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Comparative efficacy and safety of CDK4/6 and PI3K/AKT/mTOR inhibitors in women with hormone receptor-positive, HER2-negative metastatic breast cancer: a systematic review and network meta-analysis

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ABSTRACT

Background: CDK4/6 inhibitors and PI3K/AKT/mTOR inhibitors are both emerging agents for hormonal receptor (HR) positive and human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer. Evidence for the comparisons from head-to-head comparative trials is currently insufficient. This meta-analysis assessed the comparative efficacy and safety of these two groups of agents for HR+/HER2- metastatic breast cancer.

Methods: Systematic searches of PubMed, Embase, CENTRAL, SciSearch between January 2010 to December 2019 were conducted. Randomized controlled trials (RCTs) which evaluated clinical benefits and toxicities of CDK4/6 inhibitors or PI3K/AKT/mTOR inhibitors plus endocrine therapy were adopted. Primary endpoints were progression-free survival (PFS) and overall survival (OS). Secondary endpoint was treatment-related adverse event (TRAE). Pooled hazard ratio (HR) and risk rate (RR) were used to assess the differences between CDK4/6 and PI3K/AKT/mTOR inhibitors.

Results: A total of twenty RCTs including 9771 participants were identified in this study. Pooled results showed that PFS was considerably prolonged by targeted therapy plus endocrine therapy. PFS was relatively better in CDK4/6 inhibitors than that of PI3K inhibitor group (HR, 1.43; 95%CrI, 1.12-1.61). Similar results were demonstrated in results after balancing lines of therapy or metastatic sites, both in viscera and bone-only. Coalesced outcomes revealed that CDK4/6 inhibitors plus endocrine therapy could signif-

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icantly improve OS (HR, 0.78; 95%CrI, 0.65-0.94) than PI3K/mTOR inhibitors. Safety profiles of diarrhea and rash were consistent between CDK4/6 inhibitors and PI3K/AKT/mTOR inhibitors with no difference of estimated RR. Several TRAEs signified specificity, for instance, myelosuppression in CDK4/6 inhibitors or hyperglycemia in PI3K/mTOR inhibitors.
Conclusions: Clinical efficacy is in favor of CDK4/6 inhibitors, and safety profiles are comparable between CDK4/6 inhibitors or PI3K/AKT/mTOR inhibitors plus endocrine therapy.

ARTICLE INFO

Keywords: CDK4/6 inhibitors; PI3K/AKT/mTOR inhibitors; Endocrine therapy; HR+/HER2- metastatic breast cancer; Network meta-analysis

Introduction

Breast cancer is the most common malignancy and the second leading cancer-related cause of death in women [1]. Standard categories have been long established based on molecular features, including hormonal receptor (HR) and human epidermal growth factor 2 (HER2), of which around 70% of patients are HR-positive and HER2-negative (HR+/HER2-) phenotype [2]. Endocrine therapy, which is tailored for HR-positive breast cancer, has extensively evolved with the in-depth clarification of molecular microenvironment and cell signaling pathways.

Cyclin-dependent kinase (CDK) 4/6-Cyclin D-pRb axis and phosphatidylinositol 3-kinase (PI3K) /protein kinase B (AKT) /mammalian target of rapamycin (mTOR) signaling pathways have been proven to play essential role in endocrine therapy of advanced breast cancer. As one of the hallmarks of cancer cell, the dysregulation of cell cycle attributes to excessive proliferation and organ metastasis [3]. CDK4/6, combining with cyclin D, promotes the hyperphosphorylation of Rb gene product (pRb) by releasing transcriptional factor E2F and transition from phase G1 to S [4], which is required for cancer biologic behaviors. PI3K protein family is widely implicated in human cancer [5], and the somatic mutations in genes encoding components of the PI3K pathways occurs in more than 70% breast cancer [6]. The aberrant activation of PI3K/AKT/mTOR pathway, which includes the mutations or amplifications of PI3K subunits and PI3K modulators, such as AKT, mTOR, was confirmed in more than 50% HR+ metastatic breast cancer [7]. The acknowledge of molecular mechanisms has enabled the device and development of novel agents. Nowadays, highly selective CDK4/6 inhibitors and the pan or selective inhibitors of PI3K, AKT, mTOR have been emerging, and provide clinical benefit to HR+/HER2- metastatic breast cancer [6,8]. In the combination with endocrine therapy, both two groups of targeted agents are constantly taking great advantages of clinical efficacy and well-controlled safety profiles.

Under the circumstances of no reported trials which directly assess differences between CDK4/6 and PI3K/AKT/mTOR inhibitors, indirect comparisons tend to extensively beneficial for current clinical practice. Herein, we carried out a systematic review and network meta-analysis to evaluate the comparative efficacy and safety of CDK4/6 inhibitors and PI3K/AKT/mTOR inhibitors in HR+/HER2- metastatic breast cancer.

Methods

Search strategy and selection criteria

Databases including PubMed, Embase, CENTRAL, SciSearch were systematically searched for randomized controlled trials (RCTs) published between January 2010 to December 2019. We successively used key words of CDK4/6 inhibitors, PI3K inhibitors, AKT inhibitors, mTOR inhibitors

combined with hormonal receptors positive, human epidermal growth factor receptor 2 negative and metastatic breast cancer. For the supplement and integrity, abstracts were also acquired from official websites of annual conferences, including American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), San Antonio Breast Cancer Symposium (SABCS) and Chinese Society of Clinical Oncology (CSCO). Moreover, manual retrieve for updated outcomes was conducted in ClinicalTrials. No languages were limited. The cut-off date of systematic search was January 31, 2020.

RCTs which compared CDK4/6 inhibitors or PI3K/AKT/mTOR inhibitors plus endocrine therapy with endocrine monotherapy were eligible. Endocrine treatments included selective estrogen receptor modulators (SERMs), selective estrogen receptor down-regulators (SERDs), and aromatase inhibitors (AIs) in this analysis. Trials of which single-arm design, interventions including cytotoxic agents, HER2 expression positive or borderline disease, early expiration of follow-up were excluded.

