SUPPLEMENTARY MATERIAL

Title: "Endocrine therapy-based treatments in hormone receptor-positive/HER2-negative advanced breast cancer: Systematic Review and Network Meta-analysis"

Supplementary Methods

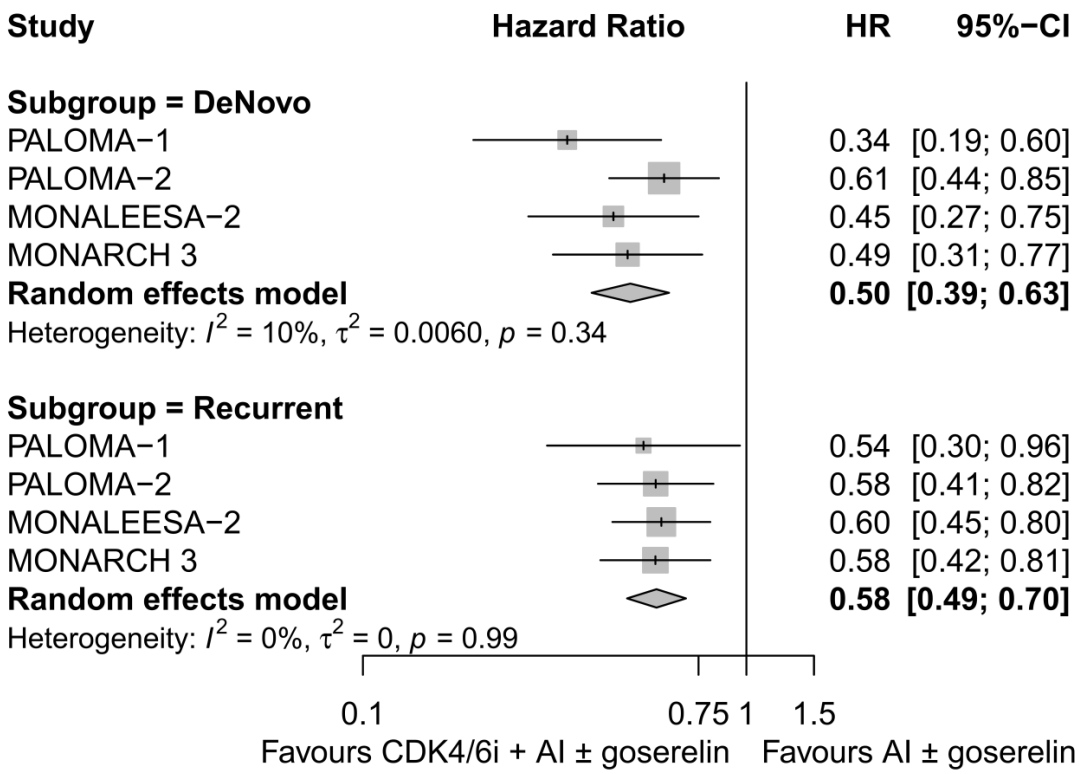
Searches covering the periods from inception of the database to 15th October 2019)

Search strategy used in **MEDLINE**:

("breast cancer" OR "breast neoplasm" OR "breast tumor" OR "breast tumors" OR "breast tumour" OR "breast tumours" OR "Breast Neoplasms"[MeSH]) AND ("metastatic" OR "advanced" OR "palliative" OR "relapsed") AND ("hormone receptor positive" OR "endocrine receptor positive" OR "endocrine receptor" OR "hormone receptor" OR "estrogen receptor" OR "oestrogen receptor" OR "progesterone receptor" OR "ER-positive" OR "ER+" OR "HR+" OR "HR-positive") AND ("endocrine therapy" OR "hormone therapy" OR "tamoxifen" OR "toremifene" OR "megestrol" OR "letrozole" OR "anastrozole" OR "fulvestrant" OR "exemestane" OR "aromatase inhibitors" OR "selective estrogen receptor degraders" OR "SERDs" OR "Abemaciclib" OR "palbociclib" OR "ribociclib" OR "cyclin-dependent kinase 4/6 inhibitors" OR "CDK4/6 inhibitors" OR "everolimus" OR "temsirolimus" OR "mammalian target of rapamycin inhibitors" OR "mTOR inhibitors" OR "phosphatidylinositol 3-kinase inhibitors" OR "PI3K inhibitors" OR "alpelisib" OR "taselisib" OR "buparlisib" OR "bevacizumab" OR "antiangiogenic agents") AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])

Brandão M, *et al. ESMO Open* 2020; 5:e000842. doi: 10.1136/esmoopen-2020-000842

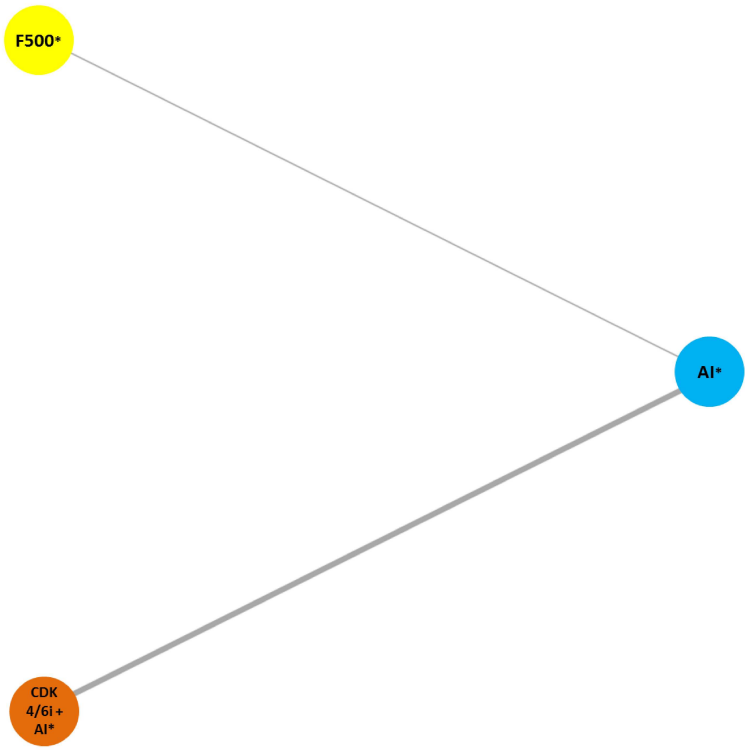
Supplementary Figure 1 – Frequentist pairwise meta-analysis forest plot of the comparison of CDK4/6 inhibitors (CDK4/6i) + aromatase inhibitors (AI) ± goserelin *vs* AI ± goserelin in endocrine-sensitive patients with *de novo* or recurrent metastatic disease.



