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Scoping review

CDK4/6 inhibitors in HR-positive/HER2-negative breast cancer: a scoping review of randomized clinical trials

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Summary

Introduction. Breast cancer is the most common malignancy in women and a leading cause of cancer mortality. The HR-positive/HER2-negative subtype accounts for most cases and is characterized by initial endocrine sensitivity followed by resistance. This study aimed to map and interpret randomized clinical trial evidence on the efficacy and safety of CDK4/6 inhibitor-based treatment strategies across different clinical settings in HR-positive/HER2-negative breast cancer.

Methods. A scoping review of randomized phase II/III trials (2015–2025) was conducted using PubMed/MEDLINE and manual reference screening. Studies evaluating palbociclib, ribociclib or abemaciclib with endocrine therapy were included if reporting PFS, OS or iDFS.

Results. Twenty-two randomized trials were included, covering first-line metastatic, later-line, post-CDK4/6 progression and adjuvant settings. CDK4/6 inhibitors consistently improved PFS, with the most robust benefit in first-line and endocrine-resistant disease. OS benefit was demonstrated in several trials, particularly with ribociclib and abemaciclib, though results were heterogeneous. Evidence on optimal sequencing and post-progression strategies remains limited. In the adjuvant setting, benefit was not uniform: positive results for abemaciclib and ribociclib but not for palbociclib.

Conclusion. CDK4/6 inhibitors are a cornerstone of treatment in HR-positive/HER2-negative breast cancer. However, unresolved questions include optimal sequencing, management after progression, and predictive biomarkers. Future research should focus on biomarker-driven and individualized strategies based on tumor biology and disease dynamics.

Key words: CDK4/6 inhibitors, breast cancer, palbociclib, ribociclib, abemaciclib, endocrine therapy

Introduction

According to Global Cancer Observatory (GLOBOCAN) 2020 estimates, breast cancer is the most commonly diagnosed malignancy in women and the leading cause of cancer death in this population, with approximately 2.3 million new cases and 685 000 deaths annually worldwide [1]. Among molecular subtypes, hormone receptor-positive (HR-positive)/HER2-negative breast

cancer is the most frequent, accounting for more than 70% of all cases [2]. Despite favourable initial responses to endocrine therapy, disease progression due to acquired or intrinsic resistance remains a key clinical challenge. In patients with metastatic disease previously treated with aromatase inhibitors, a substantial proportion develop resistance to endocrine therapy, which is associated with acquired ESR1 mutations and other mechanisms [3].

Resistance mechanisms involve alterations in oestrogen receptor signaling, activation of alternative pathways (PI3K/AKT/mTOR, MAPK) and increased cyclin pathway activity [4–6]. In the normal cell cycle, the cyclin D–CDK4/6 complex phosphorylates the retinoblastoma protein, allowing transition from G1 to S phase [7]. In HR-positive breast cancer, dysregulation of this pathway leads to uncontrolled proliferation, providing the biological rationale for targeted therapy [8].

Three CDK4/6 inhibitors are currently in wide clinical use: palbociclib, ribociclib and abemaciclib [9]. Their regulatory approvals were obtained between 2015 and 2018 for metastatic disease and subsequently for adjuvant therapy [10]. Although they share a common mechanism of action, they differ in pharmacological characteristics and toxicity profiles.

More recently, beyond their established efficacy in the metastatic setting, the role of CDK4/6 inhibitors has expanded to adjuvant therapy of early-stage breast cancer with a high risk of recurrence [11, 12]. At the same time, new clinical challenges have emerged, particularly regarding optimal therapy sequencing, management after progression on CDK4/6 inhibitors, and identification of predictive biomarkers [13, 14]. While individual systematic reviews and meta-analyses exist, there is still a need for a review that maps randomized evidence on CDK4/6 inhibitors across all treatment settings – from first-line metastatic disease, through post-CDK4/6 strategies, to adjuvant treatment of early-stage disease.