Data extraction and outcome measures

Trial names, study design, recruitment year, participants clinicopathological characteristics, survival outcomes were recorded according to proforma analysis. Two investigators independently contributed to extraction proceedings and the repeated discussion of controversial outcomes. Hazard ratio (HR) and 95% confidence interval (CI) were extracted for time-to-event outcomes, while occurrences of AEs were derived for dichotomous data. Primary endpoints were progression-free survival (PFS) and overall survival (OS). Secondary endpoints was grade 3–5 treatment-related adverse events (TRAEs). Safety profiles consisted of the incidences of grade 3–5 TRAEs which were classified according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

PFS was defined as the period from randomization to either disease progression or death by any causes. OS was described as the interval from randomization to death. Disease progression was determined according to Response Evaluation Criteria in Solid Tumors (RECIST). Endocrine status were classified as three categories, including primary resistance, secondary resistance and endocrine sensitivity. Primary resistance was defined as relapse within 24 months after adjuvant endocrine therapy, or progression within 6 months after endocrine therapy for metastatic disease. Secondary endocrine resistance was defined as relapse after at least 24 months of adjuvant therapy and within 12 months after the termination of adjuvant therapy, or after 6 months of endocrine therapy in metastatic stage.

Network was introduced by extracted and formalized data with RStudio software. In the network, nodes represented interventions and lines means the comparative relationship. The internal bias of inclusive RCTs was assessed by Cochrane Collaboration's tool [9]. Selection bias, performance bias, attribution bias and detection bias were consecutively evaluated. External inconsistency was verified clinically, methodologically and statistically. Consistency test protocol was introduced by the study design and network structure. Considering metastatic sites and endocrine status were common implications for practice, we did an exploratory analysis of subgroups determined by disease characteristics to further weaken heterogeneity. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the extension guideline for network meta-analysis were followed in this study [10].

Statistical analysis

Bayesian approaches were applied for this network meta-analysis. Pooled HR and 95% credible interval (CrI) of PFS or OS were used to assess the comparative clinical efficacy, and risk ratio (RR) was used to evaluate grade 3–5 TRAEs. Generic inverse variance method was utilized to indirectly estimate HR and 95% CrI [11]. Accordingly, ln(HR) and standard error(HR) were calculated and aggregated. The type of effect model was adopted based on deviance information

criterion (DIC), and the determinant was the deviation of DIC and data points [12]. A Bayes framework was used to validate models with Markov Chain Monte Carlo (MCMC) methods, by the motivation of JAGS software version 4.3.0 [13]. RR, as the indicator for prospective nature in meta-analysis, was applied for the pooled proportions of TRAEs. Ratios, responders and sample sizes were selectively synthetized. Heterogeneity was assessed using Cochran Q statistic and I^2 statistic. The Begg and Egger test were adopted to assess publication bias, and a P value <0.10 was regarded as evident asymmetry and bias.

This meta-analysis was conducted by Review Manager version 5.3 (https://community.cochrane.org) and R-Studio version 1.2 (https://www.rstudio.com). Quality assessment was performed using Revman 5.3. The whole meta-analysis proceedings were implemented with R gemtc package version 0.8-2 of R-Studio.

Results

In total, twenty RCTs were identified [14–36] (Table 1). Filtering procedure was shown in (Fig. A). A total of 9771 individuals including 5861 and 3910 participants were enrolled in interventional group and controlled group, respectively. Quality assessment of inclusive studies was shown in (Fig. B). The characteristics at baseline, the size of entry subjects, interventions and controls, trial management are well-balanced (Table 2). The P value obtained for publication bias test was 0.52, indicating funnel symmetry and acceptable bias (Fig. C) (Tables 1 and 2).

Treatment agents were sequentially embraced in a created network (Fig. D). Because of the fact that no head-to-head comparative trials were currently published, the design of this meta-analysis was adjusted indirect comparison. In this network, endocrine agents were concluded and presented as AI, fulvestrant, tamoxifen with or without CDK4/6 inhibitors, PI3K inhibitors, AKT inhibitors and mTOR inhibitors. Since almost the whole subjects were postmenopausal women, and premenopausal or perimenopausal patients were treated with GnRHa (goserelin or leuprorelin) at baseline, GnRHa was not specifically presented in the plot.

Besides, because of the absence of closed circle structure, consistency test was not applicable. Besides, since calculated $\triangle$ (Delta) of DIC and data points were generally positive (ranging, 0.1 to 3.9), a Bayes random-effects model was consistently appropriate.

Progression-free survival

Main results demonstrated that combination therapeutics were significantly better than endocrine monotherapy. PFS was generally lengthened in CDK4/6 inhibitors group (HR, 0.54; 95%CrI, 0.48-0.59), PI3K inhibitors group (HR, 0.73; 95%CrI, 0.64-0.82), AKT inhibitors group (HR, 0.56; 95%CrI, 0.37-0.86) and mTOR inhibitors group (HR, 0.55; 95%CrI, 0.47-0.67) (Figure SA).

Apropos of reciprocal comparisons, PFS was significantly prolonged in CDK4/6 inhibitors combination than PI3K/AKT/mTOR inhibitors group with a HR 0.81 (95%CrI, 0.69-0.95) (Figure SB).Furthermore, outcomes exhibited PFS superiority in CDK4/6 inhibitors plus endocrine therapy than PI3K inhibitors group (HR, 0.73; 95%CrI, 0.62-0.86), while no statistical differences were shown in AKT and mTOR inhibitors group(Figure SC).