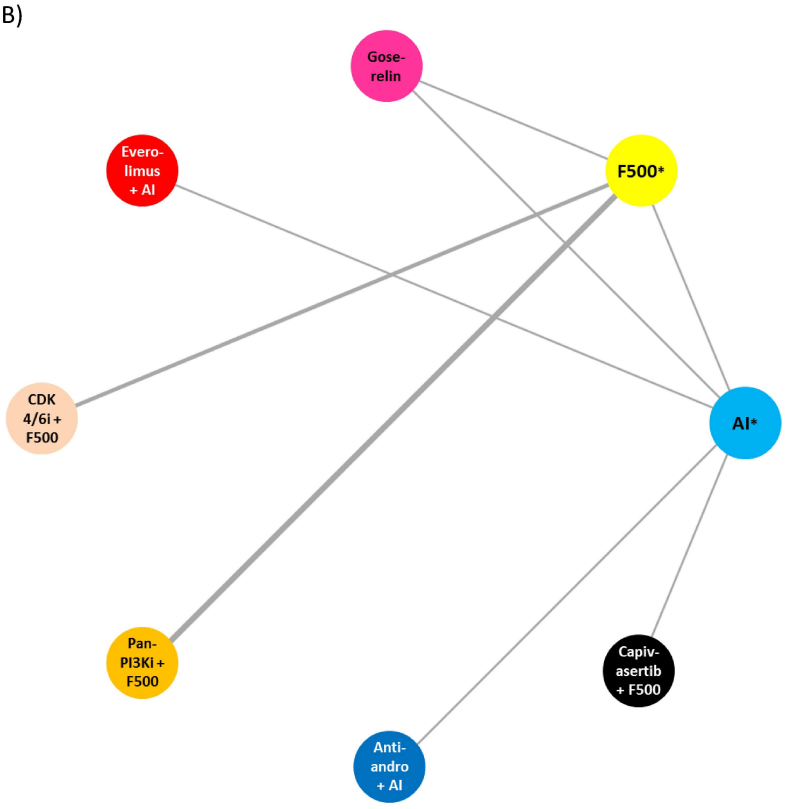
HR: hazard ratio; 95% CI: 95% confidence interval.

Supplementary Figure 2 – Network plots of progression-free survival subgroup analysis in patients with visceral disease in the (A) endocrine-sensitive and (B) endocrine-resistant settings.

A)

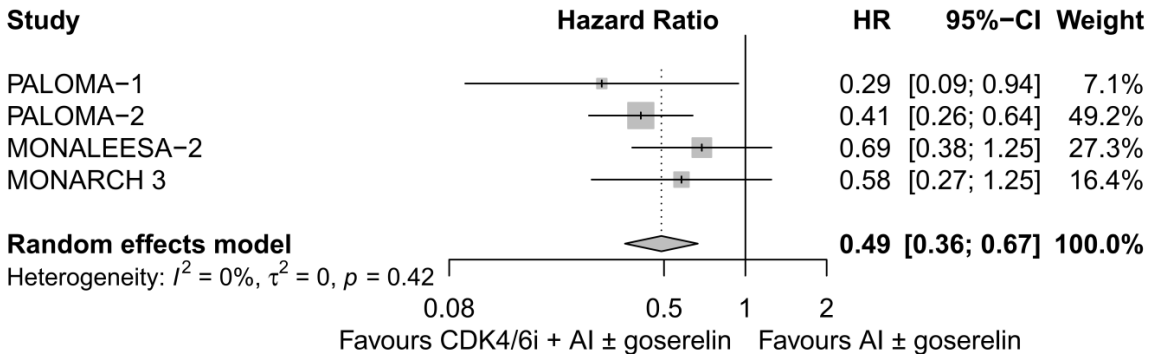


B)



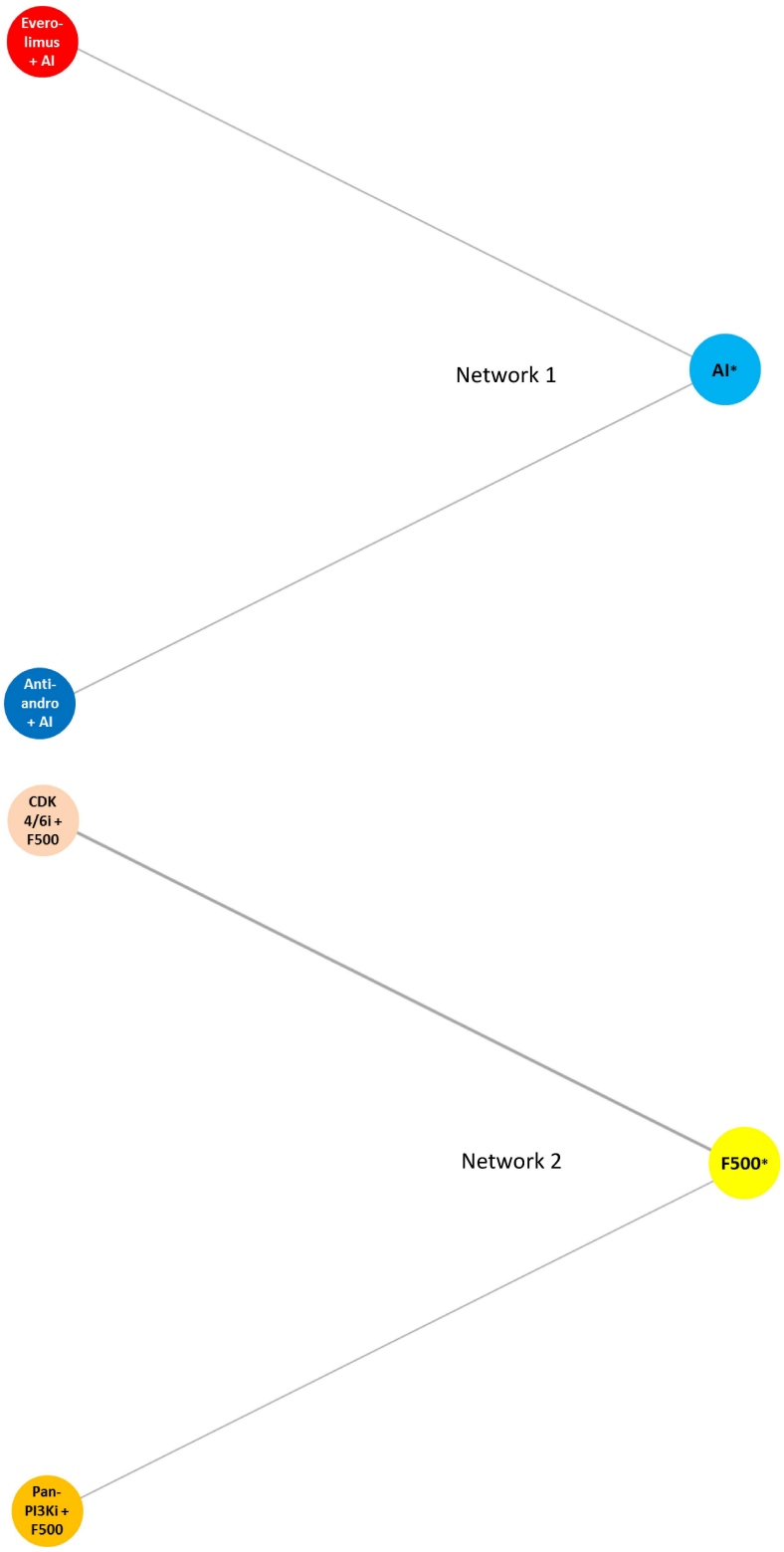
*± goserelin. AI: aromatase inhibitor; anti-andro: anti-androgen agent; CDK4/6i: CDK4/6 inhibitor; F500: fulvestrant 500 mg; pan-PI3Ki: pan-PI3K inhibitor.

