

Supplement Section S1: summary and pictorial representation of our search strategy across databases

S1.1.MEDLINE

Search number	Query	Sort By	Filters	Search Details	Results	Time
19	((((((((breast cancer*[MeSH Terms]) OR (breast tumor*[MeSH Terms]) OR (breast neoplasm[MeSH Terms]) OR (breast carcinoma[MeSH Terms]) OR (breast tumour[MeSH Terms]) AND (((((metastatic[Text Word]) OR (palliative[Text Word]) OR (advance*[Text Word]) OR (relapse*[Text Word])) AND (((((((hormone receptor[Text Word]) OR (hormone receptor positive[Text Word]) OR (endocrine receptor positive[Text Word]) OR (endocrine receptor[Text Word]) OR (estrogen receptor positive[Text Word]) OR (estrogen receptor[Text Word]) OR (ER positive[Text Word]) OR (progesterone receptor[Text Word]) OR (progesterone receptor positive[Text Word]) OR (PR positive[Text Word])) AND (((((((drug therapy[MeSH Terms]) OR (immunotherapy[MeSH Terms]) OR (((((((((((citrates, tamoxifen[MeSH Terms]) OR (anastrozole[MeSH Terms]) OR (letrozole[MeSH Terms]) OR (exemestane[Supplementary Concept]) OR (toremifene[MeSH Terms]) OR (endocrine therapy[Text Word]) OR (hormone therapy[Text Word]) OR (selective estrogen receptor modulator[MeSH Terms]) OR (SERD[Text Word]) OR (SERM[Text Word]) OR (selective estrogen receptor downregulator[Text Word]) OR (fulvestrant[MeSH Terms])) OR (((Phosphoinositide-3 Kinase Inhibitors[MeSH Terms]) OR (Alpelisib[Supplementary Concept]) OR (Taselisib[Supplementary Concept])) OR ((MTOR Inhibitors[MeSH Terms]) OR (everolimus[MeSH Terms])) OR ((Angiogenesis Inhibitors[MeSH Terms]) OR (Bevacizumab[MeSH Terms])) OR (Antineoplastic	Publication Date	Randomized Controlled Trial	(("breast cancer*[MeSH Terms] OR ("breast"[MeSH Terms] OR "breast"[All Fields] OR "breasts"[All Fields] OR "breast s"[All Fields]) AND "tumor*[MeSH Terms] OR "breast neoplasms"[MeSH Terms] OR "breast neoplasms"[MeSH Terms] OR "breast neoplasms"[MeSH Terms] AND ("metastatic"[Text Word] OR "palliative"[Text Word] OR "advance*[Text Word] OR "relapse*[Text Word]) AND ("hormone receptor"[Text Word] OR "hormone receptor positive"[Text Word] OR "endocrine receptor positive"[Text Word] OR "endocrine receptor"[Text Word] OR "estrogen receptor positive"[Text Word] OR "estrogen receptor"[Text Word] OR "er positive"[Text Word] OR "progesterone receptor"[Text Word] OR "progesterone receptor positive"[Text Word] OR "pr positive"[Text Word]) AND ("drug therapy"[MeSH Terms] OR "immunotherapy"[MeSH Terms] OR ("tamoxifen"[MeSH Terms] OR "anastrozole"[MeSH Terms] OR "letrozole"[MeSH Terms] OR "exemestane"[Supplementary Concept] OR "toremifene"[MeSH Terms] OR "endocrine therapy"[Text Word] OR "hormone therapy"[Text Word] OR "selective estrogen receptor modulators"[MeSH Terms] OR "SERD"[Text Word] OR "SERM"[Text Word] OR "selective estrogen receptor downregulator"[Text Word] OR "fulvestrant"[MeSH Terms] OR ("phosphoinositide 3 kinase inhibitors"[MeSH Terms] OR "alpelisib"[Supplementary Concept] OR "2 3 2 1 isopropyl 3 methyl 1h 1 2 4 triazol 5 yl 5 6 dihydrobenzo f imidazo 1 2 d 1 4 oxazepin 9 yl 1h pyrazol 1 yl 2 methylpropanamide"[Supplementary Concept]) OR ("mtor inhibitors"[MeSH Terms] OR "everolimus"[MeSH Terms] OR ("angiogenesis inhibitors"[MeSH Terms] OR "bevacizumab"[MeSH Terms] OR "antineoplastic agents"[MeSH Terms] OR ("cyclin dependent kinase inhibitor proteins"[MeSH Terms] OR "palbociclib"[Supplementary Concept] OR "abemaciclib"[Supplementary Concept] OR "ribociclib"[Supplementary	626	09:58:14

	Agents[MeSH Terms])) OR ((((Cyclin-Dependent Kinase Inhibitor Proteins[MeSH Terms]) OR (palbociclib[Supplementary Concept])) OR (abemaciclib[Supplementary Concept])) OR (ribociclib[Supplementary Concept]))			Concept])) AND (randomizedcontrolledtrial[Filter])		
18	((((((((breast cancer*[MeSH Terms]) OR (breast tumor*[MeSH Terms])) OR (breast neoplasm[MeSH Terms])) OR (breast carcinoma[MeSH Terms])) OR (breast tumour[MeSH Terms])) AND (((((metastatic[Text Word]) OR (palliative[Text Word])) OR (advance*[Text Word])) OR (relapse*[Text Word])))) AND ((((((((hormone receptor[Text Word]) OR (hormone receptor positive[Text Word])) OR (endocrine receptor positive[Text Word])) OR (endocrine receptor[Text Word])) OR (estrogen receptor positive[Text Word])) OR (estrogen receptor[Text Word])) OR (ER positive[Text Word])) OR (progesterone receptor[Text Word])) OR (progesterone receptor positive[Text Word])) OR (PR positive[Text Word])))) AND (((((((drug therapy[MeSH Terms]) OR (immunotherapy[MeSH Terms])) OR (((((((citrate, tamoxifen[MeSH Terms]) OR (anastrozole[MeSH Terms])) OR (letrozole[MeSH Terms])) OR (exemestane[Supplementary Concept])) OR (toremifene[MeSH Terms])) OR (endocrine therapy[Text Word])) OR (hormone therapy[Text Word])) OR (selective estrogen receptor modulator[MeSH Terms])) OR (SERD[Text Word])) OR (SERM[Text Word])) OR (selective estrogen receptor downregulator[Text Word])) OR (fulvestrant[MeSH Terms])) OR (((Phosphoinositide-3 Kinase Inhibitors[MeSH Terms]) OR (Alpelisib[Supplementary Concept])) OR (Taselisib[Supplementary Concept])) OR ((MTOR Inhibitors[MeSH Terms]) OR (everolimus[MeSH Terms])) OR ((Angiogenesis Inhibitors[MeSH Terms]) OR (Bevacizumab[MeSH Terms])) OR (Antineoplastic Agents[MeSH Terms])) OR ((((Cyclin-Dependent Kinase Inhibitor Proteins[MeSH Terms]) OR (palbociclib[Supplementary	Publication Date		("breast cancer*[MeSH Terms] OR (("breast"[MeSH Terms] OR "breast"[All Fields] OR "breasts"[All Fields] OR "breast s"[All Fields]) AND "tumor*[MeSH Terms]) OR "breast neoplasms"[MeSH Terms] OR "breast neoplasms"[MeSH Terms] OR "breast neoplasms"[MeSH Terms] AND ("metastatic"[Text Word] OR "palliative"[Text Word] OR "advance*[Text Word] OR "relapse*[Text Word]) AND ("hormone receptor"[Text Word] OR "hormone receptor positive"[Text Word] OR "endocrine receptor positive"[Text Word] OR "endocrine receptor"[Text Word] OR "estrogen receptor positive"[Text Word] OR "estrogen receptor"[Text Word] OR "er positive"[Text Word] OR "progesterone receptor"[Text Word] OR "progesterone receptor positive"[Text Word] OR "pr positive"[Text Word]) AND ("drug therapy"[MeSH Terms] OR "immunotherapy"[MeSH Terms] OR ("tamoxifen"[MeSH Terms] OR "anastrozole"[MeSH Terms] OR "letrozole"[MeSH Terms] OR "exemestane"[Supplementary Concept] OR "toremifene"[MeSH Terms] OR "endocrine therapy"[Text Word] OR "hormone therapy"[Text Word] OR "selective estrogen receptor modulators"[MeSH Terms] OR "SERD"[Text Word] OR "SERM"[Text Word] OR "selective estrogen receptor downregulator"[Text Word] OR "fulvestrant"[MeSH Terms]) OR ("phosphoinositide 3 kinase inhibitors"[MeSH Terms] OR "alpelisib"[Supplementary Concept] OR "2 3 2 1 isopropyl 3 methyl 1h 1 2 4 triazol 5 yl 5 6 dihydrobenzo f imidazo 1 2 d 1 4 oxazepin 9 yl 1h pyrazol 1 yl 2 methylpropanamide"[Supplementary Concept]) OR ("mtor inhibitors"[MeSH Terms] OR "everolimus"[MeSH Terms]) OR ("angiogenesis inhibitors"[MeSH Terms] OR "bevacizumab"[MeSH Terms]) OR "antineoplastic agents"[MeSH Terms] OR ("cyclin dependent kinase inhibitor proteins"[MeSH Terms] OR "palbociclib"[Supplementary Concept] OR "abemaciclib"[Supplementary Concept] OR "ribociclib"[Supplementary Concept]))	4,910	09:58:04

