CLINICAL BENEFITS OF CDK 4/6 INHIBITORS IN HR+ HER2- METASTATIC BREAST CANCER: A SYSTEMATIC REVIEW

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BACKGROUND

- Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors palbociclib, ribociclib, and abemaciclib are widely used for the first-line treatment of locally advanced or metastatic breast cancer (mBC).
- Direct comparisons of these treatments in randomized controlled trials (RCTs) are lacking.

OBJECTIVES

- The aim of the study is to gather and analyze published data on the comparative effectiveness of CDK4/6 inhibitors in combination with aromatase inhibitors (AI) in postmenopausal patients with HR+/HER2– mBC.

METHODS

- A systematic search in PubMed database was performed in September 2023.
- Inclusion criteria:
  - Target population: adult postmenopausal patients with HR+/HER2– mBC who had no prior CDK 4/6 therapy in the advanced setting;
  - Treatment: palbociclib + AI, ribociclib + AI, abemaciclib + AI, AI (only in control group);
  - Outcomes: overall survival (OS), progression free survival (PFS);
  - Trial type: original research (including randomized controlled clinical trials), prospective cohort studies (single-arm studies), retrospective comparative and non-comparative real-world evidence (RWE) trials, indirect comparisons, and meta-analyses.

RESULTS

- 2,528 publications were found of which 2,228 were excluded after titles and annotations analysis, and 281 were excluded after a full-text analysis.
- 19 publications were included (see Figure 1). These involved 7 RWE studies, 1 naïve comparison, 2 MAICs, and 9 meta-analyses.
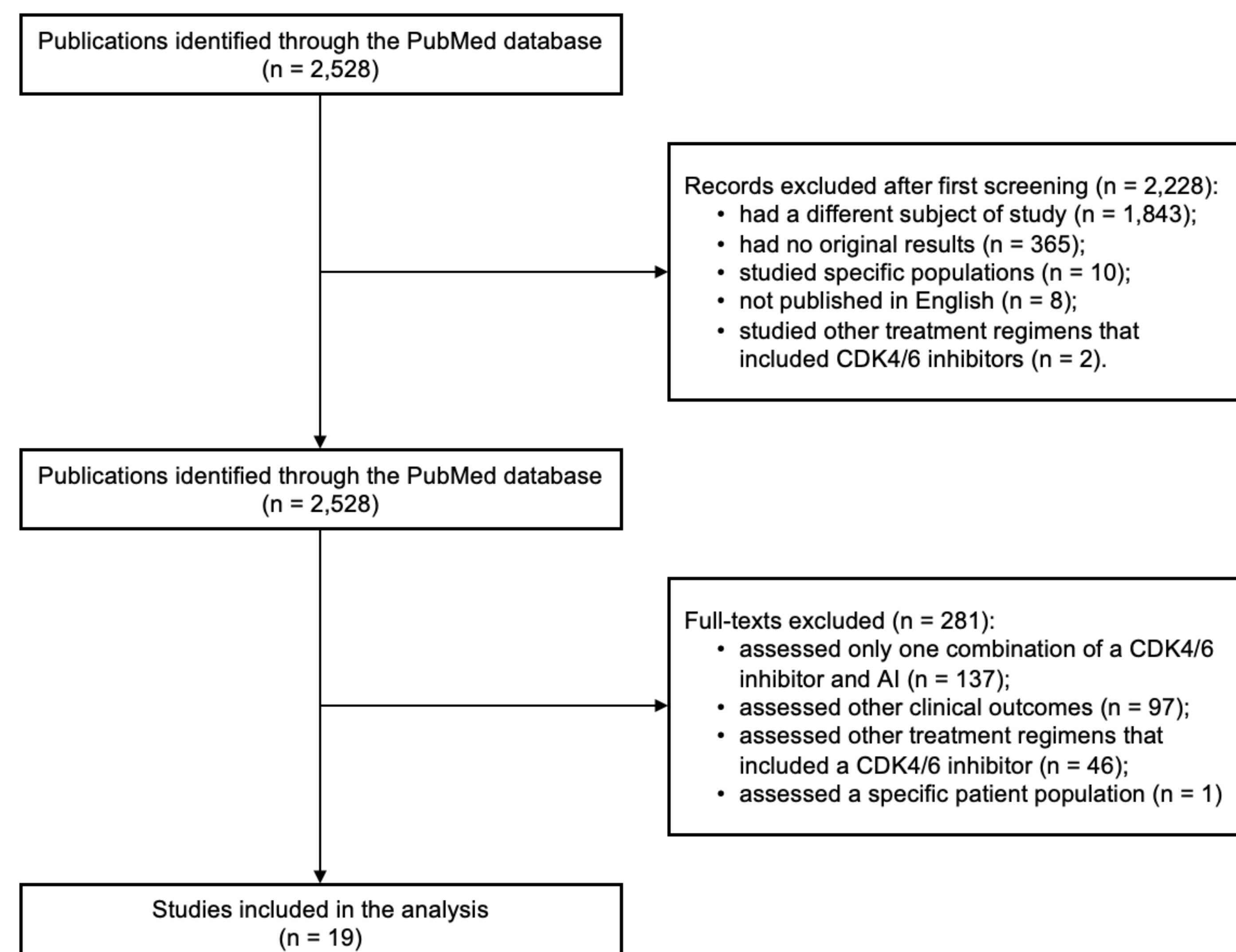

Figure 1. Flow diagram.

