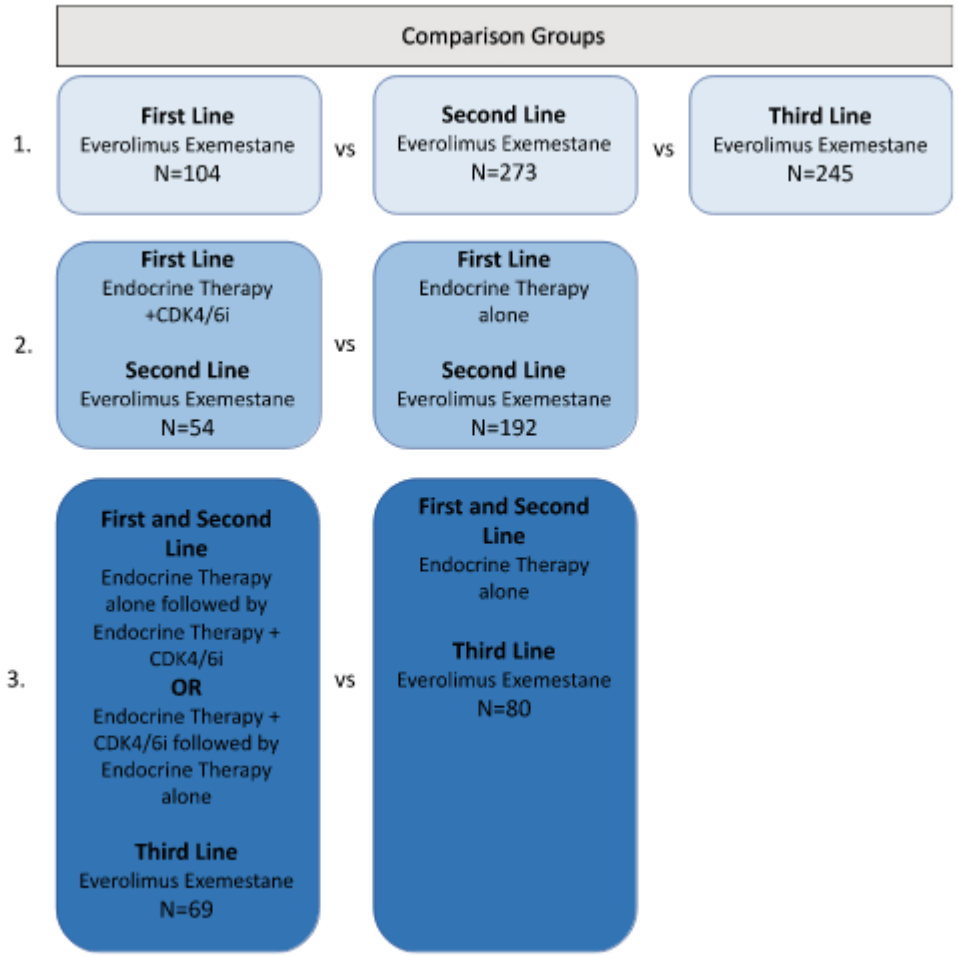
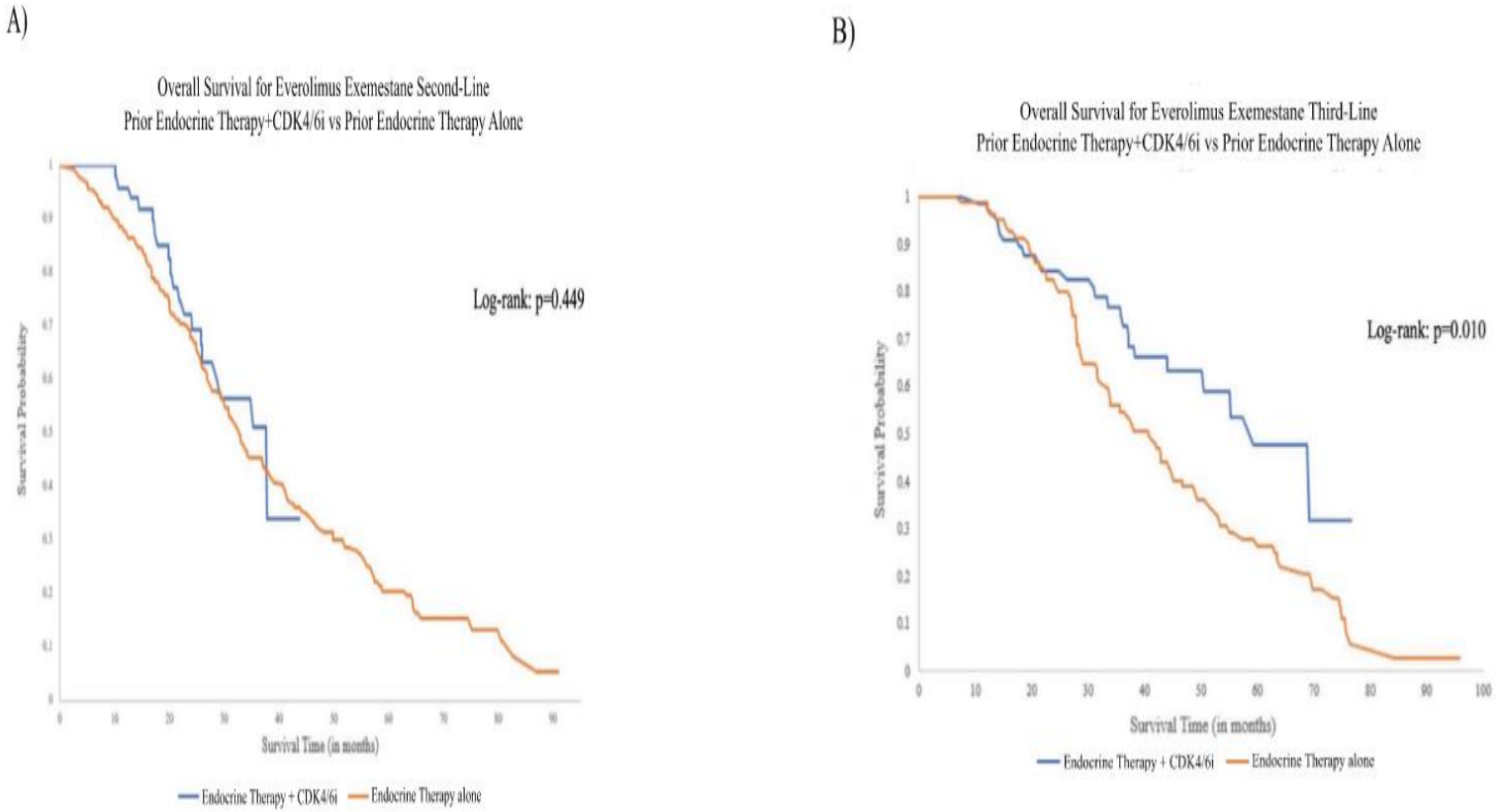