	Concept])) OR (abemaciclib[Supplementary Concept])) OR (ribociclib[Supplementary Concept]))					
17	(((((((drug therapy[MeSH Terms]) OR (immunotherapy[MeSH Terms])) OR (((((((((citrate, tamoxifen[MeSH Terms]) OR (anastrozole[MeSH Terms])) OR (letrozole[MeSH Terms])) OR (exemestane[Supplementary Concept])) OR (toremifene[MeSH Terms])) OR (endocrine therapy[Text Word])) OR (hormone therapy[Text Word])) OR (selective estrogen receptor modulator[MeSH Terms])) OR (SERD[Text Word])) OR (SERM[Text Word])) OR (selective estrogen receptor downregulator[Text Word])) OR (fulvestrant[MeSH Terms])) OR (Phosphoinositide-3 Kinase Inhibitors[MeSH Terms]) OR (Alpelisib[Supplementary Concept])) OR (Taselisib[Supplementary Concept])) OR ((MTOR Inhibitors[MeSH Terms]) OR (everolimus[MeSH Terms])) OR ((Angiogenesis Inhibitors[MeSH Terms]) OR (Bevacizumab[MeSH Terms])) OR (Antineoplastic Agents[MeSH Terms]) OR (Cyclin-Dependent Kinase Inhibitor Proteins[MeSH Terms]) OR (palbociclib[Supplementary Concept])) OR (abemaciclib[Supplementary Concept])) OR (ribociclib[Supplementary Concept]))	Publication Date		"drug therapy"[MeSH Terms] OR "immunotherapy"[MeSH Terms] OR "tamoxifen"[MeSH Terms] OR "anastrozole"[MeSH Terms] OR "letrozole"[MeSH Terms] OR "exemestane"[Supplementary Concept] OR "toremifene"[MeSH Terms] OR "endocrine therapy"[Text Word] OR "hormone therapy"[Text Word] OR "selective estrogen receptor modulators"[MeSH Terms] OR "SERD"[Text Word] OR "SERM"[Text Word] OR "selective estrogen receptor downregulator"[Text Word] OR "fulvestrant"[MeSH Terms] OR "phosphoinositide 3 kinase inhibitors"[MeSH Terms] OR "alpelisib"[Supplementary Concept] OR "2 3 2 1 isopropyl 3 methyl 1h 1 2 4 triazol 5 yl 5 6 dihydrobenzo f imidazo 1 2 d 1 4 oxazepin 9 yl 1h pyrazol 1 yl 2 methylpropanamide"[Supplementary Concept] OR "mtor inhibitors"[MeSH Terms] OR "everolimus"[MeSH Terms] OR "angiogenesis inhibitors"[MeSH Terms] OR "bevacizumab"[MeSH Terms] OR "antineoplastic agents"[MeSH Terms] OR "cyclin dependent kinase inhibitor proteins"[MeSH Terms] OR "palbociclib"[Supplementary Concept] OR "abemaciclib"[Supplementary Concept] OR "ribociclib"[Supplementary Concept]	21,66,524	09:57:49
16	(((((((breast cancer*[MeSH Terms]) OR (breast tumor*[MeSH Terms])) OR (breast neoplasm[MeSH Terms])) OR (breast carcinoma[MeSH Terms])) OR (breast tumour[MeSH Terms])) AND (((((metastatic[Text Word]) OR (palliative[Text Word])) OR (advance*[Text Word])) OR (relapse*[Text Word])) AND (((((((((hormone receptor[Text Word]) OR (hormone receptor positive[Text Word])) OR (endocrine receptor positive[Text Word])) OR (endocrine receptor[Text Word])) OR (estrogen receptor positive[Text Word])) OR (estrogen receptor[Text Word])) OR (ER positive[Text Word])) OR (progesterone receptor[Text Word])) OR (progesterone	Publication Date		("breast cancer*[MeSH Terms] OR ("breast"[MeSH Terms] OR "breast"[All Fields] OR "breasts"[All Fields] OR "breast s"[All Fields]) AND "tumor*[MeSH Terms] OR "breast neoplasms"[MeSH Terms] OR "breast neoplasms"[MeSH Terms] OR "breast neoplasms"[MeSH Terms] AND ("metastatic"[Text Word] OR "palliative"[Text Word] OR "advance*[Text Word] OR "relapse*[Text Word]) AND ("hormone receptor"[Text Word] OR "hormone receptor positive"[Text Word] OR "endocrine receptor positive"[Text Word] OR "endocrine receptor"[Text Word] OR "estrogen receptor positive"[Text Word] OR "estrogen receptor"[Text Word] OR "er positive"[Text Word] OR "progesterone receptor"[Text Word] OR "progesterone receptor positive"[Text Word] OR "pr positive"[Text Word])	8,466	09:56:58