Supplementary Figure 3 – Frequentist pairwise meta-analysis forest plot of the comparison of CDK4/6 inhibitors (CDK4/6i) + aromatase inhibitors (AI) ± goserelin *vs* AI ± goserelin in endocrine-sensitive patients with bone-only disease.



HR: hazard ratio; 95% CI: 95% confidence interval.

Supplementary Figure 4 – Two network plots of progression-free survival subgroup analyses in endocrine-resistant patients with bone-only disease.



*± goserelin. AI: aromatase inhibitor; anti-andro: anti-androgen agent; CDK4/6i: CDK4/6 inhibitor; F500: fulvestrant 500 mg; pan-PI3Ki: pan-PI3K inhibitor.

Supplementary Table 1 – Cochrane Risk of Bias Evaluation of the included studies in the systematic review

Trial name / first author, publication year	RISK OF BIAS EVALUATION AREAS						
	Allocation Sequence	Allocation Conceal	Doubled Blinded	Outcome Blind	Incomplete Outcome	Selective Reporting	Other sources of bias
Ibrahim et al, 2011[1]	Unclear risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Unclear risk[b]
SWOG S0226, 2012[2]	Unclear risk	Unclear risk	High risk	High risk	Low risk	Low risk	High risk[c]
Paul et al[a], 2013[3]	Unclear risk	Unclear risk	High risk	High risk	Unclear risk	Unclear risk	Unclear risk[a]
PALOMA-1, 2015[4–6]	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk	Low risk
PALOMA-2, 2016[7–10]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk[d]
MONALEESA-2, 2016[11–14]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk[d]
FALCON, 2016[15–17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
MINT, 2016[18]	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk
MONARCH 3, 2017[19,20]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk[d]
MONALEESA-7, 2018[21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk[d]
TAMRAD, 2012[22]	Unclear risk	Unclear risk	High risk	High risk	Low risk	High risk	Low risk
BOLERO-2, 2012[23–27]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk[d]
SoFEA, 2013[28]	Low risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Low risk
CALGB 40302, 2014[29]	Unclear risk	Unclear risk	High risk	High risk	Low risk	Low risk	Unclear risk[d]
SAKK21/08, 2015[30]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk[e]
Adelson et al, 2015[31]	Unclear risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Low risk
PALOMA-3, 2015[10,32–34]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk[d]
O'Shaughnessy et al, 2016[35]	Unclear risk	Unclear risk	High risk	High risk	Low risk	Low risk	Low risk
FERGI, 2016[36]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk[d]
BELLE-2, 2017[37,38]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk[d,f]
MONARCH 2, 2017[20,39]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk[d]
Musolino et al, 2017[40]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk[d]
Zhao et al, 2017[41]	Unclear risk	Unclear risk	High risk	High risk	Unclear risk	Unclear risk	Low risk
MANTA, 2019[42]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
PrE0102, 2018[43]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk[d]
BELLE-3, 2018[44]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk[d,f]
ACE, 2019[45]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Unclear risk[e]
FAKTION[a], 2019[46]	Unclear risk	Unclear risk	high risk	High risk	Low risk	Low risk	Unclear risk
EGF30008, 2009[47]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk	Unclear risk[d]
Krop et al[a], 2017[48]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk[a]
KCSG BR10-04 / FLAG, 2018[49]	Unclear risk	Unclear risk	High risk	High risk	Low risk	Low risk	Low risk
MONALEESA-3, 2018[50]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk[d]

[a] Results published only in meeting abstracts (without a full publication).

[b] Interim analysis should have been triggered after the randomization of the first 31 patients, but the study was stopped only after 110 patients were randomized.

[c] Crossover biasing the overall survival analysis.

[d] Though the trial is placebo controlled, the very specific toxicity profile associated with the targeted agent being tested could lead investigators to infer what arm the patient was on and bias assessments and decision-making during trial participation.

[e] Inappropriate definition of intention-to-treat population.

[f] Buparlisib has the potential for adverse events of emotional/psychological nature that are very hard to accurately grade, which can bias safety reporting.

Supplementary Table 2 – Rankograms and SUCRA values for all strategies in endocrine-sensitive (ES) patients, both for progression-free survival and overall survival.