Sensitive analysis was conducted to explore the lines of therapy and clinical efficacy. After removing the survival outcomes from former lines therapy of CDK4/6 inhibitors (PALOMA-1/TRIO-18, PALOMA-2, MONALESSA-2, MONALESSA-7, MONARCH-3, MONARCH Plus cohort A) and later lines therapy (BELLE-3, FERGI, BOLERO-2) as well as unknown results (SANDPIPER, FAKTION, TAMRAD, PrE0102) of PI3K/AKT/mTOR inhibitors, pooled resulted suggested that the estimated HR of CDK4/6 inhibitors, comparing with PI3K/mTOR inhibitors, was 0.69 (95%CrI,0.52-0.88) (Figure SD).

Subgroup analysis was conducted to explore the effectiveness stratified by visceral and bone-only metastases. In terms of advanced disease with visceral metastasis, pooled results showed

that HR+/HER2- metastatic breast cancer could be widely beneficial from targeted therapy in addition to endocrine therapy. The computed HR was 0.55 (95%CrI, 0.48-0.63) of CDK4/6 inhibitors, 0.61 (95%CrI, 0.49-0.77) of PI3K inhibitors and 0.47 (95%CrI, 0.29-0.74) of mTOR inhibitors. No statistical divergences were detected among these three combination groups(Figure SE). As for non-visceral metastatic disease, both CDK4/6 inhibitors (HR, 0.55;95%CrI, 0.45-0.66) and mTOR inhibitors (HR, 0.41;95%CrI, 0.28-0.62) could intensively decrease HR by 45% and 59%, yet no discrepancy between the counterparts. None but PI3K inhibitor group was statistically indifferent(Figure SF).

As for bone-only metastatic disease, CDK4/6 inhibitors (HR, 0.55, 95%CrI,0.45-0.66) and mTOR inhibitors (HR, 0.41; 95%CrI, 0.28-0.62) could considerably improve PFS comparing endocrine monotherapy, while the effectiveness of PI3K inhibitors were inconspicuous. Efficacy between CDK4/6 inhibitors and PI3K inhibitors were analogous(Figure SG). The survival data of endocrine status were extremely insufficient, we decided against merging them to avoid potential bias.

Overall survival

Prognosis was were improved by targeted therapy plus endocrine therapy. In comparison with endocrine monotherapy, the evaluated HR were 0.78 (95%CrI, 0.67-0.91) and 0.84 (95%CrI, 0.69-0.99) in CDK4/6 inhibitor group and PI3K/mTOR inhibitor concerted group, respectively(Figure SH). However, exhaustive analysis indicated that clinical prognosis was merely improved by CDK4/6 inhibitors (HR, 0.78; 95%CrI, 0.65-0.94). Despite no obvious benefit was revealed, the tendency for potential effectiveness was implicated by HR of PI3K inhibitors and mTOR inhibitors plus endocrine treatment(Figure SI). Besides, no differences were illustrated between CDK4/6 inhibitors and PI3K/mTOR inhibitors, else independent groups. No OS data of AKT inhibitors has been coalesced owing to the absence.

Grade 3–5 treatment-related adverse events

Treatment-related adverse events are specific between CDK4/6 inhibitors and PI3K/AKT/mTOR inhibitors. Neutropenia and leucopenia were significantly particular in CDK4/6 inhibitors, whereas hyperglycemia, elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentration mainly exhibited in PI3K/AKT/mTOR inhibitor combinations. We separately aggregated and estimated RR of toxicities in two combination groups.

Among CDK4/6 inhibitors, the estimated RR of neutropenia and leucopenia, comparing with pabociclib, showed no differences were shown in ribociclib combination group. Combined RR was significantly decreased in abemaciclib with values of 0.024 (95%CrI, 0.0016-0.30) (Figure SJ)and 0.018 (95%CrI, 0.00045-0.23)(Figure SK), respectively. As for PI3K/AKT/mTOR inhibitors, the synthetized outcome of hyperglycemia and increased ALT/AST concentration showed no difference between PI3K inhibitors and mTOR inhibitors.

Additionally, diarrhea and rash were relatively common among two combination groups. No statistical difference of diarrhea was shown between CDK4/6 and PI3K/AKT/mTOR inhibitors. As comparing with endocrine monotherapy, the estimated rate of diarrhea was consistently increased in targeted therapy plus endocrine therapy. Though no significance showing between CDK4/6 inhibitors and PI3K/AKT/mTOR inhibitors, the coalited RR was in tendency for CDK4/6 inhibitor group. Accordant results were manifested in the outcomes of rash. Several AEs, during extraction proceedings, suggested associated specificity among targeted agents. Increased rates of thrombocytopenia, elevated ALT/AST concentration, stomatitis and pneumonitis were suggested in CDK4/6 inhibitors, PI3K inhibitors and mTOR inhibitors, respectively.

Discussion

Currently, advanced breast cancer with distant metastasis is regarded as an incurable disease with available treatments, of which 5-year survival rate is just 25% [37]. For HR-positive advanced breast cancer, endocrine therapy is the mainstay of the multidisciplinary treatment tailoring for individuals. The effectiveness of endocrine single-agent is limited, which constantly encourages the novel agents to be developed. Both Cyclin D-CDK4/6-pRb axis [37] and PI3K/AKT/mTOR pathway [6] play crucial roles in the endocrine treatment of advanced breast cancer. Based on the great efficacy and controllable toxicities, the highly selective CDK4/6 inhibitors and PI3K/AKT/mTOR inhibitors are concurrently recommended for HR+/HER2- metastatic breast cancer [38]. To our knowledge, this is the first pooling analysis for the comparative profiles of the two groups agents, and promising results of both efficacy and safety were provided.