	receptor positive[Text Word])) OR (PR positive[Text Word]))))					
15	((((Cyclin-Dependent Kinase Inhibitor Proteins[MeSH Terms]) OR (palbociclib[Supplementary Concept])) OR (abemaciclib[Supplementary Concept])) OR (ribociclib[Supplementary Concept]))	Publication Date		"cyclin dependent kinase inhibitor proteins"[MeSH Terms] OR "palbociclib"[Supplementary Concept] OR "abemaciclib"[Supplementary Concept] OR "ribociclib"[Supplementary Concept]	28,157	09:56:20
14	Antineoplastic Agents[MeSH Terms]	Publication Date		"antineoplastic agents"[MeSH Terms]	4,74,792	09:54:48
13	(Angiogenesis Inhibitors[MeSH Terms]) OR (Bevacizumab[MeSH Terms])	Publication Date		"angiogenesis inhibitors"[MeSH Terms] OR "bevacizumab"[MeSH Terms]	34,178	09:53:55
12	(MTOR Inhibitors[MeSH Terms]) OR (everolimus[MeSH Terms])	Publication Date		"mtor inhibitors"[MeSH Terms] OR "everolimus"[MeSH Terms]	5,572	09:53:01
11	((Phosphoinositide-3 Kinase Inhibitors[MeSH Terms]) OR (Alpelisib[Supplementary Concept])) OR (Taselisib[Supplementary Concept])	Publication Date		"phosphoinositide 3 kinase inhibitors"[MeSH Terms] OR "alpelisib"[Supplementary Concept] OR "2 3 2 1 isopropyl 3 methyl 1h 1 2 4 triazol 5 yl 5 6 dihydrobenzo f imidazo 1 2 d 1 4 oxazepin 9 yl 1h pyrazol 1 yl 2 methylpropanamide"[Supplementary Concept]	9,568	09:52:11
10	((phosphotidyl 3 kinase inhibitor[MeSH Terms]) OR (alpelisib[Supplementary Concept])) OR (taselisib[Supplementary Concept])	Publication Date		"alpelisib"[Supplementary Concept] OR "2 3 2 1 isopropyl 3 methyl 1h 1 2 4 triazol 5 yl 5 6 dihydrobenzo f imidazo 1 2 d 1 4 oxazepin 9 yl 1h pyrazol 1 yl 2 methylpropanamide"[Supplementary Concept]	207	09:50:46
9	((Phosphoinositide-3 Kinase Inhibitors[MeSH Terms]) OR (alpelisib[MeSH Terms])) OR (taselisib[MeSH Terms])	Publication Date		"phosphoinositide 3 kinase inhibitors"[MeSH Terms]	9,434	09:49:39
8	((((((((((citrate, tamoxifen[MeSH Terms]) OR (anastrozole[MeSH Terms])) OR (letrozole[MeSH Terms])) OR (exemestane[Supplementary Concept])) OR (toremifene[MeSH Terms])) OR (endocrine therapy[Text Word])) OR (hormone therapy[Text Word])) OR (selective estrogen receptor modulator[MeSH Terms])) OR (SERD[Text Word])) OR (SERM[Text Word])) OR (selective estrogen receptor downregulator[Text Word])) OR (fulvestrant[MeSH Terms]))	Publication Date		"tamoxifen"[MeSH Terms] OR "anastrozole"[MeSH Terms] OR "letrozole"[MeSH Terms] OR "exemestane"[Supplementary Concept] OR "toremifene"[MeSH Terms] OR "endocrine therapy"[Text Word] OR "hormone therapy"[Text Word] OR "selective estrogen receptor modulators"[MeSH Terms] OR "SERD"[Text Word] OR "SERM"[Text Word] OR "selective estrogen receptor downregulator"[Text Word] OR "fulvestrant"[MeSH Terms]	51,810	09:47:59
7	((((((((((endocrine therapy[Text Word]) OR (hormone therapy[Text Word])) OR (selective estrogen receptor modulator[MeSH Terms])) OR (tamoxifen[MeSH Terms])) OR (citrate, toremifene[MeSH Terms]))OR (anastrozole[MeSH Terms])) OR (letrozole[MeSH Terms])) OR (aromatase inhibitors[MeSH Terms])) OR (fulvestrant[MeSH Terms])) OR	Publication Date		"endocrine therapy"[Text Word] OR "hormone therapy"[Text Word] OR "selective estrogen receptor modulators"[MeSH Terms] OR "tamoxifen"[MeSH Terms] OR "toremifene"[MeSH Terms] OR "anastrozole"[MeSH Terms] OR "letrozole"[MeSH Terms] OR "aromatase inhibitors"[MeSH Terms] OR "fulvestrant"[MeSH Terms] OR "selective estrogen receptor downregulator"[Text Word] OR "SERD"[Text Word] OR	54,760	09:45:29

	(selective estrogen receptor downregulator[Text Word])) OR (SERD[Text Word])) OR (SERM[Text Word])) OR (exemestane[Supplementary Concept])			"SERM"[Text Word] OR "exemestane"[Supplementary Concept]		
6	(((((endocrine therapy[Text Word]) OR (hormone therapy[Text Word])) OR (selective estrogen receptor modulator[MeSH Terms])) OR (tamoxifen[MeSH Terms])) OR (citrate, toremifene[MeSH Terms])) OR (exemestane[MeSH Terms])) OR (anastrozole[MeSH Terms])) OR (letrozole[MeSH Terms])) OR (aromatase inhibitors[MeSH Terms])) OR (fulvestrant[MeSH Terms])) OR (selective estrogen receptor downregulator[Text Word])) OR (SERD[Text Word])) OR (SERM[Text Word])	Publication Date		"endocrine therapy"[Text Word] OR "hormone therapy"[Text Word] OR "selective estrogen receptor modulators"[MeSH Terms] OR "tamoxifen"[MeSH Terms] OR "toremifene"[MeSH Terms] OR "anastrozole"[MeSH Terms] OR "letrozole"[MeSH Terms] OR "aromatase inhibitors"[MeSH Terms] OR "fulvestrant"[MeSH Terms] OR "SERD"[Text Word] OR "SERM"[Text Word]	54,599	09:42:52
5	immunotherapy[MeSH Terms]	Publication Date		"immunotherapy"[MeSH Terms]	3,19,626	09:33:24
4	drug therapy[MeSH Terms]	Publication Date		"drug therapy"[MeSH Terms]	14,75,057	09:33:06
3	(((((hormone receptor[Text Word]) OR (hormone receptor positive[Text Word])) OR (endocrine receptor positive[Text Word])) OR (endocrine receptor[Text Word])) OR (estrogen receptor positive[Text Word])) OR (estrogen receptor[Text Word])) OR (ER positive[Text Word])) OR (progesterone receptor[Text Word])) OR (progesterone receptor positive[Text Word])) OR (PR positive[Text Word])	Publication Date		"hormone receptor"[Text Word] OR "hormone receptor positive"[Text Word] OR "endocrine receptor positive"[Text Word] OR "endocrine receptor"[Text Word] OR "estrogen receptor positive"[Text Word] OR "estrogen receptor"[Text Word] OR "er positive"[Text Word] OR "progesterone receptor"[Text Word] OR "progesterone receptor positive"[Text Word] OR "pr positive"[Text Word]	96,285	09:31:58
2	((metastatic[Text Word]) OR (palliative[Text Word])) OR (advance*[Text Word]) OR (relapse*[Text Word])	Publication Date		"metastatic"[Text Word] OR "palliative"[Text Word] OR "advance*[Text Word] OR "relapse*[Text Word]	14,22,626	09:30:04
1	((breast cancer*[MeSH Terms]) OR (breast tumor*[MeSH Terms])) OR (breast neoplasm[MeSH Terms])) OR (breast carcinoma[MeSH Terms])) OR (breast tumour[MeSH Terms])	Publication Date		"breast cancer*[MeSH Terms] OR ("breast"[MeSH Terms] OR "breast"[All Fields] OR "breasts"[All Fields] OR "breast s"[All Fields]) AND "tumor*[MeSH Terms] OR "breast neoplasms"[MeSH Terms] OR "breast neoplasms"[MeSH Terms] OR "breast neoplasms"[MeSH Terms]	3,59,552	09:29:23