Progression-free survival												Overall survival				
RANK 10	**RANK 9**	**RANK 8**	**RANK 7**	**RANK 6**	**RANK 5**	**RANK 4**	**RANK 3**	**RANK 2**	**RANK 1**	**SUCRA**	**RANK**	**SUCRA**	**RANK 1**	**RANK 2**	**RANK 3**	**RANK 4**
<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	0.1%	0.6%	3.0%	16.4%	80.0%	**97.3%**	**CDK4/6i + F500**	**91.0%**	78.6%	17.0%	3.2%	1.2%
<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	0.4%	8.1%	74.5%	17.1%	**89.8%**	**CDK4/6i + AI***	**78.6%**	20.7%	54.3%	24.5%	0.5%
<0.1%	0.4%	1.6%	4.6%	12.3%	23.5%	31.0%	26.4%	0.3%	<0.1%	**61.8%**	**F500***	**57.3%**	0.7%	26.2%	51.3%	21.8%
<0.1%	0.3%	1.0%	4.6%	14.0%	28.1%	31.6%	20.0%	0.4%	<0.1%	**60.6%**	**F250 + AI**	N/A	N/A	N/A	N/A	N/A
2.0%	4.9%	8.3%	9.1%	12.1%	15.7%	17.6%	25.1%	4.2%	1.1%	**55.6%**	**Anti-andro + AI**	N/A	N/A	N/A	N/A	N/A
14.3%	13.2%	15.0%	7.5%	9.7%	9.6%	10.1%	14.5%	4.2%	1.8%	**40.6%**	**AS1402 + AI**	N/A	N/A	N/A	N/A	N/A
1.1%	5.0%	14.4%	26.0%	30.1%	16.1%	5.9%	1.5%	<0.1%	<0.1%	**39.8%**	**Lapatinib + AI**	N/A	N/A	N/A	N/A	N/A
1.3%	9.3%	35.5%	37.8%	13.9%	2.1%	<0.1%	<0.1%	<0.1%	<0.1%	**28.9%**	**AI***	**14.1%**	<0.1%	2.5%	21.0%	76.5%
16.4%	43.1%	17.9%	8.1%	6.5%	4.1%	2.4%	1.5%	<0.1%	<0.1%	**19.4%**	**Sapat 40 mg + AI**	N/A	N/A	N/A	N/A	N/A
64.8%	23.8%	6.4%	2.3%	1.5%	0.7%	0.4%	0.1%	<0.1%	<0.1%	**6.3%**	**Sapat 20 mg + AI**	N/A	N/A	N/A	N/A	N/A

*± goserelin. AI: aromatase inhibitor; CDK4/6i: CDK4/6 inhibitor; F250: fulvestrant 250 mg; F500: fulvestrant 500 mg; N/A: not applicable; sapat: sapatinib. SUCRA: Surface Under the Cumulative Ranking curve values.

Supplementary Table 3A – Rankograms and SUCRA values for all strategies in endocrine-resistant (ER) patients, for progression-free survival.

		Progression-free survival																			
RANK	**SUCRA**	**RANK 1**	**RANK 2**	**RANK 3**	**RANK 4**	**RANK 5**	**RANK 6**	**RANK 7**	**RANK 8**	**RANK 9**	**RANK 10**	**RANK 11**	**RANK 12**	**RANK 13**	**RANK 14**	**RANK 15**	**RANK 16**	**RANK 17**	**RANK 18**	**RANK 19**	**RANK 20**
CDK4/6i + F500	**95.7%**	43.5%	36.8%	14.6%	4.1%	0.8%	0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%
Capivasertib + F500	**88.7%**	25.0%	20.6%	18.9%	13.7%	8.5%	5.4%	3.6%	2.4%	1.3%	0.4%	0.2%	0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%
Everolimus + F500	**86.1%**	8.5%	17.0%	25.2%	22.7%	14.0%	7.3%	3.7%	1.1%	0.4%	0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%
MultiTKI + F500	**78.0%**	11.8%	10.3%	12.5%	13.0%	10.7%	9.2%	8.8%	8.0%	6.8%	4.4%	1.9%	1.1%	0.5%	0.3%	0.2%	0.2%	0.2%	0.1%	0.1%	<0.1%
Everolimus + AI	**75.4%**	7.3%	7.5%	10.5%	11.8%	11.4%	10.3%	10.7%	10.5%	10.6%	9.3%	0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%
Bortezomib + F500	**73.9%**	3.5%	6.0%	10.5%	12.9%	13.2%	12.8%	11.9%	11.3%	9.0%	4.7%	1.9%	1.0%	0.4%	0.3%	0.2%	0.2%	0.1%	0.1%	0.1%	<0.1%
Pan-PI3Ki + F500	**72.6%**	<0.1%	0.2%	2.3%	9.2%	20.6%	26.9%	22.6%	12.5%	4.5%	0.8%	0.3%	0.1%	0.0%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%
Vistus. int + F500	**70.4%**	0.4%	1.4%	4.6%	9.8%	14.4%	16.7%	19.1%	17.9%	8.7%	3.8%	1.5%	0.8%	0.4%	0.2%	0.2%	0.1%	0.1%	0.1%	<0.1%	<0.1%
Vistus. cont + F500	**60.6%**	<0.1%	<0.1%	0.5%	1.7%	4.4%	8.3%	14.1%	22.7%	23.8%	12.8%	5.5%	2.7%	1.2%	0.7%	0.5%	0.4%	0.3%	0.3%	0.2%	0.1%
F500*	**51.5%**	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	0.1%	1.0%	5.9%	22.1%	43.3%	13.7%	7.0%	2.8%	1.5%	0.9%	0.6%	0.6%	0.4%	0.2%	0.1%
Tucidinostat + AI	**46.4%**	<0.1%	0.1%	0.2%	0.5%	1.0%	1.4%	2.2%	3.5%	5.8%	9.0%	32.7%	25.4%	10.3%	4.1%	1.9%	0.9%	0.6%	0.3%	0.1%	<0.1%
Lapatinib + AI	**43.3%**	<0.1%	0.1%	0.2%	0.5%	0.8%	1.1%	1.8%	2.9%	4.6%	7.2%	24.7%	26.4%	13.3%	6.4%	3.6%	2.4%	1.7%	1.2%	0.7%	0.3%
Anti-androgen + AI	**25.5%**	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	0.1%	0.2%	0.3%	0.5%	0.8%	2.8%	7.5%	15.8%	15.7%	13.0%	11.9%	11.3%	10.8%	7.3%	2.2%
AI*	**23.3%**	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	0.1%	0.2%	0.9%	6.4%	17.4%	24.5%	23.1%	16.0%	8.2%	2.7%	0.4%
F250 + AI	**23.1%**	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	0.1%	0.2%	0.3%	0.6%	1.7%	5.1%	11.9%	13.8%	14.3%	14.7%	14.3%	11.8%	7.9%	3.3%
Goserelin	**22.0%**	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	0.1%	0.2%	0.4%	0.8%	6.4%	9.1%	12.8%	9.3%	7.8%	7.4%	7.9%	9.8%	14.1%	13.9%
Lapatinib + F250	**18.6%**	<0.1%	<0.1%	<0.1%	<0.1%	0.1%	0.1%	0.1%	0.2%	0.5%	0.8%	2.4%	4.9%	8.6%	8.9%	8.8%	9.3%	11.5%	14.4%	16.7%	12.8%
F250	**17.4%**	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	0.1%	0.2%	0.5%	1.5%	4.5%	8.7%	11.6%	14.8%	18.3%	20.1%	14.6%	5.0%
Anti-andro (single)	**14.5%**	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	0.1%	0.2%	0.3%	1.0%	2.4%	5.2%	7.4%	7.9%	9.1%	11.1%	14.8%	21.7%	18.9%
Metformin + AI	**13.0%**	<0.1%	<0.1%	<0.1%	<0.1%	0.1%	0.2%	0.2%	0.4%	0.6%	0.8%	2.6%	4.2%	5.9%	5.3%	4.6%	5.0%	6.0%	7.8%	13.5%	42.8%