- The hazard ratio (HR) range for progressive-free survival (PFS) was 0.97-1.25 in case of palbociclib vs. ribociclib, 1.00-1.27 in case of palbociclib vs. abemaciclib, and 1.03-1.10 in case of ribociclib vs. abemaciclib (see Figure 2).
- None of the studies established statistically significant differences in PFS between the different CDK4/6 inhibitors.
- The HR range for overall survival (OS) was 1.06-1.47 in case of palbociclib vs. ribociclib, 1.08-1.23 in case of palbociclib vs. abemaciclib, and 1.01-1.06 in case of ribociclib vs. abemaciclib (see Figure 3).
- A statistically significant superiority of ribociclib over palbociclib in terms of OS was observed in a single MAIC (Jhaveri K. et al., 2022), while five other studies of various types did not find significant differences between the investigated drugs in terms of this efficacy endpoint. The MAIC methodology remains controversial due to potential hidden differences between studies, especially in early relapse frequency in the underlying RCTs and patient management after treatment failure.
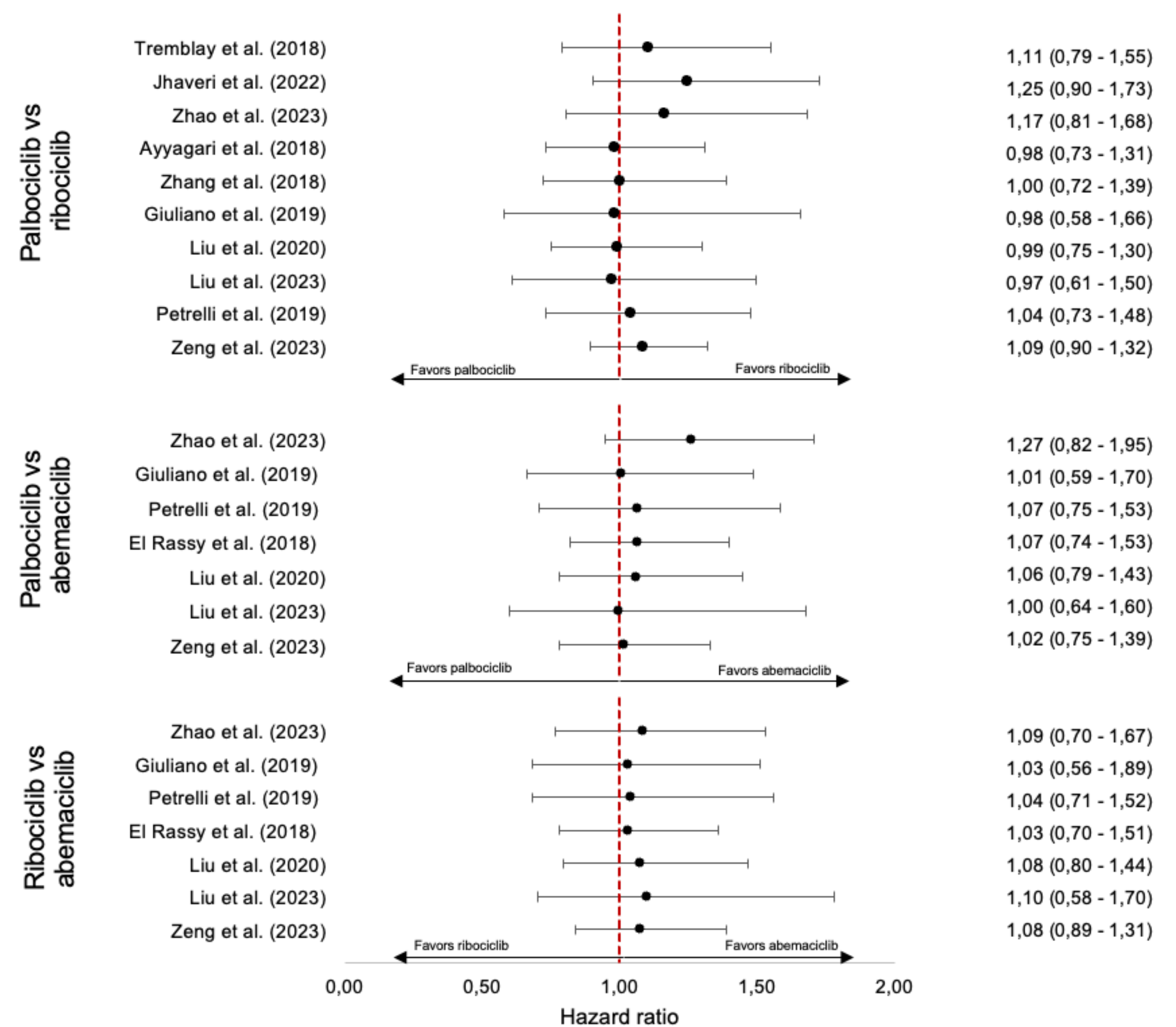