At present, considerable heterogeneity exists across treatment settings, including first-line metastatic disease, endocrine-resistant disease, sequencing approaches, post-progression strategies and adjuvant therapy. Additional heterogeneity relates to outcome definitions, such as progression-free survival (PFS), overall survival (OS), invasive disease-free survival (iDFS) and PFS2, as well as to study design features including crossover and the use of subsequent therapies. In this context, a scoping review is a more appropriate methodological approach than a conventional systematic review with meta-analysis. A scoping approach enables structured mapping of heterogeneous evidence, identification of major patterns and consistent findings, and clarification of key gaps in the literature, without requiring quantitative pooling of clinically non-comparable studies [15, 16].

Therefore, this work was conceived as a scoping review aiming to systematically map the scope and structure of randomized clinical trial evidence on CDK4/6 inhibitor-based treatment strategies in HR-positive/HER2-negative breast cancer. The objective was not to generate a pooled estimate of effect, but rather to identify patterns of efficacy, safety, sequencing approaches and unresolved clinical questions across different therapeutic settings.

The aim of this study was to map and interpret randomized clinical trials investigating CDK4/6 inhibitors in HR-positive/HER2-negative breast cancer, with particular focus on treatment settings, key efficacy outcomes, safety profiles and open questions in therapy sequencing and treatment individualization.

Methods

Study design

This study was conducted as a scoping review of randomized clinical trials evaluating CDK4/6 inhibitor-based treatment strategies

in HR-positive/HER2-negative breast cancer. The review was undertaken to map the available randomized evidence across different clinical settings, including first-line metastatic disease, later-line treatment, biomarker-guided or post-CDK4/6 approaches, and adjuvant therapy. The review process was conceptually informed by the PRISMA Extension for Scoping Reviews (PRISMA-ScR) framework [15]. Because of the marked heterogeneity of study settings, comparators, endpoints and therapeutic contexts, the objective of this review was structured evidence mapping rather than formal quantitative synthesis.

Literature search strategy

A structured literature search was performed in the PubMed/MEDLINE database for studies published between 1 January 2015 and 31 December 2025. The search was conducted on 10 January 2026. PubMed/MEDLINE was selected as the primary database because it provides comprehensive coverage of high-quality biomedical literature, particularly for phase II and III oncology trials. Because the aim of this work was to map the landscape of randomized clinical evidence rather than to perform an exhaustive systematic review with meta-analysis, the search was restricted to one major bibliographic database and to English-language publications. This should be recognized as a methodological limitation.

The following PubMed search string was used:

- ("cyclin-dependent kinase 4"[MeSH] OR "cyclin-dependent kinase 6"[MeSH] OR CDK4[tiab] OR CDK6[tiab] OR "CDK4/6 inhibitor"[tiab] OR palbociclib[tiab] OR ribociclib[tiab] OR abemaciclib[tiab]) AND ("breast neoplasms"[MeSH] OR "breast cancer"[tiab]) AND ("receptor, erbB-2"[MeSH] OR "HER2 negative"[tiab] OR "HER2-"[tiab]) AND ("receptors, estrogen"[MeSH] OR "receptors, progesterone"[MeSH] OR "HR positive"[tiab] OR "ER+"[tiab]) AND (randomized controlled trial[pt] OR clinical trial, phase III[pt] OR clinical trial, phase II[pt]) AND ("2015/01/01"[PDat] : "2025/12/31"[PDat]) AND (english[Filter])

Reference lists of key articles were also examined manually in order to identify any additional relevant publications that may not have been captured by the initial search.

Study selection

Study selection was performed in two stages: initial screening of titles and abstracts, followed by full-text assessment of potentially relevant articles. The objective was to identify randomized phase II and III clinical trials relevant to the contemporary use of CDK4/6 inhibitor-based strategies in HR-positive/HER2-negative breast cancer. Two reviewers independently assessed study eligibility, and disagreements were resolved by discussion and consensus.

After full-text evaluation, 22 unique randomized clinical trials met the inclusion criteria including primary reports and later follow-up publications with updated survival results. Reasons for exclusion during full-text assessment included inappropriate study design, ineligible population, lack of clinically relevant outcomes, or duplicate/secondary publication without substantially new data. A flow diagram of the identification, screening and inclusion process is provided in the Appendix.