Supplementary Table 3B – Rankograms and SUCRA values for all strategies in endocrine-resistant patients, for overall survival.

	Overall survival												
RANK	**SUCRA**	**RANK 1**	**RANK 2**	**RANK 3**	**RANK 4**	**RANK 5**	**RANK 6**	**RANK 7**	**RANK 8**	**RANK 9**	**RANK 10**	**RANK 11**	**RANK 12**
CDK4/6i + F500	**69.9%**	4.6%	20.8%	21.4%	12.2%	9.1%	10.3%	11.6%	7.4%	2.3%	0.3%	0.0%	0.0%
Capivasertib + F500	**84.7%**	48.3%	17.6%	7.8%	5.8%	5.5%	5.7%	3.6%	2.3%	1.7%	1.1%	0.5%	0.1%
Everolimus + F500	**22.7%**	0.5%	1.3%	2.0%	2.6%	3.6%	7.1%	5.3%	5.6%	7.9%	12.6%	27.2%	24.5%
MultiTKI + F500	**60.0%**	15.2%	15.1%	8.7%	7.8%	7.6%	7.4%	6.9%	6.4%	6.6%	8.0%	7.0%	3.2%
Everolimus + AI	**71.8%**	15.0%	18.7%	14.7%	10.9%	9.5%	10.7%	10.8%	6.0%	2.4%	1.0%	0.3%	0.0%
Bortezomib + F500	**N/A**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pan-PI3Ki + F500	**55.7%**	0.5%	3.9%	13.8%	18.3%	11.2%	9.8%	11.7%	14.7%	11.9%	3.4%	0.7%	0.1%
Vistus. int + F500	**N/A**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Vistus. cont + F500	**N/A**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
F500*	**37.8%**	0.0%	0.0%	0.4%	5.7%	15.3%	10.9%	9.0%	11.6%	17.6%	21.2%	7.5%	0.9%
Tucidinostat + AI	**N/A**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lapatinib + AI	**N/A**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Anti-androgen + AI	**N/A**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
AI*	**57.5%**	0.9%	7.5%	14.3%	14.1%	11.9%	10.7%	13.1%	14.4%	9.4%	3.2%	0.5%	0.0%
F250 + AI	**49.9%**	2.4%	5.5%	8.7%	11.2%	10.7%	9.5%	10.3%	12.3%	13.8%	10.5%	4.3%	0.8%
Goserelin	**10.4%**	0.1%	0.3%	0.5%	0.6%	0.9%	2.0%	2.9%	3.4%	4.8%	8.7%	22.4%	53.4%
Lapatinib + F250	**N/A**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
F250	**31.3%**	0.1%	0.6%	1.4%	4.6%	8.2%	8.8%	8.0%	9.4%	14.0%	20.1%	17.7%	7.0%
Anti-andro (single)	**N/A**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Metformin + AI	**48.4%**	12.4%	8.6%	6.3%	6.2%	6.5%	7.1%	6.9%	6.4%	7.7%	10.0%	11.8%	10.0%

*± goserelin. AI: aromatase inhibitor; CDK4/6i: CDK4/6 inhibitor; cont: continuous; F250: fulvestrant 250 mg; F500: fulvestrant 500 mg; int: intermittent; multiTKI: multi-tyrosine kinase inhibitor; N/A: not applicable; pan-PI3Ki: pan-PI3K inhibitor; SUCRA: Surface Under the Cumulative Ranking curve values; vistus.: vistusertib.

Supplementary Table 4 – Rankograms and SUCRA values for all strategies in endocrine-sensitive and endocrine-resistant patients with visceral disease, for progression-free survival.

Endocrine-sensitive visceral disease					Endocrine-resistant visceral disease								
RANK 3	**RANK 2**	**RANK 1**	**SUCRA**	**RANK**	**SUCRA**	**RANK 1**	**RANK 2**	**RANK 3**	**RANK 4**	**RANK 5**	**RANK 6**	**RANK 7**	**RANK 8**
N/A	N/A	N/A	**N/A**	**CDK4/6i + F500**	**94.7%**	78.2%	10.5%	7.8%	3.2%	0.3%	<0.1%	<0.1%	<0.1%
0.1%	2.9%	97.0%	**98.4%**	**CDK4/6i + AI***	**N/A**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	**N/A**	**Everolimus + AI**	**71.3%**	11.8%	24.2%	28.7%	23.5%	10.3%	1.3%	0.1%	<0.1%
N/A	N/A	N/A	**N/A**	**Pan-PI3Ki + F500**	**70.1%**	0.1%	46.9%	17.4%	19.2%	12.7%	3.1%	0.7%	<0.1%
N/A	N/A	N/A	**N/A**	**Anti-androgen + AI**	**63.1%**	9.7%	16.8%	21.5%	22.7%	18.9%	8.3%	2.1%	0.1%
49.1%	47.9%	3.0%	**27.0%**	**F500***	**40.0%**	<0.1%	<0.1%	18.2%	14.2%	23.1%	25.2%	12.8%	6.6%
N/A	N/A	N/A	**N/A**	**Tucidinostat + AI**	**37.9%**	0.2%	1.5%	6.1%	15.0%	26.3%	35.7%	14.5%	0.8%
N/A	N/A	N/A	**N/A**	**Goserelin**	**13.4%**	<0.1%	0.1%	0.4%	2.0%	5.7%	16.3%	33.7%	41.9%
50.8%	49.2%	<0.1%	**24.6%**	**AI***	**9.4%**	<0.1%	<0.1%	<0.1%	0.3%	2.7%	10.0%	36.2%	50.7%

*± goserelin. AI: aromatase inhibitor; CDK4/6i: CDK4/6 inhibitor; F500: fulvestrant 500 mg SUCRA: Surface Under the Cumulative Ranking curve values; pan-PI3Ki: pan-PI3K inhibitor.