Survival outcomes of CDK4/6 inhibitors and PI3K/AKT/mTOR inhibitors was evaluated by PFS and OS. Pooled results showed that HR+/HER2- metastatic breast cancer patients could overwhelmingly gain benefits from targeted therapy plus endocrine therapy. However, the overview of prognosis superiority was in favor of CDK4/6 inhibitor combination. Comparing with PI3K/AKT/mTOR inhibitors, CDK4/6 inhibitors could further decreased HR by 19%, which powerfully inhibit disease progression and benefit survival rate. As for crossed comparisons, PI3K inhibitors showed weakness of PFS than CDK4/6 inhibitors, while the other three groups were indifferent. Considering the fact that a larger proportion of enrolled patients of PI3K/AKT/mTOR inhibitors were in tendency for later lines, we analyzed the PFS outcomes by balancing the lines of therapy. Pooled results showed that PFS superiority was also exhibited in CDK4/6 inhibitors which could not affect the stability of results. The exploratory analysis was conducted with stratification by metastatic site and the response to prior endocrine therapy, which were common standards for registered clinical trials. Subgroup outcomes were roughly consistent with those of integral analyses. Targeted therapy plus endocrine therapy was considerably beneficial to patients with visceral metastasis with estimated HR decreased by 45% in CDK4/6 inhibitors, 39% in PI3K inhibitors and 53% in mTOR inhibitors, respectively. However, no obvious advantages were detected among them. For HR+/HER2- breast cancer patients with non-visceral metastasis, both CDK4/6 inhibitors and mTOR inhibitors could significantly improve PFS with coalesced HR decreased by 45% and 69%, respectively. No statistical differences were signified between them. In addition, CDK4/6 inhibitors also exhibited PFS improvements for bone-only metastasis. While PI3K inhibitors were nor comparable. Previous indirect comparisons for interventions were most stratified by lines of treatment [39,40]. The OS outcomes of CDK4/6 inhibitor combinations were favorable to HR+/HER2- metastatic breast cancer. Interestingly, the concerted OS results of PI3K/AKT/mTOR were similarly beneficial, while the independent analysis showed no statistical difference among the three combinations. Considering several trials were undergoing with immature OS data, such as MONARCH plus, SANDPIPER, FAKTION and MIRACLE, these outcomes might be alternative the appropriated point. As a positive result, the prognosis advantage was exhibited in CDK4/6 inhibitor plus endocrine therapy. However, this original results were obtained from the trials which mainly enrolled postmenopausal female or pre- or perimenopausal participants treated with GnRHa. Thus, the pooled data for non-postmenopausal female were inadequate.

Safety profile is considerably vital for decisions on systemic treatment, especially in the context of metastatic disease. Based on the diverse toxicities reported from each trial, we conducted an exploratory analysis of grade 3–5 TRAEs. The overview of TRAEs outcomes enabled us to divide them into two groups, classified by communality and specificity. Because of the immature data of AKT inhibitors, we could not adopt this category into this section of analysis. The estimated RR of diarrhea and rash, as the common toxicities of both CDK4/6 inhibitors and PI3K/ mTOR inhibitors, was not statistically different. Myelosuppression, comprising neutropenia, leucopenia and thromocytopenia, was remarkable among CDK4/6 inhibitors. The rates of neutropenia and leucopenia were not divergent in two pabociclib and ribociclib, except for

abemaciclib. On the other hand, hyperglycemia and increased ALT/AST concentration relatively prevailed among PI3K inhibitors and mTOR inhibitors. These results were consistent with previous studies in single [41,42] or combination treatment [37,43]. The specificity tend to be as the results of molecular mechanisms and targets [44]. Individualized protocol could be introduced by physicians from these results of safety profile.

Indeed, this meta-analysis has some limitations. First, to guarantee the integrity of reported trials, several intermittent results from abstracts were included, which might lead to potential bias as the result of incompleteness of follow-up. Also, because Bayes random-effect model was well applicable and subgroup analysis was conducted, we did not successively explore the heterogeneities, like meta regression. Moreover, the administration of endocrine treatments of control groups was not distinguished. For instance, the administration of GnRHa in premenopausal or perimenopausal patients could not be included into analysis. Because GnRHa plus AI or fulvestrant showed confirmed effectiveness for HR+ metastatic breast cancer, it might weaken the results to some extent. Last, the prior treatment could not be included in analyses with the insufficient data.

This meta-analysis showed the initial consequences of the effectiveness and safety differences between CDK4/6 inhibitors and PI3K/AKT/mTOR inhibitors, which could provide guidelines for current endocrine practice. In addition, the optimum sequential treatments remain to be determined from the approaching data with equivalent results [15] suggested from the exploratory administration. Although PI3K/mTOR inhibitors are currently recommended for later-line treatment of HR+/HER2- breast cancer, clinical trials, which manage to evaluate them in upfront therapy, are recruiting or ongoing. For instance, PI3K inhibitors in neoadjuvant therapy (ClinialTrials.gov Identifier: NCT01923168), MK-2206 in adjuvant therapy (ClinialTrials.gov Identifier: NCT01776008) and everolimus in 1st-line treatment of metastatic breast cancer [45]. The inhibitors of PI3K/AKT/mTOR, which is the most frequent altered pathway in metastatic breast cancer [44], tend to provide increasing benefits for breast cancer patients at earlier lines of therapy, especially for the individuals who has progressed on primary resistance to endocrine therapy. Both PI3K/AKT/mTOR and CDK4/6 inhibitors have been considered as beneficial to HR+/HER2- breast cancer with the improvement of clinical efficacy and prognosis. With the differences of disease status and availability of agents, the optimization of treatment is for not only cost-effectiveness and out-of-pocket expenses, but also the improved prognosis with decent quality of life. Under this circumstance, the selection of the advantageous population seems to be important. Considering the apparent specificities, TRAEs should be taken into consideration when introducing the personalized protocol of endocrine treatment. Importantly, the biomarkers, which were fairly different among the trials of both two groups of agents, could play a guiding role in clinical practice. Several trials have explored the predictors for effectiveness and prognosis, for instance, by circulating tumor DNA (ctDNA) detecting the amplification of cyclin D1 in PALOMA-1 [15] and PIK3CA-mutated status in SOLAR-1 [25]. Promising biomarkers are waiting be identified and applicated in clinical practice. Biomarkers, to select the dominant individuals, are waiting to be identified. Preclinical studies indicated that CDK4/6 inhibitors and PI3K/AKT/mTOR inhibitors are synergetic in combination and could effectively depress the growth and proliferation of breast cancer cells in vitro [46]. CDK4/6 inhibitors, combined with PI3Kα inhibitors, could overcome endocrine resistance in PI3KCA-mutated xenografts [47]. All these results suggested that treatment in combination is promising to inhibit and reverse cancer resistance and metastasis. Most importantly, the knowledge of molecular features and cell signaling pathways has paved the way for the development of novel agents. Treatment concepts and guidelines would be durably ameliorated for clinical practice.