Fig. 2 Treatment comparison groups for analyzing the duration of therapy and overall survival

Rosenblitz M et al, Breast Can Res 2021

OS with everolimus + exemestane



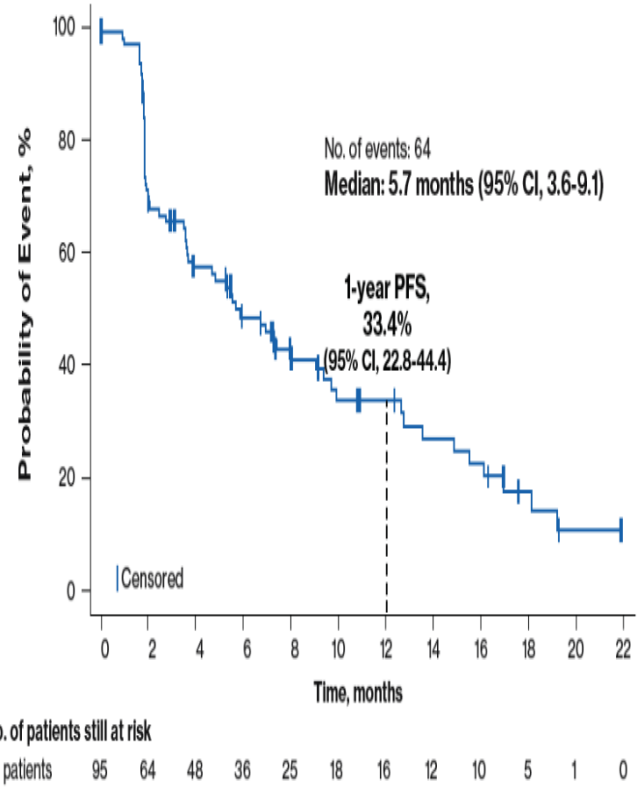
Rosenblitz M et al, Breast Can Res 2021

TRINITI1

- Ribociclib + everolimus+ exemestane in MBC and prior progression on CDK4/6 inhibitors
- 104 patients enrolled (25 phase I and 79 phase II)

Table 2. Best Overall Response[a]

	Total Patients (n = 95)
CBR at week 24, n (%) [95% CI][b]	39 (41.1) [31.1-51.6]
ORR, n (%) [95% CI][c]	8 (8.4) [3.7-15.9]
Best overall response, n (%)	
CR	1 (1.1)
PR	7 (7.4)
SD	47 (49.5)
PD	32 (33.7)
Non-CR/non-PD, n (%)	3 (3.2)
DCR, n (%) [95% CI][d]	58 (61.1) [50.5-70.9]



Bardia A et al, Clin Cancer Res 2021

Conclusions

CDK4/6 inhibitors and PI3k Inhibitors play a Key role in MBC

The optimal sequential strategy today is unknown and few data are available in PI3k Inhibitors post CDK4/6 progressions

Lack of predictors markers of response is important and sudies evaluating this factors remain crucial

Grazie per la attenzione