Supplementary Table 5 – Comparisons between treatments (Hazard Ratio, 95% Credibility Interval) for progression-free survival in endocrine-sensitive (row *vs* column) and endocrine-resistant (column *vs* row) patients with visceral disease.

Progression-free survival, HR (95% CrI) – endocrine-sensitive visceral disease	Progression-free survival, HR (95% CrI) – endocrine-resistant visceral disease								
Treatments	**AI***	**Goserelin**	**Tucidinos-tat + AI**	**F500***	**Anti-andro + AI**	**Everolimus + AI**	**Pan-PI3Ki + F500**	**CDK4/6i + AI***	**CDK4/6i + F500**
AI*		0.97 (0.51-1.82)	0.69 (0.50-0.96)	0.65 (0.29-1.47)	**0.51 (0.33-0.81)**	**0.47 (0.37-0.60)**	0.45 (0.20-1.04)	-	**0.31 (0.13-0.72)**
Goserelin	-		0.71 (0.35-1.46)	0.67 (0.34-1.34)	0.53 (0.24-1.15)	**0.49 (0.25-0.96)**	0.47 (0.23-0.95)	-	**0.32 (0.16-0.65)**
Tucidinos-tat + AI	-	-		0.95 (0.39-2.27)	0.74 (0.42-1.30)	0.68 (0.45-1.02)	0.66 (0.27-1.61)	-	0.45 (0.18-1.11)
F500*	1.00 (0.61-1.66)	-	-		0.78 (0.31-2.00)	0.72 (0.31-1.69)	**0.70 (0.60-0.80)**	-	**0.48 (0.39-0.58)**
Anti-andro + AI	-	-	-	-		0.92 (0.55-1.54)	0.89 (0.34-2.28)	-	0.61 (0.23-1.57)
Everolimus + AI	-	-	-	-	-		0.97 (0.41-2.30)	-	0.66 (0.28-1.58)
Pan-PI3Ki + F500	-	-	-	-	-	-		-	**0.68 (0.53-0.88)**
CDK4/6i + AI*	**0.58 (0.44-0.76)**	-	-	0.59 (0.34-1.04)	-	-	-		-
CDK4/6i + F500	-	-	-	-	-	-	-	-	

Treatments in the cells closer to the upper-right corner of the table are usually better than treatments in the cells closer to the upper-left corner. Cells in bold: statistically significant difference.

*± goserelin. Treatment abbreviations: AI: aromatase inhibitor; anti-andro: anti-androgen agent; CDK4/6i: CDK4/6 inhibitor; F500: fulvestrant 500 mg; pan-PI3Ki: pan-PI3K inhibitor.

Supplementary Table 6 – Rankograms and SUCRA values for all strategies in endocrine-resistant patients with bone-only disease, for progression-free survival, in the two networks.

Network 1	**Endocrine-resistant bone-only disease**			
RANK	**SUCRA**	**RANK 1**	**RANK 2**	**RANK 3**
Everolimus + AI	**100.0%**	100.0%	0.0%	0.0%
AI*	**49.0%**	<0.1%	98.1%	1.9%
Anti-androgen + AI	**1.0%**	<0.1%	1.9%	98.1%
Network 2	**Endocrine-resistant bone-only disease**			
RANK	**SUCRA**	**RANK 1**	**RANK 2**	**RANK 3**
CDK4/6i + F500	**80.3%**	63.1%	34.3%	2.6%
Pan-PI3Ki + F500	**63.3%**	36.3%	54.0%	9.7%
F500*	**6.5%**	0.6%	11.7%	87.7%

*± goserelin. AI: aromatase inhibitor; CDK4/6i: CDK4/6 inhibitor; F500: fulvestrant 500 mg; pan-PI3Ki: pan-PI3K inhibitor. SUCRA: Surface Under the Cumulative Ranking curve values.

Supplementary Table 7: Comparisons between treatments (Hazard Ratio, 95% Credibility Interval) for progression-free survival (column *vs* row) in endocrine-resistant patients with bone-only disease, in the two networks.

Network 1:

	Progression-free survival, HR (95% CrI) – endocrine-resistant bone-only disease		
Treatments	**Anti-andro + AI**	**AI***	**Everolimus + AI**
Anti-andro + AI		**0.48 0.24-0.96)**	**0.16 (0.07-0.36)**
AI*			**0.33 (0.21-0.52)**
Everolimus + AI			

Network 2:

	Progression-free survival, HR (95% CrI) – endocrine-resistant bone-only disease		
	F500*	**Pan-PI3Ki + F500**	**CDK4/6i + F500**
F500*		0.66 (0.31-1.39)	0.58 (0.34-1.03)
Pan-PI3Ki + F500			0.88 (0.35-2.23)
CDK4/6i + F500			

Treatments in the cells closer to the upper-right corner of the table are usually better than treatments in the cells closer to the upper-left corner. Cells in bold: statistically significant difference.

*± goserelin. AI: aromatase inhibitor; anti-andro: anti-androgen agent; CDK4/6i: CDK4/6 inhibitor; F500: fulvestrant 500 mg; pan-PI3Ki: pan-PI3K inhibitor.