Conclusion

In conclusion, targeted therapy in combination with endocrine therapy could significantly improve prognosis, comparing with endocrine monotherapy, of HR+/HER2- metastatic breast cancer. CDK4/6 inhibitors plus endocrine therapy exhibit PFS and OS superiority than

PI3K/AKT/mTOR inhibitor group. Safety profiles demonstrate specificity, to some extent, between the two groups of agents. Based on the results, a randomized, large-scale, controlled clinical trial is worth comparing the efficacy and safety between CDK4/6 inhibitors and PIEK/AKT/mTOR inhibitors. Currently, since there was no head-to-head comparative trial as well as the limited availability of novel agents, this meta-analysis tend to be promising for current clinical practice.

Vitae

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Declarations of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2020.100606.

Appendices

Table 1
Clinical characteristics of inclusive RCTs.
According to the individual trial protocols, eligible studies were selectively divided into two cohorts based on intervention or molecular profiles. In MONALESSA-7 trial, participants were mainly divided by interventional agents (AI vs fulvestrant) which was identical to that of MANTA trial (vistusertib vs everolimus). PI3K mutation was the concerted standard for SOLAR-1, SANDPIPER and FERGI trial, while endocrine therapy response was for the two cohorts of MONARCH Plus. (NA=not available; TAM=tamoxifen; NSAI=non-steroidal aromatase inhibitors)

Study	Author. Published Time	Phase	Recruitment Year	Regimen (No. of Patients)		Prior Lines of Therapy (%)		Visceral Metastasis (%)	
				Interventional group (5861)	Control group (3910)	Interventional group	Control group	Interventional group	Control group
PALOMA-1/TRIO-18 [14]	Richard S Finn, et al. 2015.01	II	2009.12–2012.05	Pabociclib+Letrozole (84)	Letrozole (81)	0(100)	0(100)	44	53
PALOMA-2 [15]	Richard S Finn, et al. 2016.11	III	2013.02–2014.07	Pabociclib+Letrozole (444)	Letrozole (222)	0(100)	0(100)	48.2	49.5
PALOMA-3 [16,17]	Nicholas C Turner, et al. 2015.07/2018.10	III	2013.10–2014.08	Pabociclib+Fulvestrant (347)	Placebo+Fulvestrant (174)	0(24)/1(38)/2(26)/≥3(12)	0(26)/1(40)/2(24)/≥3(10)	59.4	60.3
MONALESSA-2 [18,19]	Gabriel N Hortobagyi, et al. 2018.04/2018.11	III	2014.01–2015.03	Ribociclib+Letrozole (334)	Placebo+Letrozole (334)	0(100)	0(100)	59	58.7
MONALESSA-3 [20]	Dennis J Slamon, et al. 2018.06	III	2015.06–2016.06	Ribociclib+Fulvestrant (484)	Placebo+Fulvestrant (242)	0(49.2)/1(48.8)	0(53.3)/1(48.0)	60.5	60.3
MONALESSA-7 (a) [21,22]	Debu Tripathy, et al. 2018.05/2019.06	III	2014.12–2016.08	Ribociclib+TAM (87)	Placebo+TAM (90)	0(100)	0(100)	58	56
MONALESSA-7 (b) [21,22]		III	2014.12–2016.08	Ribociclib+NSAI (248)	Placebo+NSAI (247)	0(100)	0(100)		
MONARCH-2 [23]	George W Sledge, et al. 2017.06	III	2014.08–2015.12	Abemaciclib+Fulvestrant (446)	Placebo+Fulvestrant (223)	0/1(NA)	0/1(NA)	54.9	57.4
MONARCH-3 [24]	Matthew P Geotz, et al. 2017.10	III	2014.11–2015.11	Abemaciclib+NSAI (328)	Placebo+NSAI (165)	0(100)	0(100)	52.4	53.9
MONARCH plus (a)	Zefei Jiang, et al. 2019.09	III	Recruiting (2016.12-)	Abemaciclib+NSAI (204)	Placebo+NSAI (102)	0/1(NA)	0/1(NA)	NA	NA
MONARCH plus (b)		III	Recruiting (2016.12-)	Abemaciclib+Fulvestrant (104)	Placebo+Fulvestrant (53)	0/1(NA)	0/1(NA)	NA	NA

(*continued on next page*)

Table 1 (*continued*)