Inclusion and exclusion criteria

Studies were eligible if they met the following criteria:

- (1) randomized phase II or III clinical trial design;
- (2) evaluation of approved CDK4/6 inhibitors (palbociclib, ribociclib or abemaciclib),

either alone as the main investigational strategy or as a core component of a combination strategy;
- (3) inclusion of patients with HR-positive/HER2-negative breast cancer; and
- (4) reporting clinically relevant outcomes, including PFS, OS, iDFS or comparable survival endpoints.

Studies were excluded if they involved non-HR-positive/HER2-negative populations, evaluated non-approved CDK4/6 inhibitors, were preclinical studies, biomarker-only studies without clinical outcomes, phase I studies without relevant efficacy data, or neoadjuvant studies without survival-oriented endpoints. Real-world studies, translational studies and non-randomized designs were not systematically included, although they could be considered in the discussion when relevant for biological interpretation.

Data extraction and synthesis

Because this was a scoping review, the synthesis was descriptive and interpretative rather than quantitative. Data were extracted on study setting, patient population, intervention and comparator, sample size, major efficacy outcomes and key safety findings. The purpose of the synthesis was to map patterns of evidence across treatment settings, identify areas of consistency and inconsistency, and highlight clinically important gaps, particularly in sequencing, post-progression management and adjuvant use.

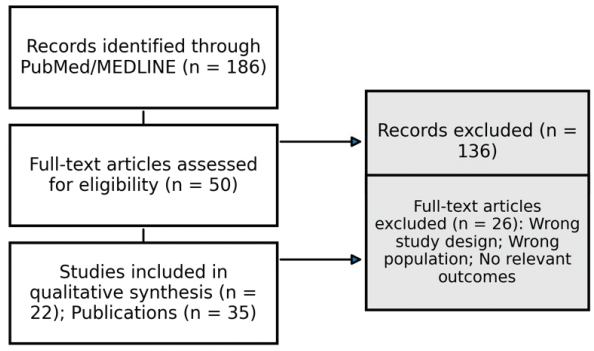
Methodological considerations

A formal standardized risk-of-bias assessment, such as ROB 2, was not undertaken because the aim of the present study was evidence mapping rather than formal appraisal for pooled comparative inference. This approach is consistent with the methodological purpose of scoping reviews, which focus on evidence mapping rather than critical appraisal for pooled effect estimation. Nevertheless, important methodological features of the included trials—such as phase, comparator selection, follow-up maturity, crossover and the availability of survival updates—were considered when interpreting the results.

Protocol and registration

This review was not prospectively registered, and no formal review protocol was published in advance.

Appendix



Results

Characteristics of included studies

The included studies covered a wide spectrum of treatment settings, from firstline metastatic disease to adjuvant therapy for earlystage disease. A total of 22 randomized phase III clinical trials met the inclusion criteria. A complete list of the included randomized studies with their key characteristics is presented in Table 1 (firstline metastatic), Table 2 (endocrineresistant/secondline), Table 3 (postCDK4/6 progression), Table 4 (adjuvant) and Table 5 (safety profile).

All firstline trials demonstrated significant PFS improvement with CDK4/6 inhibitor

addition (HR 0.540.58). OS benefit was observed for ribociclib in MONALEESA2 and MONALEESA7, while palbociclib and abemaciclib did not show statistically significant OS improvement in their respective phase III trials (Table 1).