References

1. Ibrahim NK, Yariz KO, Bondarenko I, et al. Randomized phase II trial of letrozole plus anti-MUC1 antibody AS1402 in hormone receptor-positive locally advanced or metastatic breast cancer. *Clin Cancer Res*. 2011;17(21):6822-6830. doi:10.1158/1078-0432.CCR-11-1151

2. Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. *N Engl J Med*. 2012;367(5):435-444. doi:10.1056/NEJMoa1201622

3. Paul D, Vukelja SJ, Holmes FA, et al. Abstract S3-07: Letrozole plus dasatinib improves progression-free survival (PFS) in hormone receptor-positive, HER2-negative postmenopausal metastatic breast cancer (MBC) patients receiving first-line aromatase inhibitor (AI) therapy. *Cancer Res*. 2013;73(24 Supplement):S3-07-S3-07. doi:10.1158/0008-5472.SABCS13-S3-07

4. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol*. 2015;16(1):25-35. doi:10.1016/S1470-2045(14)71159-3

5. Finn RS, Crown JP, Ettl J, et al. Efficacy and safety of palbociclib in combination with letrozole as first-line treatment of ER-positive, HER2-negative, advanced breast cancer: expanded analyses of subgroups from the randomized pivotal trial PALOMA-1/TRIO-18. *Breast Cancer Res BCR*. 2016;18(1):67. doi:10.1186/s13058-016-0721-5

6. Finn RS, Crown J, Lang I, et al. Overall survival results from the randomized phase II study of palbociclib (P) in combination with letrozole (L) vs letrozole alone for frontline treatment of ER+/HER2– advanced breast cancer (PALOMA-1; TRIO-18). *J Clin Oncol*. 2017;35(15_suppl):1001-1001. doi:10.1200/JCO.2017.35.15_suppl.1001

7. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. *N Engl J Med*. 2016;375(20):1925-1936. doi:10.1056/NEJMoa1607303

8. Finn RS, Dieras V, Rugo HS, et al. Palbociclib (PAL) + letrozole (L) as first-line (1L) therapy (tx) in estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC): Efficacy and safety across patient (pt) subgroups. *J Clin Oncol*. 2017;35(15_suppl):1039-1039. doi:10.1200/JCO.2017.35.15_suppl.1039

9. Rugo H, Finn R, Dieras V, et al. Abstract P5-21-03: Palbociclib (PAL) + letrozole (LET) as first-line therapy in estrogen receptor–positive (ER+)/human epidermal growth factor receptor 2–negative (HER2−) advanced breast cancer (ABC): Efficacy and safety updates with longer follow-up across patient subgroups. *Cancer Res*. 2018;78:P5-21. doi:10.1158/1538-7445.SABCS17-P5-21-03

10. Turner NC, Finn RS, Martin M, et al. Clinical considerations of the role of palbociclib in the management of advanced breast cancer patients with and without visceral metastases. *Ann Oncol*. 2018;29(3):669-680. doi:10.1093/annonc/mdx797

11. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med*. 2016;375(18):1738-1748. doi:10.1056/NEJMoa1609709

12. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol*. 2018;29(7):1541-1547. doi:10.1093/annonc/mdy155

13. O'Shaughnessy J, Petrakova K, Sonke GS, et al. Ribociclib plus letrozole versus letrozole alone in patients with de novo HR+, HER2- advanced breast cancer in the randomized MONALEESA-2 trial. *Breast Cancer Res Treat*. 2018;168(1):127-134. doi:10.1007/s10549-017-4518-8

14. Burris HA, Chan A, Campone M, et al. Abstract P4-22-16: First-line ribociclib + letrozole in patients with HR+, HER2– advanced breast cancer (ABC) presenting with visceral metastases or bone-only disease: A subgroup analysis of the MONALEESA-2 trial. *Cancer Res*. 2017;77(4 Supplement):P4-22-16-P4-22-16. doi:10.1158/1538-7445.SABCS16-P4-22-16

15. Robertson JFR, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. *Lancet*. 2016;388(10063):2997-3005. doi:10.1016/S0140-6736(16)32389-3

16. Robertson JFR, Noguchi S, Shao Z, Grinsted LM, Fazal M, Ellis MJ. Abstract P2-08-02: Progression-free survival results in patient subgroups from a Phase 3 randomized trial of fulvestrant 500 mg vs anastrozole for hormone receptor-positive advanced breast cancer (FALCON). *Cancer Res*. 2017;77(4 Supplement):P2-08-02-P2-08-02. doi:10.1158/1538-7445.SABCS16-P2-08-02

17. Robertson JFR, Leo AD, Fazal M, Lichfield J, Ellis MJ. Abstract PD5-09: Fulvestrant for hormone receptor-positive advanced breast cancer in patients with visceral vs non-visceral metastases: Findings from FALCON, FIRST, and CONFIRM. *Cancer Res*. 2018;78(4 Supplement):PD5-09-PD5-09. doi:10.1158/1538-7445.SABCS17-PD5-09

18. Johnston S, Basik M, Hegg R, et al. Inhibition of EGFR, HER2, and HER3 signaling with AZD8931 in combination with anastrozole as an anticancer approach: Phase II randomized study in women with endocrine-therapy-naïve advanced breast cancer. *Breast Cancer Res Treat*. 2016;160(1):91-99. doi:10.1007/s10549-016-3979-5

19. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. *J Clin Oncol*. 2017;35(32):3638-3646. doi:10.1200/JCO.2017.75.6155

20. Leo AD, Dickler M, Sledge GW, et al. Abstract P5-21-02: Efficacy and safety of abemaciclib in patients with liver metastases in the MONARCH 1, 2, and 3 studies. *Cancer Res*. 2018;78(4 Supplement):P5-21-02-P5-21-02. doi:10.1158/1538-7445.SABCS17-P5-21-02

21. Tripathy D, Im S-A, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol*. 2018;19(7):904-915. doi:10.1016/S1470-2045(18)30292-4

22. Bachelot T, Bourgier C, Cropet C, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. *J Clin Oncol*. 2012;30(22):2718-2724. doi:10.1200/JCO.2011.39.0708

23. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2012;366(6):520-529. doi:10.1056/NEJMoa1109653

24. Campone M, Bachelot T, Gnant M, et al. Effect of visceral metastases on the efficacy and safety of everolimus in postmenopausal women with advanced breast cancer: subgroup analysis from the BOLERO-2 study. *Eur J Cancer*. 2013;49(12):2621-2632. doi:10.1016/j.ejca.2013.04.011

25. Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. *Adv Ther*. 2013;30(10):870-884. doi:10.1007/s12325-013-0060-1

26. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†. *Ann Oncol*. 2014;25(12):2357-2362. doi:10.1093/annonc/mdu456

27. Beck JT, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane as first-line therapy in HR^+, $HER2^-$ advanced breast cancer in BOLERO-2. *Breast Cancer Res Treat*. 2014;143(3):459-467. doi:10.1007/s10549-013-2814-5