Study	Author. Published Time	Phase	Recruitment Year	Regimen (No. of Patients)		Prior Lines of Therapy (%)		Visceral Metastasis (%)	
				Interventional group (5861)	Control group (3910)	Interventional group	Control group	Interventional group	Control group
SOLAR-1 (a) [25]	F. André, et al. 2019.05	III	2015.07–2017.07	Alpelisib+Fulvestrant (169)	Placebo+Fulvestrant (172)	1(52.1)/2(46.7)	1(51.7)/2(47.7)	55.8	58.1
SOLAR-1 (a) [25]		III	2015.07–2017.07	Alpelisib+Fulvestrant (115)	Placebo+Fulvestrant (116)	1(61.7)/2(36.5)	1(53.4)/2(45.7)	57.4	63.8
BELLE-2 [26,48]	José Baselga, et al. 2017.05/2018.08	II	2012.09–2014.09	Buparlisib+Fulvestrant (576)	Placebo+Fulvestrant (571)	0(27)/1(53)/≥2(19)	0(25)/1(53)/≥2(22)	59	59
BELLE-3 [28]	Angelo Di Leo, et al. 2017.12	III	2013.01–2016.03	Buparlisib+Fulvestrant (289)	Placebo+Fulvestrant (143)	1(30)/2(57)/≥3(13)	1(34)/2(53)/≥3(13)	73	72
SANDPIPER (a) [27]	José Baselga, et al. 2018.06	III	Recruiting (2015.04-)	Taselisib+Fulvestrant (417)	Placebo+Fulvestrant (214)	NA	NA	NA	NA
SANDPIPER (b) [27]		III	Recruiting (2015.4.9-)	Taselisib+Fulvestrant (77)	Placebo+Fulvestrant (38)	NA	NA	NA	NA
FERGI (a) [29]	Ian E Krop, et al. 2016.06	II	2011.09–2013.01	Pictilisib+Fulvestrant (89)	Placebo+Fulvestrant (79)	0(27)/1(37)/2(26)/≥3(10)	0(25)/1(46)/2(19)/≥3(10)	57	53
FERGI (b) [29]		II	2013.03–2014.01	Pictilisib+Fulvestrant (41)	Placebo+Fulvestrant (20)	0(12)/1(27)/2(20)/≥3(41)	0(10)/1(35)/2(25)/≥3(30)	51	50
FAKTION [30]	Robert Hugh Jones, et al. 2019.06	II	2015.03–2018.03	Capivasertib+Fulvestrant (69)	Placebo+Fulvestrant (71)	NA	NA	NA	NA
BOLERO-2 [31,32]	José Baselga, et al. 2011.12 M. Piccart, et.al. 2014.09	III	2009.06–2011.01	Everolimus+Exemestane (485)	Exemestane (239)	1(16)/2(30)/≥3(54)	1(18)/2(30)/≥3(53)	56	56
TAMRAD [33]	Thomas Bachelot, et al. 2012.05	II	2008.03–2009.03	Everolimus+Tamoxifen (54)	Tamoxifen (57)	NA	NA	49	57
MANTA (a) [34]	Peter Schmid, et al. 2019.08	II	2014.04–2016.10	Vistusertib+Fulvestrant (196)	Fulvestrant (66)	0(44)/1(45)/≥2(12)	0(44)/1(41)/≥2(15)	63	62
MANTA (b) [34]		II	2014.04–2016.10	Everolimus+Fulvestrant (64)	Fulvestrant (66)	0(42)/1(39)/≥2(19)	0(44)/1(41)/≥2(15)	69	62
PrE0102 [35]	Noah Kornblum, et al. 2018.06	II	2013.05–2015.11	Everolimus+Fulvestrant (66)	Placebo+Fulvestrant (65)	NA	NA	69	61
MIRACLE [36]	Binghe Xu, et al. 2019.11	II	Recruiting (2014.12-)	Everolimus+Letrozole (101)	Letrozole (98)	0(100)	0(100)	57.4	58.2

Table 2
Extracted data from inclusive RCTs.
(NA=not available)

Study	Median PFS (HR,95%CI,*P*)	Median OS (HR,95%CI,*P*)	visceral metastasis(HR,95%CI)	non-visveral metastasis(HR,95%CI)	bone-only metastasis(HR,95%CI)
PALOMA-1/TRIO-18	20.2m vs 10.2m (0.488,0.319–0.748,0.0004)	37.5m vs 34.5m (0.897,0.623–1.294,0.281)	0.547 (0.317–0.944)	NA	0.294 (0.092–0.945)
PALOMA-2	24.8m vs 14.5m (0.58,0.46–0.72,<0.001)	NA	0.63 (0.47–0.85)	0.50 (0.36–0.70)	0.36 (0.22–0.59)
PALOMA-3	9.5m vs 4.6m (0.46,0.36–0.59,<0.001)	34.9m vs 28.0m (0.81,0.64–1.03,0.09)	0.45 (0.32–0.63)	0.36 (0.22–0.60)	NA
MONALESSA-2	25.3m vs 16.0m (0.568,0.457–0.704,$3.29^{*}10^{-6}$)	NR vs 33.0m (0.746,0.517–1.078,$9.63^{*}10^{-8}$)	0.57 (0.41–0.79)	0.55 (0.36–0.83)	0.69 (0.38–1.25)
MONALESSA-3	20.5m vs 12.8m (0.593,0.480–0.732,<0.001)	NA	0.645 (0.483–0.861)	0.563 (0.415–0.764)	0.379 (0.234–0.613)
MONALESSA-7 (a)	22.1m vs 11.1m (0.59,0.39–0.88,NA)	(0.79,0.45–1.38)	0.50 (0.38–0.68)	0.64 (0.45–0.91)	0.70 (0.41–1.19)
MONALESSA-7 (b)	27.5m vs 13.8m (0.57,0.44–0.74,NA)	(0.70,0.50–0.98)	NA	NA	NA
MONARCH-2	16.9m vs 9.3m (0.536,0.445–0.645,<0.0001)	46.7m vs 37.3m (0.757,0.606–0.945,0.0137)	0.481 (0.369–0.627)	NA	0.543 (0.355–0.833)
MONARCH-3	28.2m vs 14.8m (0.525,0.415–0.665,0.000021)	NA	0.61 (0.42–0.87)	0.57 (0.41–0.78)	0.58 (0.27–1.25)
MONARCH plus (a)	NR vs 14.73m (0.499,0.346–0.719,0.0001)	NA	NA	NA	NA
MONARCH plus (b)	11.47m vs 5.69m (0.376,0.240–0.588,<0.0001)	NA	NA	NA	NA
SOLAR-1 (a)	11.0m vs 5.7m (0.65,0.50–0.85,0.00065)	NA	0.62 (0.44–0.89)	0.69 (0.47–1.01)	0.62 (0.33–1.18)