Table 1. Randomized phase III trials of CDK4/6 inhibitors in the firstline metastatic setting (HRpositive/HER2negative breast cancer)

Study	Population / context	Regimen vs comparator	N	Median PFS (months)	HR (95% CI) for PFS	OS outcome
PALOMA2 [17–19]	Postmenopausal, firstline	PAL + LET vs LET	666	24.8 vs 14.5	0.58 (0.460.72)	Not significant
MONALEESA2 [20, 21]	Postmenopausal, firstline	RIB + LET vs LET	668	25.3 vs 16.0	0.57 (0.460.70)	Improved
MONARCH 3 [22, 23]	Postmenopausal, firstline	ABE + AI vs AI	493	28.2 vs 14.8	0.54 (0.410.72)	Not significant
MONALEESA7 [24, 25]	Premenopausal, firstline	RIB + ET vs ET	672	23.8 vs 13.0	0.55 (0.440.69)	Improved
RIGHT Choice [26, 27]	Visceral crisis / aggressive disease	RIB + ET vs chemotherapy	222	24.0 vs 12.3	0.54 (0.360.79)	NR
SONIA [28, 29]	Strategy trial (early vs delayed CDK4/6)	CDK4/6 early vs delayed	1050	24.7 vs 26.8	0.87 (0.741.03)	Not significant
FLIPPER [30]	Endocrinesensitive, elderly	PAL + FUL vs FUL	189	31.8 vs 22.0	0.64 (0.430.95)	NR
PARSIFAL [31]	Endocrinesensitive, firstline	PAL + FUL vs PAL + LET	486	27.9 vs 32.8	1.13 (0.851.44)	NR

Abbreviations: PAL - palbociclib; RIB - ribociclib; ABE - abemaciclib; LET - letrozole; FUL - fulvestrant; ET - endocrine therapy; AI - aromatase inhibitor; PFS - progressionfree survival; OS - overall survival; NR - not reported or not mature.

In endocrineresistant disease, all three CDK4/6 inhibitors combined with fulvestrant improved PFS. OS benefit was observed for ribociclib (MONALEESA3) and abemaciclib (MONARCH 2), but not for palbociclib (PALOMA3). The PEARL and YoungPEARL trials compared palbociclib plus endocrine therapy versus capecitabine and did not show consistent statistically significant benefit (Table 2).

Table 2. Randomized phase III trials of CDK4/6 inhibitors in endocrineresistant / secondline setting (HRpositive/HER2negative breast cancer)

Study	Population / context	Regimen vs comparator	N	Median PFS (months)	HR (95% CI) for PFS	OS outcome
PALOMA3 [32, 33]	Progression on endocrine therapy	PAL + FUL vs FUL	521	9.5 vs 4.6	0.46 (0.360.59)	Not significant
MONARCH 2 [32, 33]	Endocrineresistant disease	ABE + FUL vs FUL	669	16.4 vs 9.3	0.55 (0.450.68)	Improved
MONALEESA3 [34, 35]	First and secondline	RIB + FUL vs FUL	726	20.5 vs 12.8	0.59 (0.480.73)	Improved
PEARL [38]	Aromatase inhibitorresistant	PAL + ET vs capecitabine	601	7.5 vs 9.5	1.13 (0.941.36)	Not significant
YoungPEARL [39, 40]	Premenopausal, endocrineresistant	PAL + ET vs capecitabine	184	20.1 vs 14.4	0.66 (0.431.02)	NR

Abbreviations: PAL - palbociclib; RIB - ribociclib; ABE - abemaciclib; FUL - fulvestrant; ET - endocrine therapy; PFS - progressionfree survival; OS - overall survival; NR - not reported or not mature.

In the postprogression setting after prior CDK4/6 therapy, simple continuation of the same inhibitor generally does not lead to clinical benefit (PACE, PALMIRA). Modest but statistically significant PFS improvements were seen with biomarkerguided switching (PADA1), switching the endocrine partner and changing the CDK4/6 inhibitor to ribociclib (MAINTAIN) or to abemaciclib (postMONARCH) (Table 3).