S1.2. Embase

Embase

Search Embase Journals Results

Search tips

Default strategy: jcrs

Results: e.g. 4 items

Advanced search cancer jcrs 6 synonyms all

Interventions: e.g. insulin

☒ venous line therapy jcrs OR ☒ cyclin dependent kinase inhibitor jcrs 5 synonyms all OR ☒ palbocicb jcrs 19 synonyms all OR ☒ abiraterone jcrs 12 synonyms all OR ☒ ribocicb jcrs 16 synonyms all OR ☒ hormonal therapy jcrs 6 synonyms all OR ☒ letrozole jcrs OR ☒ anastrozole jcrs 16 synonyms all OR ☒ exemestane jcrs OR ☒ fulvestrant jcrs 16 synonyms all OR ☒ endoxifen jcrs 27 synonyms all OR ☒ maximal target of epigenetic inhibitor jcrs 5 synonyms all OR ☒ metformin jcrs 17 synonyms all OR ☒ pioglitazone jcrs 15 synonyms all OR ☒ chemotherapy jcrs 7 synonyms all OR ☒ immunotherapy jcrs 18 synonyms all OR ☒ alpelisib jcrs 12 synonyms all OR ☒ Akt signaling jcrs 34 synonyms all OR ☒ 27 synonyms of endoxifen all OR ☒ bevacizumab jcrs 147 synonyms all OR ☒ lapatinib jcrs 44 synonyms all OR ☒ selective estrogen receptor modulator jcrs 18 synonyms all OR ☒ selective estrogen receptor downregulator jcrs OR ☒ histone deacetylase jcrs 6 synonyms all OR ☒ vorinostat jcrs 16 synonyms all OR ☒ torsemide jcrs 9 synonyms all

Comparative: e.g. placebo

☒ placebo jcrs 1 synonyms all OR ☒ chemotherapy jcrs 7 synonyms all OR ☒ hormonal therapy jcrs 6 synonyms all OR ☒ letrozole jcrs 11 synonyms all OR ☒ anastrozole jcrs 16 synonyms all OR ☒ exemestane jcrs 11 synonyms all OR ☒ fulvestrant jcrs OR ☒ anastrozole jcrs 16 synonyms all OR ☒ endoxifen jcrs 27 synonyms all OR ☒ immunotherapy jcrs 18 synonyms all OR ☒ cyclin dependent kinase inhibitor jcrs 5 synonyms all OR ☒ palbocicb jcrs 19 synonyms all OR ☒ abiraterone jcrs 12 synonyms all OR ☒ ribocicb jcrs 16 synonyms all OR ☒ Akt signaling jcrs 34 synonyms all OR ☒ alpelisib jcrs OR ☒ selective estrogen receptor modulator jcrs 18 synonyms all OR ☒ selective estrogen receptor downregulator jcrs OR ☒ histone deacetylase jcrs 6 synonyms all OR ☒ vorinostat jcrs 16 synonyms all OR ☒ torsemide jcrs 9 synonyms all OR ☒ bc2 inhibitor jcrs

Outcomes: e.g. rct

☒ survival jcrs 1 synonyms all

Study design: e.g. randomised controlled trial

☒ randomised controlled trial jcrs 6 synonyms all

Limit to

Show 2,132 results

S1.3. Scopus

SCOPUS SEARCH-449 results

Keyword [Clear \(2\)](#)

- ☒ Limited to Human 449
- ☒ Limited to Humans 381
- ☐ Female 383
- ☐ Breast Neoplasms 371
- ☐ Breast Tumor 328
- ☐ Cyclin Dependent Kinase 4 274
- ☐ Antineoplastic Agent 268

[Show all](#)

{ TITLE-ABS-KEY (breast AND cancer OR breast AND neoplasm* OR breast AND carcinoma* OR breast AND tumo*r*) AND TITLE-ABS-KEY (metastatic OR palliative OR relapse* OR advance*) AND TITLE-ABS-KEY (hormone AND positive OR hormone AND receptor AND positive OR estrogen AND positive OR estrogen AND receptor AND positive OR progesterone AND positive OR progesterone AND receptor AND positive) AND TITLE-ABS-KEY (antineoplastic OR anticancer OR chemotherapy OR immunotherapy OR hormonal AND therapy OR cyclin AND dependent AND kinase AND inhibitor OR "PI3K/AKT/MTOR" OR antiangiogenic)) AND (LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "PHAR")) AND (LIMIT-TO (EXACTKEYWORD , "Human") OR LIMIT-TO (EXACTKEYWORD , "Humans")) }

- With limits of human/humans and medicine and pharmacology studies

Author name

Subject area [Clear \(2\)](#)

- ☒ Limited to Medicine 432
- ☒ Limited to Pharmacology, Toxicology and Pharmaceuticals 43
- ☐ Biochemistry, Genetics and Molecular Biology 240
- ☐ Nursing 8
- ☐ Health Professions 4
- ☐ Chemistry 2
- ☐ Immunology and Microbiology 2

[Show all](#)

S1.4. Cochrane

+

View fewer lines

Print search history

-	+	#1	MeSH descriptor: [Breast Neoplasms] explode all trees	MeSH	14801
-	+	#2	(hormone receptor positive):ti,ab,kw (Word variations have been searched)	S	Limits 4097
-	+	#3	(estrogen receptor positive):ti,ab,kw (Word variations have been searched)	S	Limits 2944
-	+	#4	progesterone receptor positive	Limits	1272
-	+	#5	estrogen receptor	Limits	5487
-	+	#6	progesterone receptor	Limits	2258
-	+	#7	ER positive	Limits	4470
-	+	#8	PR positive	Limits	3616
-	+	#9	hormone positive	Limits	10012
-	+	#10	metastatic	Limits	31755
-	+	#12	palliative	Limits	11009
-	+	#13	advance	Limits	87622
-	+	#14	hormonal therapy	Limits	36542
-	+	#15	selective estrogen receptor modulators	Limits	1030
-	+	#16	selective estrogen receptor downregulators	Limits	42
-	+	#17	tamoxifen	Limits	5258
-	+	#18	anastrozole	Limits	1327
-	+	#19	letrozole	Limits	2477
-	+	#20	exemestane	Limits	1006
-	+	#21	toremifene	Limits	222
-	+	#22	fulvestrant	Limits	934

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#23 cyclin dependent kinase inhibitors (Word variations have been searched)	Limits	445
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#24 cdk inhibitors (Word variations have been searched)	Limits	192
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#25 palbociclib (Word variations have been searched)	Limits	526
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#26 ribociclib (Word variations have been searched)	Limits	268
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#27 abemaciclib (Word variations have been searched)	Limits	255
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#28 chemotherapy (Word variations have been searched)	Limits	91517
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#29 MeSH descriptor: [Drug Therapy] explode all trees	MeSH ▾	148428
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#30 MeSH descriptor: [Antineoplastic Agents] explode all trees	MeSH ▾	13298
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#31 MeSH descriptor: [Immunotherapy] explode all trees	MeSH ▾	8777
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#32 MeSH descriptor: [Selective Estrogen Receptor Modulators] explode all trees	MeSH ▾	415
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#33 MeSH descriptor: [Angiogenesis Inhibitors] explode all trees	MeSH ▾	1360
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#34 MeSH descriptor: [Bevacizumab] explode all trees	MeSH ▾	2253
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#35 MeSH descriptor: [MTOR Inhibitors] explode all trees	MeSH ▾	1610

