

Supplementary Material

Supplementary Table 1. Results for the use of mTOR and PI3K inhibitors in hormone sensitive metastatic breast cancer, modified from [64]

Substance	Inhibition	Phase	N	combination partners	clinical benefit
Everolimus (BOLERO-2)	mTOR	III	724	exemestane	PFS: 10.6 months versus 4.1 months OS: no significant benefit [65]
Tamoxifen (TAMRAD)	mTOR	II	111	tamoxifen	TTP: 8.6 months versus 4.5 months [66]
Ridaforolimus	mTOR	II / random.	80	dalotuzumab / exemestane	PFS not significant ¹ HR 1.18; 80%-CI:0.8-1.72; (p=0.565) [67]
BKM120 (Burparlisib)	PI3K class I (pan)	Ib	51	letrozole	Clinical benefit rate: 31% [68]
BKM120 (Burparlisib)	PI3K class I (pan)	I	31	fulvestrant	evidence for antitumor activity [69]
GDC 0941 (Pictilisip) FERGIE-Trial	PI3K class I (pan)	II / Random.	168	fulvestrant	PFS: 6.6 months versus 5.1 months [70] ² more benefit for ER/PR positive tumors
BYL719	PI3K selective (class 1, α)	I	64	fulvestrant stratified for PI3K mutations	evidence for antitumor activity [71] ³
BYL719	PI3K selective (class 1, α)	I	14	letrozol or exemestane	evidence for antitumor activity [72]

¹ 23.3 weeks (with Ridaforolimus) versus 31.9 weeks.

² not statistically significant; PIK3CA-mutations were not predictive for response.

³ partial remissions were only seen in patients with PIK3CA-mutations.

Supplementary Material

Supplementary Table 2. Active studies with CDK4/6 inhibitors in metastatic breast cancer

Agent	Phase	Regimen	Patients (Planned Enrollment, N)
Palbociclib (PD0332991)	phase 3 (PALOMA-2) (NCT01740427)	palbociclib+LET vs LET+PBO	ER+, HER2- MBC (450)
	phase 2 (INGE-B) (Eudract 2015-001603- 32)	palbociclib + LET vs letrozole	ER+, HER2- MBC with- out previous endocrine treatment for MBC (120)
LEE011	phase 3 (MONALEESA-2) (NCT01958021)	LEE011+LET vs LET+PBO	ER+, HER2- MBC without previous treatment for MBC (500)
	phase 1/2 (NCT01857193)	LEE011+EVE+EXE	ER+, HER2- MBC or LABC resistant towards LET or ANA (185)
	phase 1/2 (NCT01872260)	LEE011+BYL719+LET	ER+ MBC or LABC (130)
Abemaciclib (LY2835219)	phase 3 (MONARCH-2) NCT02107703	abemaciclib+FUL vs FUL	ER+, HER2- MBC (no previous endocrine therapy or progression on previous therapy with AI or TAM) (550)

(MBC: metastatic breast cancer; LET: letrozole, PBO: placebo; FUL: fulvestrant; ANA: anastrozole; EVE: everolimus; AI: aromatase inhibitor; TAM: tamoxifen; EXE: exemestan; LABC: locally advanced breast cancer)

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Supplementary Material

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Supplementary Material

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Supplementary Material

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