Table 3. Randomized phase III trials of CDK4/6 inhibitors in the postCDK4/6 progression setting (HRpositive/HER2negative breast cancer)

Study	Population / context	Regimen vs comparator	N	Median PFS (months)	HR (95% CI) for PFS	OS outcome
PADA1 [13]	ESR1mutated disease	Switch ET + PAL vs continue AI	1017	11.9 vs 5.7	0.63 (0.490.81)	NR
MAINTAIN [41]	After prior CDK4/6 inhibitor	RIB + ET vs ET	119	5.3 vs 2.8	0.57 (0.390.82)	NR
PACE [42]	After prior CDK4/6 inhibitor	FUL + PAL vs FUL	220	4.6 vs 4.8	1.10 (0.791.56)	NR
postMONARCH [14]	After prior CDK4/6 inhibitor	ABE + FUL vs FUL	368	6.0 vs 5.3	0.73 (0.570.95)	NR
PALMIRA [43]	After prior CDK4/6 inhibitor	PAL + ET vs ET	198	4.9 vs 3.6	0.84 (0.661.07)	NR

Abbreviations: PAL - palbociclib; RIB - ribociclib; ABE - abemaciclib; FUL - fulvestrant; ET - endocrine therapy; AI - aromatase inhibitor; PFS - progressionfree survival; OS - overall survival; NR - not reported or not mature.

Adjuvant benefit of CDK4/6 inhibitorbased therapy is not a uniform class effect. Abemaciclib (monarchE) and ribociclib (NATALEE) demonstrated significant improvement in invasive diseasefree survival, while palbociclib did not show comparable benefit in two large randomized adjuvant studies (PALLAS, PENELOPEB) (Table 4).

Table 4. Randomized phase III adjuvant trials of CDK4/6 inhibitors in earlystage HRpositive/HER2negative breast cancer

Study	Population	Intervention	Comparator	N	Key outcome	HR (95% CI)	Result
monarchE [11, 44]	Highrisk, nodepositive	Abemaciclib + ET	ET	5637	iDFS (4year)	0.68 (0.600.77)	Positive
NATALEE [12, 45]	Stage II–III	Ribociclib + ET	ET	5101	iDFS (3year)	0.75 (0.620.91)	Positive
PALLAS [46]	Stage II–III	Palbociclib + ET	ET	5760	iDFS	0.97 (0.791.18)	Negative
PENELOPEB [47]	Highrisk after neoadjuvant chemotherapy	Palbociclib + ET	ET	1250	iDFS	0.93 (0.741.17)	Negative

Abbreviations: ET - endocrine therapy; iDFS - invasive diseasefree survival; HR - hazard ratio.

Palbociclib and ribociclib are predominantly associated with haematologic toxicity, particularly neutropenia. Ribociclib additionally requires ECG and liver enzyme monitoring due to the risk of QT prolongation and hepatotoxicity. Abemaciclib is characterised by less myelosuppression but a higher frequency of gastrointestinal adverse events, especially diarrhoea, which requires early intervention and dose adjustment (Table 5).

Table 5. Safety profile of CDK4/6 inhibitors in HRpositive/HER2negative breast cancer

Drug	Dominant toxicity	Grade ≥3 (%)	Key monitoring requirement
Palbociclib	Neutropenia	~60–65%	Regular blood count monitoring
Ribociclib	Neutropenia + QT prolongation + hepatotoxicity	~60%	ECG, liver enzyme monitoring
Abemaciclib	Diarrhoea (gastrointestinal)	~10–15%	Early intervention, dose adjustment

Discussion

This scoping review shows that randomized evidence on CDK4/6 inhibitor-based treatment strategies in HR-positive/HER2-negative breast cancer is distributed across several clinically distinct settings, with the most consistent benefit observed in prolongation of progression-free survival. In contrast, findings related to overall survival, optimal sequencing and treatment after progression are more heterogeneous and require cautious interpretation.

CDK4/6 inhibitors as a core component of treatment

The available randomized trials consistently support the use of CDK4/6 inhibitors in combination with endocrine therapy as a central component of treatment in HR-positive/HER2-negative advanced breast cancer. Across first-line and endocrine-resistant settings, the most robust and reproducible finding is prolongation of PFS. However, the degree and consistency of OS benefit vary across trial programs. Although OS improvement was demonstrated in several studies involving ribociclib and abemaciclib, cross-trial comparisons should not be interpreted as evidence of superiority of one agent over another, because the included studies differed in patient populations, prior treatments, study design, follow-up maturity and access to subsequent therapies.