(*continued on next page*)

Table 2 (*continued*)

Study	Median PFS (HR,95%CI,*P*)	Median OS (HR,95%CI,*P*)	visceral metastasis(HR,95%CI)	non-visveral metastasis(HR,95%CI)	bone-only metastasis(HR,95%CI)
SOLAR-1 (b)	7.4m vs 5.6m (0.85,0.58–1.85,NA)	NA	NA	NA	NA
BELLE-2	6.9m vs 5.0m (0.78,0.67–0.89,0.00021)	33.2m vs 30.4m (0.87,0.74–1.02,0.045)	NA	NA	NA
BELLE-3	3.9m vs 1.8m (0.67,0.53–0.84,0.0003)	NA	0.56 (0.43–0.74)	0.96 (0.61–1.50)	1.06 (0.52–2.15)
SANDPIPER (a)	7.4m vs 5.4m (0.70,0.56–0.89,0.0037)	NA	NA	NA	NA
SANDPIPER (b)	5.6m vs 4.0m (0.69,0.44–1.08,0.1062)	NA	NA	NA	NA
FERGI (a)	6.6m vs 5.1m (0.74,0.52–1.06,0.096)	NA	0.74 (0.46–1.18)	0.70 (0.41–1.27)	0.57 (0.32–1.02)
FERGI (b)	5.4m vs 10.0m (1.07,0.53–2.18,0.84)	NA	NA	NA	NA
FAKTION	10.3m vs 4.8m (0.57,0.39–0.84,0.0035)	26.0m vs 20.0m (0.59,0.34–1.05,0.071)	NA	NA	NA
BOLERO-2	10.6m vs 4.1m (0.36,0.27–0.47,<0.001)	31.0m vs 26.6m (0.89,0.73–1.10,0.14)	0.47 (0.37–0.80)	0.41 (0.31–0.55)	NA
TAMRAD	8.6m vs 4.5m (0.54,0.36–0.81,0.0021)	NR vs 32.9m (0.45,0.24–0.81,0.007)	NA	NA	NA
MANTA (a)	(a) 7.6m vs 5.4m (0.88,0.63–1.24,0.46) (b) 8.0m vs 5.4m (0.79,0.55–1.12,0.16)	NA	NA	NA	NA
MANTA (b)	12.3m vs 5.4m (0.63,0.42–0.92,0.01)	NA	NA	NA	NA
PrE0102	10.3m vs 5.1m (0.61,0.40–0.92,0.02)	31.4m vs 28.3m (1.31,0.72–2.38,0.37)	NA	NA	NA

Appendix A

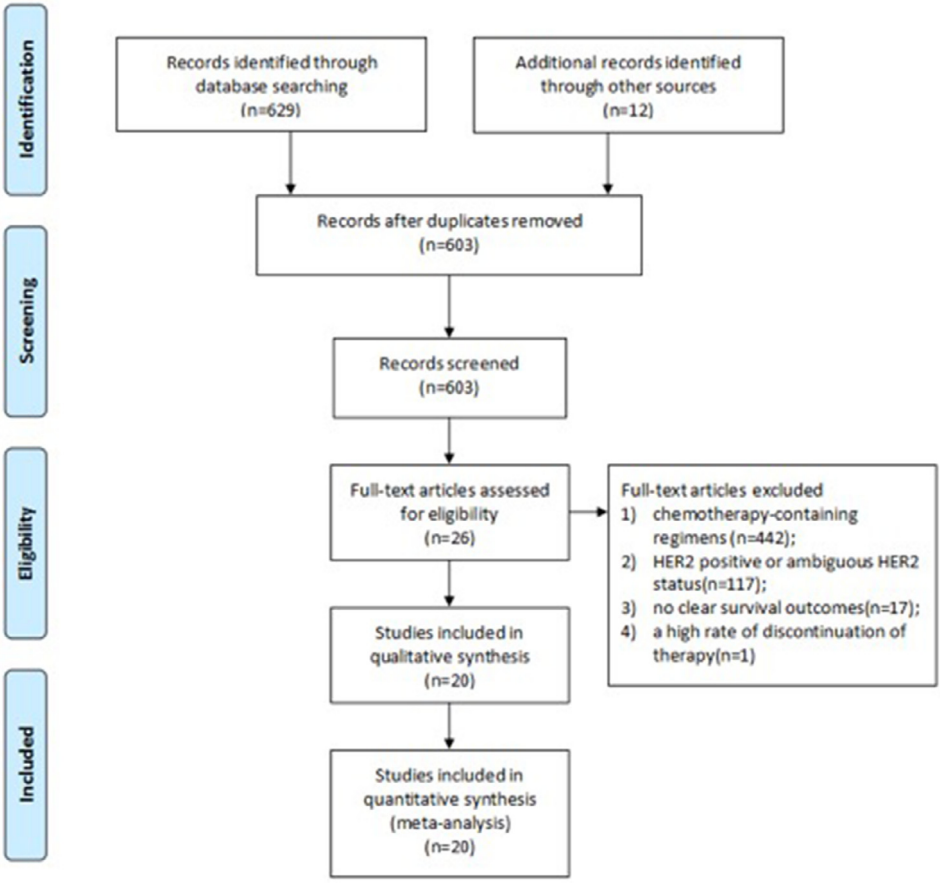

Fig. A. Flowchart of filtering proceedings for eligible trials.