28. Johnston SR, Kilburn LS, Ellis P, et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. *Lancet Oncol*. 2013;14(10):989-998. doi:10.1016/S1470-2045(13)70322-X

29. Burstein HJ, Cirrincione CT, Barry WT, et al. Endocrine Therapy With or Without Inhibition of Epidermal Growth Factor Receptor and Human Epidermal Growth Factor Receptor 2: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Fulvestrant With or Without Lapatinib for Postmenopausal Women With Hormone Receptor–Positive Advanced Breast Cancer—CALGB 40302 (Alliance). *J Clin Oncol*. 2014;32(35):3959-3966. doi:10.1200/JCO.2014.56.7941

30. Zaman K, Winterhalder R, Mamot C, et al. Fulvestrant with or without selumetinib, a MEK 1/2 inhibitor, in breast cancer progressing after aromatase inhibitor therapy: a multicentre randomised placebo-controlled double-blind phase II trial, SAKK 21/08. *Eur J Cancer*. 2015;51(10):1212-1220. doi:10.1016/j.ejca.2015.03.016

31. Adelson K, Ramaswamy B, Sparano JA, et al. Randomized phase II trial of fulvestrant alone or in combination with bortezomib in hormone receptor-positive metastatic breast cancer resistant to aromatase inhibitors: a New York Cancer Consortium trial. *NPJ Breast Cancer*. 2016;2:16037. doi:10.1038/npjbcancer.2016.37

32. Turner NC, Ro J, André F, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. *N Engl J Med*. 2015;373(3):209-219. doi:10.1056/NEJMoa1505270

33. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol*. 2016;17(4):425-439. doi:10.1016/S1470-2045(15)00613-0

34. Turner NC, Slamon DJ, Ro J, et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. *N Engl J Med*. 2018;15(379):1926-1936. doi:10.1056/NEJMoa1810527

35. O'Shaughnessy J, Campone M, Brain E, et al. Abiraterone acetate, exemestane or the combination in postmenopausal patients with estrogen receptor-positive metastatic breast cancer. *Ann Oncol*. 2016;27(1):106-113. doi:10.1093/annonc/mdv487

36. Krop IE, Mayer IA, Ganju V, et al. Pictilisib for oestrogen receptor-positive, aromatase inhibitor-resistant, advanced or metastatic breast cancer (FERGI): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2016;17(6):811-821. doi:10.1016/S1470-2045(16)00106-6

37. Baselga J, Im S-A, Iwata H, et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(7):904-916. doi:10.1016/S1470-2045(17)30376-5

38. Campone M, Im S-A, Iwata H, et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant for postmenopausal, hormone receptor-positive, human epidermal growth factor receptor 2-negative, advanced breast cancer: Overall survival results from BELLE-2. *Eur J Cancer*. 2018;103:147-154. doi:10.1016/j.ejca.2018.08.002

39. Sledge GW, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. *J Clin Oncol*. 2017;35(25):2875-2884. doi:10.1200/JCO.2017.73.7585

40. Musolino A, Campone M, Neven P, et al. Phase II, randomized, placebo-controlled study of dovitinib in combination with fulvestrant in postmenopausal patients with HR+, HER2- breast cancer that had progressed during or after prior endocrine therapy. *Breast Cancer Res BCR*. 2017;19(1):18. doi:10.1186/s13058-017-0807-8

41. Zhao Y, Gong C, Wang Z, et al. A randomized phase II study of aromatase inhibitors plus metformin in pre-treated postmenopausal patients with hormone receptor positive metastatic breast cancer. *Oncotarget*. 2017;8(48):84224-84236. doi:10.18632/oncotarget.20478

42. Schmid P, Zaiss M, Harper-Wynne C, et al. Fulvestrant Plus Vistusertib vs Fulvestrant Plus Everolimus vs Fulvestrant Alone for Women With Hormone Receptor-Positive Metastatic Breast Cancer: The MANTA Phase 2 Randomized Clinical Trial. *JAMA Oncol*. August 2019. doi:10.1001/jamaoncol.2019.2526

43. Kornblum N, Zhao F, Manola J, et al. Randomized Phase II Trial of Fulvestrant Plus Everolimus or Placebo in Postmenopausal Women With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy: Results of PrE0102. *J Clin Oncol*. 2018;36(16):1556-1563. doi:10.1200/JCO.2017.76.9331

44. Di Leo A, Johnston S, Lee KS, et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2018;19(1):87-100. doi:10.1016/S1470-2045(17)30688-5

45. Jiang Z, Li W, Hu X, et al. Tucidinostat plus exemestane for postmenopausal patients with advanced, hormone receptor-positive breast cancer (ACE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(6):806-815. doi:10.1016/S1470-2045(19)30164-0

46. Jones RH, Carucci M, Casbard AC, et al. Capivasertib (AZD5363) plus fulvestrant versus placebo plus fulvestrant after relapse or progression on an aromatase inhibitor in metastatic ER-positive breast cancer (FAKTION): A randomized, double-blind, placebo-controlled, phase II trial. *J Clin Oncol*. 2019;37(15_suppl):1005-1005. doi:10.1200/JCO.2019.37.15_suppl.1005

47. Johnston S, Pippen J, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol*. 2009;27(33):5538-5546. doi:10.1200/JCO.2009.23.3734

48. Krop I, Abramson V, Colleoni M, et al. Abstract GS4-07: Results from a randomized placebo-controlled phase 2 trial evaluating exemestane ± enzalutamide in patients with hormone receptor–positive breast cancer. *Cancer Res*. 2018;78(4 Supplement):GS4-07-GS4-07. doi:10.1158/1538-7445.SABCS17-GS4-07

49. Kim J-Y, Im S-A, Jung KH, et al. Fulvestrant plus goserelin versus anastrozole plus goserelin versus goserelin alone for hormone receptor-positive, HER2-negative tamoxifen-pretreated premenopausal women with recurrent or metastatic breast cancer (KCSG BR10-04): a multicentre, open-label, three-arm, randomised phase II trial (FLAG study). *Eur J Cancer*. 2018;103:127-136. doi:10.1016/j.ejca.2018.08.004

50. Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: MONALEESA-3. *J Clin Oncol*. 2018;36(24):2465-2472. doi:10.1200/JCO.2018.78.9909