Differential impact across clinical settings

The magnitude and clinical meaning of benefit differ according to treatment context. In endocrine-resistant disease, CDK4/6 inhibitor-based combinations appear particularly relevant, supporting the biological rationale that these agents may help overcome mechanisms of endocrine escape. In contrast, in the first-line setting, where endocrine sensitivity is often greater, interpretation of long-term outcomes is more strongly influenced by post-protocol therapies and other design-related factors. This distinction is important when interpreting both efficacy results and future sequencing strategies.

Sequencing and biomarker-guided strategies

One of the major unresolved issues identified by this review is the optimal sequencing of CDK4/6 inhibitor-based treatment. The SONIA trial [27-29] suggests that early universal use may not

necessarily provide a clinically meaningful advantage for every patient when compared with deferred introduction in later-line therapy, thereby supporting a more individualized approach. From a health-economic perspective, deferring CDK4/6 inhibitors to second line may reduce treatment costs and exposure to adverse events without compromising long-term outcomes, as suggested by the PFS2 results of SONIA. At the same time, studies of post-progression strategies indicate that simple continuation of the same CDK4/6 inhibitor after disease progression is generally not beneficial. More nuanced approaches, including change of endocrine partner and, in selected circumstances, change of CDK4/6 inhibitor, may provide modest benefit.

The PADA-1 study [13] is particularly important because it demonstrates that emerging endocrine resistance can be detected through circulating tumor DNA before overt clinical progression. This supports the future integration of molecular monitoring into therapeutic decision-making and represents one of the clearest examples of a transition from fixed-line treatment algorithms towards adaptive, biomarker-guided management. However, no biomarker is currently validated for routine clinical decision-making in this context.

Early-stage disease

Mapping of adjuvant trials shows that benefit is not uniformly established across all CDK4/6 inhibitors. Positive findings with abemaciclib [11, 44] and ribociclib [12, 45] contrast with the lack of benefit observed in large palbociclib-based adjuvant trials [46, 47]. These differences are unlikely to be explained by a single factor alone and probably reflect the interplay of patient selection, disease-risk definition, treatment duration, adherence, dose exposure and biological differences between therapeutic agents. Therefore, current evidence does not support the assumption that adjuvant efficacy is a universal class effect.

Safety profile and quality of life

A clinically important strength of CDK4/6 inhibitors is that their toxicity profile is generally predictable and manageable. Nevertheless, their use requires treatment-specific monitoring. Palbociclib and ribociclib are more strongly associated with neutropenia, whereas abemaciclib more frequently causes gastrointestinal toxicity, especially diarrhea. Ribociclib additionally requires attention to liver function and electrocardiographic monitoring. In routine practice, these adverse effects are usually manageable through dose modification and supportive care, which contributes to the clinical feasibility of prolonged treatment [19, 21, 23].

Beyond safety, patient-reported outcomes from pivotal trials indicate that CDK4/6 inhibitors generally maintain or improve quality of life compared with endocrine therapy alone or with chemotherapy. In the RIGHT Choice study [26], the ribociclib-based regimen was associated with a better tolerability profile and preserved quality of life relative to combination chemotherapy, which is particularly relevant for patients with aggressive disease.

A conceptual shift towards dynamic, biology-driven treatment

Taken together, the evidence mapped in this review suggests a gradual shift from fixed-line treatment algorithms towards more dynamic, biology-driven therapeutic strategies. In the metastatic setting, the availability of several CDK4/6 inhibitors, together with the emergence of biomarker-guided approaches such as ESR1 monitoring, challenges the notion of a single universal sequencing strategy. In early-stage disease, the non-uniform adjuvant benefit across the class underlines the importance of risk stratification and careful patient selection. These observations support the need for continued refinement of treatment individualization based on tumor biology,

prior therapy and molecular evolution during treatment.