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#36 MeSH descriptor: [Everolimus] explode all trees	MeSH ▾	1637
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#37 MeSH descriptor: [Phosphoinositide-3 Kinase Inhibitors] explode all trees	MeSH ▾	29
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#38 alpelisib (Word variations have been searched)	Limits	111
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#39 taselisib (Word variations have been searched)	Limits	46
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#40 MeSH descriptor: [Histone Deacetylase Inhibitors] explode all trees	MeSH ▾	69
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#41 entinostat (Word variations have been searched)	Limits	64
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#42 buparlisib (Word variations have been searched)	Limits	67
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#43 #10 OR #11 CR #12 OR #13 (Word variations have been searched)	Limits	150908
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#44 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	Limits	14975
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#45 #14 OR #15 CR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 CR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 CR #36 OR #37 OR #38 OR #39 CR #40 OR #41 OR #42	Limits	323086
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	#46 #1 AND (OR #10-#13) AND (OR #2-#9) AND (OR #14-#42)	Limits	1106

Cochrane Reviews

59

Cochrane Protocols

0

Trials

1047

Editorials

0

Special Collections

0

Clinical Answers

0

More

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Supplemental tables

N o	Study	Pt Populatio n, N	Intervention	ORR/C BR	PFS	OS	AE	QoL/Co mments
1.	NCT034 01385 (TROPIO N- Pantum our01), phase II	HR+HER2- MBC post median 5 lines of therapy 95% had prior CDK 4/6i , n=41	Dato-DXD	29% /85%	-	-	15% had serious TEAEs	SABCS 2022 PD13-08, full paper awaited
2.	Coombe s et al ⁵⁸ , phase II,2022	HR+HER2- MBC post Ai and prior CDK 4/6i , n=31	Samuraciclib (CDK7 inh)	-/ 35%	-	-	Grade ≥ 3 diarrhea (19%), nausea(10%), vomitive (3%), fatigue(3%)	Full paper awaited
3.	Hamilto n et al ⁵⁹ , phase II	HR+HER2- MBC,85% CDK 4/6i exposed, 3 median lines of therapy, n=94	H3B-6545 (SERCA)	17% /32%	5.1m	-	Gr ≥ 2 anemia (19%), nausea (17%), fatigue (16%)diarrhea (12%), creatinine clearance dec(39%)lymp hopenia (37%), ALT/AST inc (14%)bilirubin inc (12%)	Full paper awaited
4.	Bardia et al 2021 ⁶⁰ (TRINITI) , phase I/II	HR+ HER2- MBC with PD after up to 3 lines of therapy incl CDK 4/6i, n=95	Ribociclib + exemestane + everolimus	8.4% /41%	5.7m	-	Gr ≥ 3 , Neutropenia(5 1%), Anemia (9.6%),hypergly cemia (6.7%), Hypophosphat emia (5.8%), stomatitis (2.9%)	-

5.	Seth et al ⁶¹ , 2022 (TAKTIC), Phase IB	HR+/HER2 - MBC; with PD on 1 st line; up to 2 prior lines of chemotherapy, 84% post CDK 4/6i, n=77(A-19/B-16/C-42)	Arms: A. Ipat+ AI B. Ipat+ fulv C. Ipat+ Fulv+ palbociclib	-/48%	5.5m	24.5m	Grade ≥3 neutropenia (50.6%), leukopenia (19.5%), diarrhea (14/3%), transaminitis (9.1%), lymphopenia (7.8%), rash (7.8%), and thrombocytopenia (3.9%)	Interim results
6.	AMEERA-1, phase I/II Part B ⁶² Part C and D ⁶³	HR+/HER2 - MBC, 1 CDK4/6i allowed, n=46 HR+/HER2 - MBC, CDK4/6i allowed, n=39	Amcenestrant(SAR439859-SERD) Amcenestrant + palbociclib	10.9% /28.3% 32.4% / 73.5%	-	-	Grade ≥3 ALT/AST inc(6.1%), fatigue(4%) Nausea, vomiting and diarrhea-2% each 56.4% gr≥3 neutropenia, no non hemat gr≥3 toxicities	Interim results, full paper awaited
7.	Kalinsky et al ⁶⁴ ,2022, phase I	HR+/HER2 - MBC, 1 CDK4/6i allowed in 68%	ZN-c5 (SERD)	-/31%	3.8m	-	Gr≥3: 2/56 GGT inc, hyponatremia (2/56); no Grade 4 TEAEs	Full paper awaited
8.	Schott et al ⁶⁵ , 2023, VERITAC study, phase I/II	HR+/HER2 - MBC, PD post CDk4/6i	ARV-471, PROTAC (Proteolysis Targeting Chimera) 200mg (n=35) 500mg (n=36)	- /37.1% - /38.9%	-	-	Gr≥3 TRAE in 7% cases overall	Full paper awaited
9.	Patel et al ⁶⁶ , 2022, Phase I/II	HR+/HER2 - MBC, 1 CDK4/6iex posed, n=40	OP-1250, (CERAN/SERD)	In the anticipated RP2D range, ORR-18% &	-	-	Gr ≥3 in 24.3% pts, Nausea and vomiting (2.7% each), neutropenia (8.1%)	Full paper awaited

				CBR-38%				
10.	Wesolowski et al ⁶⁷ , 2023, phase Ib/II	HR+ HER2-MBC exposed to CDK 4/6i post ≥2 lines of treatment (subset C & D), n= C32/ D 27	Gedatolisib (PI3K & mTOR inh) + palbociclib + fulvestrant	ORR C/D: 36% /63% No CBR	C/D: 5.1m/ 12.9m	-	Gr ≥3 in all subsets: neutropenia (63%), stomatitis (27%), rash (20%), fatigue (11%) and hyperglycemia (7%)	Full paper awaited
11.	Pistilli et al ⁶⁸ , 2020, phase II	HR+, HER2 low (IHC 1+/IHC 2+ with negative FISH) MBC post CDK 4/6i and <4 lines ET & <3 lines CT, n=48	Zenocutuzumab + ET (bispecific Ab targeting HER2 and HER3)	-/45%	-	-	Gr ≥3 Asthenia/fatigue (2%)	Full paper awaited
12.	Bardia et al ⁶⁹ , 2021, phase Ib	HR+, HER2-MBC post AI & CDK 4/6i (group 2, n=17)	Ribociclib + everolimus + exemestane	- /14.3%	1.9m	-	Gr ≥3 total (76.5%), Anemia, neutropenia (35.3%), Leucopenia (29.4%)	-
13.	Rugo et al ^{70,71} , BYLieve, phase II	PIK3CA-mutant, HR+, HER2-MBC PD on/after prior CDK4/6i combination therapy. Cohort A, n=127 Cohort B, n=126	Alpelisib + fulv (cohort A) Alpelisib + AI (cohort B)	A: 21% /55% B: 15.7% / 32.2%	A: 7.3 m B: 5.7 m	A: 17.3 m	Cohort A: Gr ≥ 3 AE hyperglycemia (28%), rash (9%), rash maculopapular (9%) & diarrhea (6%) Cohort B: hyperglycemia (25.4%), rash (9.5%), rash maculopapular (7.9%)	Non-comparative phase II study with 2 arms
14.	Albanell et	HR+, HER2-MBC PD	Palbociclib + different ET	- /34.4%	2.6m	-	Gr ≥3: All 51.6%,	-