Appendix B

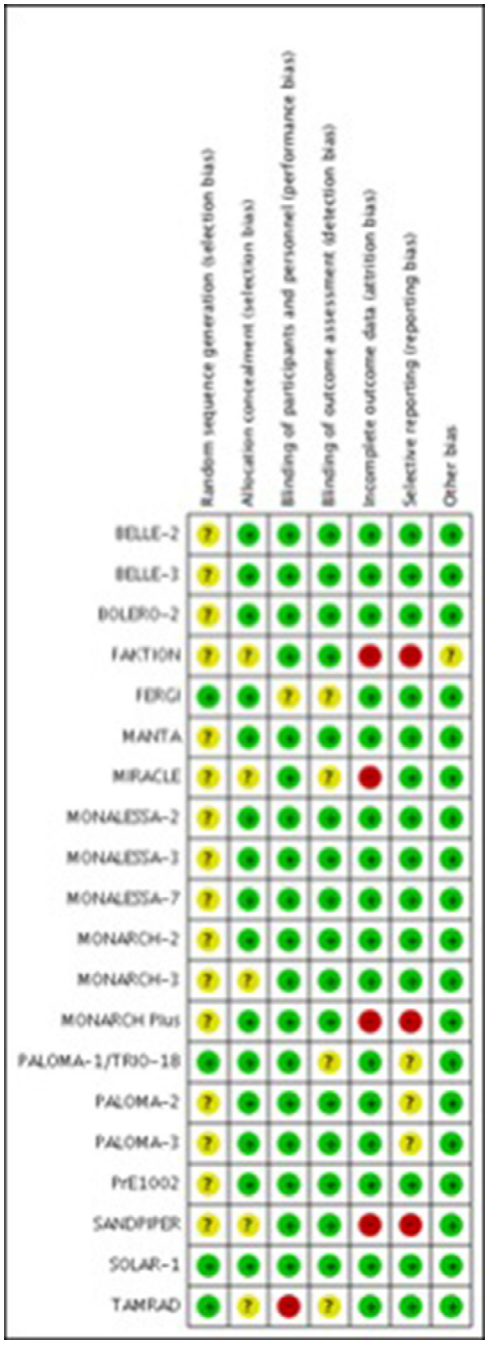

Fig. B. Quality assessment for bias items of RCTs.

Appendix C

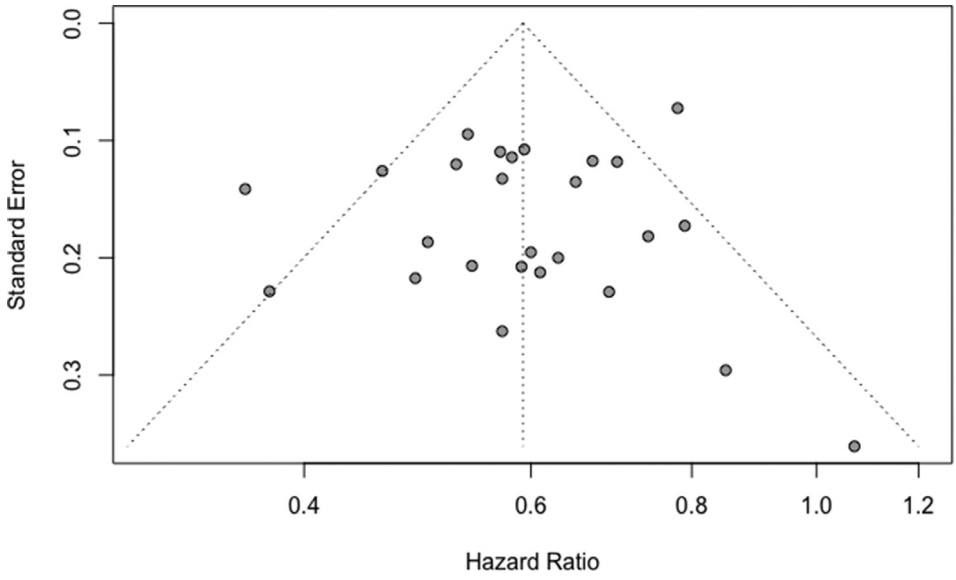

Fig. C. Funnel plot of included studies (P=0.52).

Appendix D

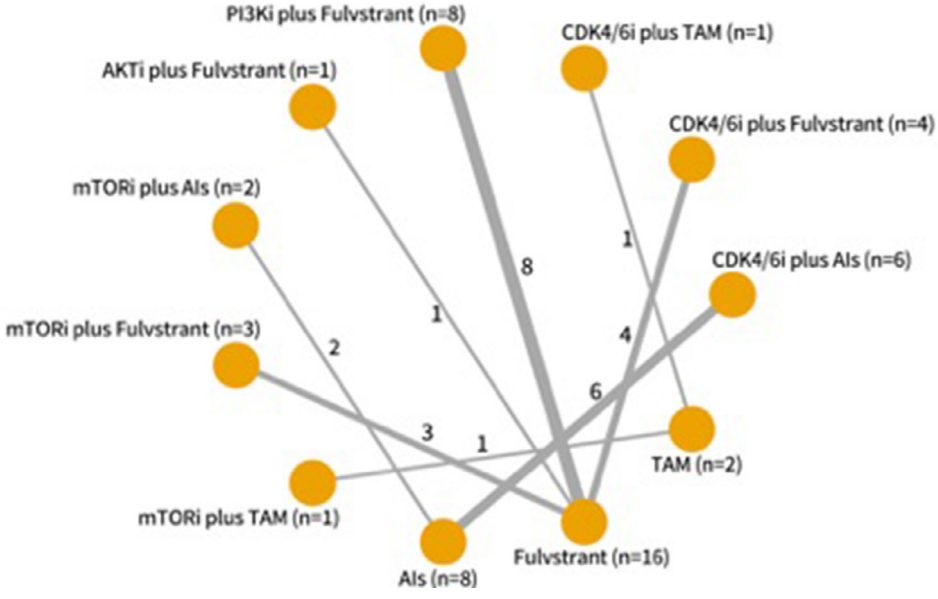

Fig. D. Network of comparative interventions.
Each node represents a variety of interventions in this study (n=11). Lines correspond the direct comparison relationships with the thickness related to available numbers (n=25). Treatments included CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib), PI3K inhibitors (alpelisib, buparlisib, taselisib, pictilisib), AKT inhibitor (capivasertib) and mTOR inhibitors (everolimus, vistusertib).

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