Limitations

This review has several limitations. First, the literature search was restricted to a single bibliographic database and to English-language publications, which may have resulted in omission of some relevant studies. Second, as this was a scoping review, no formal risk-of-bias assessment was undertaken, and no meta-analysis was performed. Third, the substantial heterogeneity of populations, treatment settings, comparators and endpoints limited direct comparison across trials. Finally, because no head-to-head randomized comparisons between individual CDK4/6 inhibitors were available, any interpretation suggesting relative superiority of one agent over another must remain cautious.

Despite these limitations, the scoping approach is appropriate for the present objective, namely structured mapping of a broad and heterogeneous body of randomized clinical evidence. Future research should focus on biomarker integration, especially circulating tumor DNA, and on the development of clinically useful personalized sequencing strategies based on biological evolution during therapy. In addition, well-designed head-to-head trials or robust network meta-analyses are needed to clarify comparative effectiveness among the CDK4/6 inhibitors.

Conclusion

CDK4/6 inhibitors have fundamentally transformed the treatment landscape of HR-positive/HER2-negative breast cancer, with consistent improvements in progression-free survival across clinical settings and variable effects on overall survival.

Despite these advances, several clinically important questions remain unresolved. Optimal sequencing strategies are not well defined, particularly in the post-progression setting, and there is a clear need for high-quality evidence to guide treatment decisions after failure of CDK4/6 inhibition.

In the adjuvant setting, differences in outcomes across individual agents suggest that treatment effects are not uniform and highlight the importance of drug-specific characteristics and patient selection.

Future research should focus on the identification of predictive biomarkers, optimization of treatment sequencing and development of individualized therapeutic strategies based on tumor biology and disease dynamics.

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CDK4/6 inhibitori u HR-pozitivnom/HER2-negativnom karcinomu dojke: *scoping* pregled randomizovanih kliničkih studija

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Uvod. Karcinom dojke je najčešća maligna bolest kod žena i vodeći uzrok smrtnosti od malignite-ta. Podtip HR-pozitivnog/HER2-negativnog karcinoma čini većinu slučajeva i karakteriše ga početna osjetljivost na endokrinu terapiju uz kasniji razvoj rezistencije. Cilj ovog rada je da mapira i inter-pretira dokaze iz randomizovanih kliničkih studija o efikasnosti i bezbjednosti terapijskih strategija zasnovanih na CDK4/6 inhibitorima u različitim kliničkim kontekstima HR-pozitivnog/HER2-negativ-nog karcinoma dojke.

Metode. Sproveden je *scoping* pregled randomizovanih studija faze II/III korištenjem PubMed/MED-LINE (2015–2025) i ručnim pretraživanjem referenci. Uključene su studije koje su evaluirale palboci-klib, ribociklib ili abemaciklib u kombinaciji s endokrinom terapijom i izvještavale o PFS, OS ili iDFS.

Rezultati. Uključene su 22 randomizovane studije koje pokrivaju prvu liniju metastatske bolesti, ka-snije linije, post-CDK4/6 progresiju i adjuvantno liječenje. CDK4/6 inhibitori konzistentno poboljša-vaju PFS, s najizraženijim efektom u prvoj liniji i endokrino rezistentnoj bolesti. Poboljšanje OS poka-zano je u nekoliko studija, posebno s ribociklibom i abemaciklibom, iako su rezultati heterogeni. Do-kazi o optimalnom sekvenciranju i strategijama nakon progresije ostaju ograničeni. U adjuvantnom okruženju, benefit nije uniforman: pozitivni rezultati za abemaciklib i ribociklib, ali ne i za palbociklib.

Zaključak. CDK4/6 inhibitori su temelj liječenja HR-pozitivnog/HER2-negativnog karcinoma dojke. Međutim, neriješena pitanja uključuju optimalno sekvenciranje, pristup nakon progresije i identifika-ciju prediktivnih biomarkera. Buduća istraživanja treba da se fokusiraju na pristupe vođene biomar-kerima i individualizovane strategije zasnovane na biologiji tumora.

Ključne riječi: CDK4/6 inhibitori, karcinom dojke, palbociklib, ribociklib, abemaciklib, endokrina te-rapija