	al ⁷² ,2023 . BioPER, phase II	on/after prior Palbociclib + ET, n=33. Two lines of prior ET and 1 line of CT allowed.					Neutropenia (42.4%),leucop enia (6.1%) anemia (3%)	
1 5.	Jhaveri et al ⁷³ , 2021, phase I/Ib	HR+, HER2– MBC, PD after ET. CDK 4/6i allowed in 49.2%, n=199 (A, B: 78 each C: 43) PI3K/AKT inh not allowed in arm C	A: LSZ102 (SERD) B: LSZ102 + ribociclib C: LSZ102 + Alpelisib	A: 1.3% /7.8% B: 16.9% /35.1 % C: 7% /20.9 %	A: 1.8m B: 6.2m C: 3.5m	-	Gi toxicity most common for all grades. For Gr≥3, were related to ribociclib in arm B(leukopenia, neutropenia, AST inc) and alpelisib in arm C(hyperglycem ia, rash and loss of appetite)	PFS similar whetHER exposed to CDK4/6i or not
1 6.	Lim et al ⁷⁴ , 2022, phase I/II	HR+, HER2– MBC, PD after ET. CDK 4/6i allowed in n=25/31 pts.	Lenvatinib + letrozole	20%/ 52% (expos ed to CDk4/ 6i)	-	-	-	-
1 7.	Mayer et al ⁷⁵ 2021, phase Ib	HR+, HER2– MBC, PD after CDK 4/6i with FGFR1-4 amplificati on, n=26	erdafitinib(pan FGFR TKI) + palbociclib + fulvestrant	-/28%	3m	-	Gr ≥3: FN(5%), colitis(3.8%), thromboembol ism(3.8%), elevation of transaminases(3.8%)	Better response with FGFR1 & FGFR3 amplifica tion
1 8.	Pimentel et al ⁷⁶ 2022, phase II. LUZERN study	HR+, HER2– MBC with gBRCAm (cohort A), gBRCA wild type /HRD(coh ort B),	Niraparib + AI	-	5.3m	-	50% had Gr≥3 neutropenia	Interim analysis

		83% post CDK 4/6i, n=6						
19.	Lim et al ⁷⁷ , 2020, Phase Ib	HR+, HER2- MBC, cohort A post CDK 4/6i n=39(cohort A)	GDC-9545 (SERD) ± LHRH agonist	-/55%	-	-	Cohort A: gr≥3 1 case each of fatigue, transaminase inc & diarrhea. Cohort B	-
20.	Schwartzberg et al ⁷⁸ 2021, CONTESA-2 ⁷⁹ , phase II	HR+, HER2- MBC, prior taxane not allowed, n=150, 52% are post CDK 4/6i	Tesetaxel (oral taxane) + reduced dose capecitabine	51%/-	12.9m	-	Gr ≥3: neutropenia (74.0%), leukopenia (10.7%), hypokalemia (7.3%), anemia (6.7%), hand-foot syndrome (6.0%) and diarrhea (5.3%), FN(4.7%), neuropathy(2%)	Data for CDK 4/6i exposed not available separately, full paper awaited
21.	Prat et al ⁸⁰ , 2023, TATEN trial, phase II	HR+/HER2-negative, PAM50 non-luminal MBC PD post CDK4/6i, no CT in metastatic setting n=15	Pembrolizumab and paclitaxel	53.3% / 86.6%	7.5m	-	Gr ≥3 AE in 53.3%	Interim results
22.	SUMMIT ⁸¹ , phase II basket trial	HR+ MBC with HER2 mutations, n=46(breast cancer cohort), 67% got prior CDK 4/6i	Neratinib + trastuzumab + fulvestrant	40% / 47%	8.3m	-	Gr 3 diarrhea (33%), no Gr 4 diarrhea	Ongoing study
23.	Damodaran et	HR+MBC PD post 1-	lasofoxifene +	33.3% /	13.9m	-	MC AE: diarrhea,	Ongoing study

	al ⁸² , 2022 ELAINE 2, Phase II	2 lines of ET, with a ESR1 mutation, n=29 (28 pts got CDK 4/6i in prior line)	abemaciclib	62.1%			nausea, and leukopenia 2 d/c tt due to AE	
2 4	Tao et al ⁸³ , 2023, phase II	HR+/HER2 -negative with PD on 1 st line palbociclib + AI, n=58	Palbociclib + fulvestrant	-	3.7m	-	-	Ongoing study
2 5.	Bedard et al ⁸⁴ , 2023, phase Ib/II(Simon 2 stage design)	HER2- MBC post >1 line of non taxane CT. 92% HR+ HER2- MBC 81% post CDK 4/6i	CFI-402257 (inhibitor of TTK protein kinase) +paclitaxel	8% / 54.6%		-	Gr≥3 neutropenia (83.5%), lymphopenia (41%) and anemia (14%), FN(8.1%), skin infection (2.7%)	Trial closed, did not meet prespecifi ed threshold for stage 2
2 6	Miller et al ⁸⁵ 2023, phase II	HR+ MBC post 2-4 lines of tt including a CDK 4/6i(arm A),n=60	praluzatamab ravtansine (CX- 2009)	14.9% / 40.4%	11.4w eeks	-	Gr≥3 ocular (15%), neuropathic(10 %)	Full paper awaited
2 7	Haddad et al ⁸⁶ , TBCRC 041 trial, phase II with 2 arms (that are not compare d to one another)	HR+ HER 2- MBC, PD on CDK 4/6i, n=	Alisertib + fulvestrant Alisertib	ORR:2 0% and 19.6% CBR: 28.95 v 41.3%	5.4m v 5.6m	19. 8m v 22. 7m	Neutropenia (42.2% v 43.4%), leukopenia (31.1% v 17.4%), and anemia (8.9% v 19.6%), lymphopenia (15.6% v 4%), fatigue (11.1% v 0%)	Although RCT, results reported as independ ent cohorts

Abbreviations:

AE, adverse events; AI, aromatase inhibitor; AKT, protein kinase B; ALT, alanine transaminase; AST, aspartate aminotransferase; CBR, clinical benefit rate; CDK 4/6i, cyclin dependent kinase 4/6 inhibitor; CERAN, Complete Estrogen Receptor Antagonist; CT, chemotherapy; Dato-DXD, Datopotamab deruxtecan; ET endocrine therapy; FGFR, fibroblast growth factor receptor; FN, febrile neutropenia; Fulv, fulvestrant; gBRCAm, germline breast cancer gene mutated; GGT, gamma-glutamyl transferase; Gr, grade; HER2-, human epidermal growth factor receptor 2 negative;HER3, human epidermal growth factor receptor 3; HR+, hormone receptor positive; HRD, homologous recombination deficiency; inc, increase; inh, inhibitor; Ipat, ipatasertib; LHRH, luteinizing hormone-releasing hormone; MBC, metastatic breast cancer; MC, most common; mTOR, Mammalian target of rapamycin; OR, odds ratio; ORR overall response rate; OS, overall survival; PD, progressive

disease; PI3KCA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression free survival, QoL, quality of life; SABCS, San Antonio breast cancer symposium; SERCA, Selective estrogen receptor covalent antagonist; SERD, selective estrogen receptor degraders; TEAE, treatment emergent adverse events; TKI, tyrosine kinase inhibitor; TRAE, treatment related adverse events; TTK threonine and tyrosine kinase

Table S1: Summary of prospective single-arm studies

Study	Phase and design	Intervention	control	Results	Comments
Sonnenblick et al, 2021 MORPHEUS ⁸⁷	Ib/II, 2L/3L HR+ MBC, exposed to CDK 4/6i, CT naive	Atezolizumab + Entinostat (n=15)	Fulvestrant (n= 14)	ORR 6.7% v 0% PFS 1.8m v 1.8m CBR 40.0% v 21.4%	PDL1 did not correlate with response.