Figure 2. Forest plot of HR ranges for PFS with 95% confidence intervals.
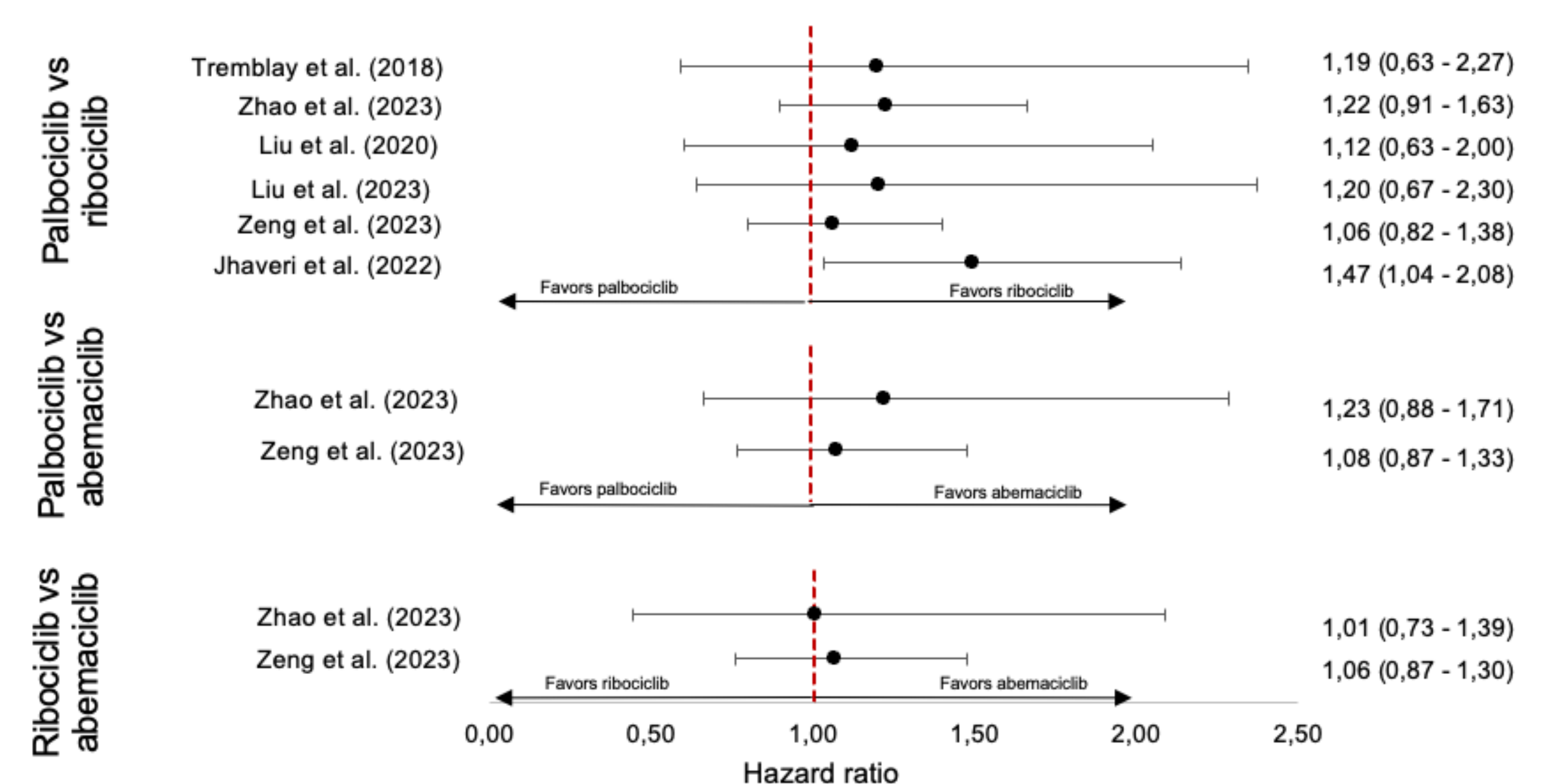

Figure 3. Forest plot of HR ranges for OS with 95% confidence intervals.

CONCLUSIONS

- There is no compelling evidence of the superiority of one CDK4/6 inhibitor over others. A preference for a specific drug within the class can only be made after conducting direct RCTs or accumulating sufficient RWE on the use of such drugs.

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