Goetz et al ⁸⁸ , 2022 ELAINE 1	II, HR+/HER2-/ESR1 mutated MBC PD on AI plus CDK4/6i	Lasofloxifene (SERM) (n=52)	Fulvestrant (n=51)	PFS 6.04m v 4.04m; HR 0.7; 95% CI 0.45 to 1.13 ORR 13.2% vs 2.9%, p 0.12 CBR 36.5% v 21.6%,	All results statistically NS
Goetz et al ⁸⁹ , 2020	II, ER+ HER 2-MBC , PD post ET,CDK 4/6i allowed, tamoxifen not allowed	Endoxifen (n=40, 42.5% post CDK 4/6i)	Tamoxifen (n=37, 29.7% post CDK 4/6i)	PFS 130days v 42 days; HR 0.8; 95% CI 0.49 to 1.22, p 0.309	-
Jimenez et al ⁹⁰ 2022, acelERA trial	II, HR+ HER2-MBC for 2L/3L tt, CDK 4/6i allowed	Giredestrant (SERD) (n=151, 43% post CDK 4/6i)	ET (n=152,41% post CDK 4/6i)	PFS 5.6m v 5.4m; HR 0.8; 95% CI 0.6 to 1.1, p 0.18 ORR 13% v 7%	-
Mayer et al ⁹¹ , 2022, PACE trial	II, HR+/HER2-MBC, PD on AI and any CDK4/6i, only 1 line of CT allowed for MBC	Three arms with 1:2:1 randomisation: Fulvestrant + Palbociclib (FP) (n=111) Fulvestrant + Palbociclib + Avelumab (FPA) (n=54)	Fulvestrant(F) (n=55)	PFS of FP v F: 4.6m v 4.8 m; HR 1.11; 90% CI 0.79 to 1.5, p 0.62 PFS of FPA v F:8.1m v 4.8m; HR 0.75; 90% CI 0.50 to 1.12, p 0.23 ORR 13% (FPA) v 9%(FP) v 7.3%(F)	PFS of FPA v F , ORR and AE
SERENA-2 ⁹²	II, HR+HER2-MBC, CDK4/6i allowed	A: Camizestrant (SERD) 75mg (n=74) B: Camizestrant 150mg (n=73)	C: Fulvestrant (n=173)	PFS A 7.2m; HR 0.58; 95% CI 0.41to 0.81, p 0.01 B 7.7m; HR 0.67; 95% CI	ORR 15.7% v 20% v 11.8%

				0.48 to 0.92, p 0.02 C 3.7m <i>CDK 4/6i exposed:</i> A 5.5m; HR; 0.49; 95% CI 0.31 to 0.75 B 3.8m; HR; 0.68; 95% CI 0.44 to 1.04 C 2.1m	CBR 47.3% v 49.3% 39.1%
PALMIRA ⁹³	II, HR+ HER2- MBC post palbociclib	Palbociclib + ET (based on prior ET) (n=136)	ET (n=62)	PFS 4.2m v 3.6m HR 0.8; 95% CI 0.6–1.1, p 0.21 ORR 6.4% v 2.3% CBR 33.0% v 29.5%	-
2L/3L, second line or third line therapy; AI, aromatase inhibitor; CBR, clinical benefit rate; CDK 4/6i, cyclin dependent kinase 4/6 inhibitor; CT, chemotherapy; ET endocrine therapy; HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; MBC, metastatic breast cancer; mTOR, ORR overall response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; PI3KCA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression free survival; SABCS, San Antonio breast cancer symposium; SERD, selective estrogen receptor degraders; tt treatment.					

Table S2: RCTs with some results that include CDK 4/6i exposed pts; their full-text publication is awaited

Trial	Design/patient population	Intervention	Control	Comments
NCT04494425/ DESTINY-breast 06	Phase III, RCT, HR+ HER2 low MBC post CDK 4/6i, with	T-DXd	TPC	-

	disease PD within 6m of first line CDK 4/6i+ ET in metastatic setting/ PD≥2 lines of ET			
NCT03939897	Phase I/II, HR+ HER2- MBC, endocrine resistant, PI3K inhibitor naïve.	Copanlisib + fulvestrant + abemaciclib	fulvestrant + abemaciclib	CDK 4/6i allowed in phase I part of the study and as prior adjuvant therapy in phase II
NCT04895358/KEYNOTE B49	Phase III RCT, HR+ HER2- MBC Group 1 and 2b are post CDK 4/6i. PI3K and mTOR inhibitors allowed	Pembrolizumab + CT	Placebo + CT	Needs to be a CT candidate. PD-L1 CPS ≥1
NCT05104866 (TROPION-Breast01)	Phase III RCT of Datopotamab deruxtecan vs TPC in HR+HER2- MBC post 1-2 lines of CT	Datopotamab deruxtecan	TPC	previous lines of chemotherapy (1 vs. 2), prior use of CDK4/6 inhibitors (Yes vs. no) & geographic region of participant.
NCT05306340 (evERA Breast Cancer)	Phase III RCT, HR+ HER2- MBC post CDK4/6i	Giredestrant + everolimus	TPET+ everolimus	Prior oral SERD, CERAN, PROTAC not allowed. Fulvestrant allowed with last dose ≥1m
NCT04802759	Phase Ib/II, randomised umbrella study HR+ HER2- MBC post CDK4/6i (cohort 1)	Giredestrant + abemaciclib	Giredestrant	Multiple treatment arms, primary endpoint is ORR
		Giredestrant + ipatasertib		
		Giredestrant + inavolisib		
		Giredestrant + ribociclib		

		Giredestrant + everolimus		
		Giredestrant + samuraciclib		
		Giredestrant + atezolizumab		
		Giredestrant + abemaciclib + atezolizumab		
NCT04215146/ Bracelet-1	Phase II RCT, three cohort study. HR+ HER2- MBC post CDK4/6i	Pelareorep + paclitaxel + avelumab Pelareorep + paclitaxel	paclitaxel	Oncolytic virus with a potential late onset adaptive immune response
NCT05169567/postMON ARCH	Phase III RCT, HR+ HER2- MBC post CDK4/6i + AI	Abemaciclib + fulvestrant	Placebo + fulvestrant	Prior fulvestrant not allowed
NCT05079360	Phase II RCT, HR+ HER2- MBC post CDK4/6i, AI and fulvestrant	Sabizabulin	Exemestane/exemestane + everolimus/ SERM	Novel microtubule disrupter, also has anti-viral activity.
NCT05038735/EPIK B5	Phase III RCT, HR+ HER2- MBC post CDK4/6i, with mutated PI3KCA	Alpelisib + fulvestrant	Placebo + fulvestrant	-
NCT05305924	Phase II RCT, HR+ HER2- MBC post CDK4/6i	Fulvestrant alone for 1m□ abemaciclib + fulvestrant	Abemaciclib + fulvestrant	Tests whether fulvestrant run-in restores drug sensitivity
NCT04650581/FINER	Phase III RCT, HR+ HER2- MBC post CDK4/6i	Ipatasertib + fulvestrant	Placebo + fulvestrant	No prior fulvestrant or PI3K/AKT/mTOR inhibitors
NCT05159778.	Phase 2, Simon's 2-Stage study of MBC pts who have progressed through prior ET with >1 CDK4/6 inhibitor	Odetiglucon + Pembrolizumab	-	Odetiglucon is a novel beta glucan, acts as a pathogen-associated molecular pattern (PAMP)

				immune modulator
NCT04305834	Phase IIa study in HR+HER2-MBC older than 70 years of age and post ET +/- ribociclib/palbociclib	abemaciclib	-	Primary outcome is AE
NCT04699630	Phase 2 study of U3-1402 (Patritumab Deruxtecan), in which parts A and B enroll HR+HER2-MBC post CDK4/6i	U3-1402	-	U3-1402 is a ADC against HER3, primary outcome ORR
NCT04965766 (ICARUS-Breast)	Phase 2 study of U3-1402, in HR+HER2-MBC resistant to CDK4/6i	Patritumab Deruxtecan (U3-1402)	-	primary outcome ORR
NCT04305834	Phase II, ≥ 70 years, HR+ HER2-MBC post palbociclib or ribociclib	abemaciclib	-	Primary outcome is grade 3+ toxicity
NCT05536128	Phase II, Umbrella study , in HR+ HER2-MBC post CDK 4/6i	Fulvestrant + Olaparib	-	-
NCT04762979	Phase II, HR+ HER2- MBC post CDK 4/6i, PI3KCA mutant	Alpelisib + fulvestrant/AI	-	-
NCT03326674 (CONTESSA)	Phase III RCT in HR+HER2- MBC treated with taxane in (neo)adjuvant setting	Tesetaxel + Capecitabine	Capecitabine	Tesetaxel is a novel oral taxane
NCT04738292 (SMILE)	Phase II study with HR+HER2-MBC progressed on ET +/- CDK4/6i, mTOR	Onapristone + fulvestrant	-	Onapristone is a antiprogestin

	inhibitors and 1 line of CT			
NCT05191914	Single arm study in HR+HER2-MBC resistant to CDK 4/6i +AI	Chidamide + fulvestrant	-	Chidamide is a histone deacetylase inhibitor
NCT04024436 (FOENIX-MBC2)	Phase 2 study with HR+HER2-MBC with FGFR1 amplification, post 1-2 ET +/- CDK 4/6i, ≤1 CT CDK4/6 inhibitor (if eligible)	Futibatinib + fulvestrant	-	FGFR1 amplification occur in 10% of MBC
NCT04460430 (SOLTI-1718 NEREA)	Phase 2 single arm Simon 2 stage design, locally advanced/MBC HR+ HER2-, with HER2-enriched(HER2-E)	Neratinib +ET	-	HER2-E subtype represents approximately 6.6-11.0% of HR+ /HER2-BC
NCT04059484	Phase II RCT, HR+HER2- MBC progressed on ET +/- CDK4/6i	SAR439859	TPET	SAR439859 is an oral SERD
NCT04720664 (OASIS)	Phase II single arm in HR+HER2-MBC with ≤4 lines of tHERapy	SM-88 +MPS (methoxsalen, phenytoin, and sirolimus)	-	SM-88 is a dysfunctional tyrosine derivative. Primary outcome: ORR
NCT05286437 (LaPemERLA)	Phase II single arm, HR+HER2-MBC with at least 1 line of prior tHERapy	Pembrolizumab+ lenvatinib + Letrozole	-	-
NCT05181033	Phase II RCT of HR+HER2- MBC progressed on ET +/- CDK4/6i	Lenvatinib + letrozole	fulvestrant	-
NCT05501886 (VIKTORIA-1)	Phase III RCT with parallel assignment to 6 arms. HR+HER2-MBC progressed	Arm A: Gedatolisib + Fulvestrant +palbociclib Arm B: Gedatolisib + Fulvestrant Arm C:	First three arms are PI3KCA WT and remaining	

	on ET +/- CDK4/6i	fulvestrant Arm D (mPI3KCA): Gedatolisib + Fulvestrant +palbociclib Arm E(mPI3KCA): Fulvestrant +alpelisib Arm F(mPI3KCA): Gedatolisib + Fulvestrant		are mPI3KCA. Primary outcome is PFS in Patients with PIK3CA WT and PIK3CA MT Breast Cancer
NCT04975308 (EMBER-3)	Phase III RCT HR+HER2- MBC progressed on ET +/- CDK4/6i	Imlunestrant + Abemaciclib	TPET	No CT/fulvestrant or other SERD allowed
NCT05392608 (SEQUEL-Breast)	Phase II single arm study, HR+HER2-MBC with mPI3KCA, must have taken CDK 4/6i in prior therapy	Alpelisib +fulvestrant	-	Last line of therapy must be fulvestrant
NCT04090398	HER2- MBC with bone metastases or non-bone only if: ≤5 visceral metastasis (≤4 cm in size) and asymptomatic Enlarged lymph nodes ≤4 cm	Radium Ra 223 Dichloride +paclitaxel	Paclitaxel	-
NCT05065411 (ENABLAR-2)	Phase III RCT in AR+ HR+ HER2- MBC with AR nuclear staining of ≥40%, PD post palbociclib +ET	Enobosarm + abemaciclib	Fulvestrant Or AI depending on prior line	Enobosarm is a oral selective AR targeting agonis
ARTEST NCT04869943	Phase III RCT in AR+ HR+ HER2- MBC with AR nuclear staining of ≥40%, PD post CDK4/6i, fulvestrant and AI	Enobosarm	Physician's choice of exemestane ± everolimus or SERM)	-
Abbreviations: AI, aromatase inhibitor; AR, androgen receptor; CBR, clinical benefit rate; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; CPS, combined positive score; CT, chemotherapy; ET, endocrine therapy; FGFR, Fibroblast growth factor receptor; HR, hazard ratio; HR+, hormone receptor positive; HER2-,human epidermal growth factor receptor2 negative; m, mutated; MBC, metastatic breast cancer; ORR, overall response rate; PI3KCA phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, PD, progressive disease; PFS, progression free survival; RCT, randomised controlled trial; SERD,				

Selective estrogen receptor degrader; SERM, Selective estrogen receptor modulators; T-DXd, Trastuzumab deruxtecan; TPC, the physician's choice of chemotherapy; TPET, the physicians choice of ET

Table S3: Relevant ongoing studies in the post-CDK 4/6i domain

Supplemental figures legends

Figure S1a. Traffic plot for risk of bias assessment.

Red circle- high risk of bias

Yellow circle- some concerns

green circle- low risk of bias

blue question mark- no information

Figure S1b. Summary plot for risk of bias assessment

Red bar- high risk of bias

Yellow bar- some concerns

green bar- low risk of bias blue bar- no information
Figure S2 : Forest plot showing the network meta analysis of progression free survival through network meta-analysis of oral Selective Estrogen Receptor Degraders to continuing ribociclib in mutated ESR1 patients
Figure S3: Forest Plot showing network meta-analysis of grade 3 and above adverse events for Selective Estrogen Receptor Degraders
Figure S4: Forest Plot showing network meta-analysis of progression free survival of all interventions compared to that of continuing ribociclib
Figure S5a: Forest plot of network meta-analysis comparison of Grade \geq 3 hematological toxicities vs ribociclib
Figure S5b: Forest plot of comparison network meta-analysis of Non-hematological grade \geq 3 adverse effects of all agents vs ribociclib.

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