Efficacy of Palbociclib Combinations Versus Endocrine Therapies in Advanced/Metastatic Breast Cancer: Network Meta-Analysis

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BACKGROUND

- Palbociclib (IBRANCE®) is the only cyclin-dependent kinase 4/6 inhibitor currently approved in the United States for the treatment of hormone receptor–positive/ human epidermal growth factor receptor 2–negative (HR+ HER2-) advanced metastatic breast cancer, in combination with either letrozole (as initial endocrine therapy) or fulvestrant (after disease progression following endocrine therapy).1-4
- Head-to-head trial data are available for only palbociclib plus letrozole vs letrozole alone and for palbociclib plus fulvestrant vs fulvestrant alone. No data are available on the efficacy of palbociclib combinations compared with other endocrine therapies.
- The single-agent comparison drugs in these trials may not be standard care in some countries; therefore, efficacy of palbociclib combination therapies compared with efficacy of other standard endocrine agents is of interest to decision makers.

OBJECTIVE

- To compare the progression-free survival (PFS) hazard ratio (HR) for approved palbociclib combination regimens with that of other endocrine therapies (ie, first line) and with that of other standard endocrine therapies, after disease progression following initial endocrine therapy (ie, previously treated) using a mixed-treatment comparison (MTC) meta-analysis of randomized controlled trials (RCTs).

METHODS

Systematic Literature Review

- A systematic literature review (SLR) search with the following characteristics was performed in January 2015:
  - Data sources: MEDLINE, Embase, and the Cochrane Library; bibliographies of all relevant SRs identified in the database searches, conference internet sites.
- Studies All RCTs of the key endocrine therapies and palbociclib used to treat postmenopausal women with estrogen receptor–positive (ER+)/HER2– locally advanced or metastatic breast cancer, first-line or second-line (previously treated).
- Scoring methods: Two independent reviewers screened identified titles and abstracts and then full-text articles, disagreements were resolved by discussion or a third reviewer.
- Data extraction: Performed using a preprepared data extraction template in Excel (Microsoft Corporation, Redmond, WA, USA).

- At the time of the SLR, only results from the PALOMA-1 trial were available, and it was planned that results from the PALOMA-2 and 3 trials would be used as they became available.

Statistical Methods

- The studies included from the SLR were further evaluated for inclusion into first-line or previously treated MTC.
- PFS is defined as the time from randomization until progression or death of any cause, whichever comes first. Time to progression (TTP), usually defined as the time from randomization until progression, also includes, in some studies, time to death. In these studies, TTP has the same definition as PFS, therefore, they were included in the analysis. Studies involving other definitions of TTP were not included in the analysis.
- Separate MTCs were conducted for trials of first- or second-line therapies through a Bayesian approach that was implemented in SADs version 9.3, SADs Institute, Cary, NC, USA) using the Merlon chiao Monte Carlo procedure. The convergence of the model-parameter estimates was checked using the visual-diagnostic plots and tests, and posterior mean deviance (Diab) and deviance information criterion (DIC) were calculated.
- The log of the PFS HR for one treatment comparison in each study was modeled using random- and fixed-effect linear mixed models. The geometry of networks (ie, study per treatment comparison in most cases) made parameter estimates unreliable and caused wide credible intervals (CIs) in the random-effect models. Therefore, fixed-effects results are presented and discussed.
- Posterior median PFS HR and 95% CIs were provided for the treatment comparisons. There was a significant difference between the treatments if the 95% CIs did not include the value 1.00.
- Based on output from MTC, treatment rankings were established using the surface under the cumulative ranking curve (SUCRA).
- Assessment of heterogeneity using the Higgins I² and sensitivity analyses were performed.

RESULTS

Systematic Literature Review

- Figure 5 presents the SLR results along with the selection of MTC studies included for the first- and second-line therapy analyses.

Figure 1. PRISMA Diagram

- Of the 103 sources considered for the meta-analysis, 65 were primary sources, and 38 were secondary sources.
- Of the 65 primary sources, 23 were classified as studies of only first-line therapy, 20 were classified as studies of second-line or later therapy, and 19 were classified as studies of both first- and second-line therapy, and 3 were classified as having an unclear line of therapy.

Palbociclib + Letrozole (First Line) Comparisons

- 3 studies were included, with a total of 926 patients and mean or median age between 61 and 67 years (Figure 2A).

- Palbociclib plus letrozole was associated with significantly longer PFS than all comparator—letrozole, tamoxifen, and anastrozole—with PFS HRs from 0.41 to 0.67 (Figure 3).

- No statistically significant difference was observed between letrozole and anastrozole (PFS HR, 1.01; 95% CI, 0.77–1.32).

- Palbociclib plus letrozole had the highest probability of being the best treatment among the 4 treatments compared (99.8%), and the SUCRA value (99.9%) was almost 100%.

- Due to the geometry of the network, no heterogeneity or sensitivity analyses were feasible to perform.

Palbociclib + Fulvestrant (First Line) Comparisons

- 4 studies were included, with a total of 984 patients and mean or median age between 60.5 and 66 years (Figure 2B).

- Palbociclib plus fulvestrant 500 mg was associated with significantly longer PFS than all single-agent comparators (PFS HRs ranging from 0.26–0.44); palbociclib plus fulvestrant 500 mg was not significantly different from exemestane. 10 mg plus exemestane 25 mg (PFS HR, 1.04; 95% CI, 0.84–1.3) (Figure 3).

- Palbociclib plus fulvestrant 500 mg had the second highest probability of being the best treatment among the 10 treatments compared (41%). Everolimus 10 mg plus exemestane 25 mg and palbociclib plus fulvestrant 500 mg had the 2nd highest probability (similar SUCRA values, 95% and 96%, respectively).

- The formal heterogeneity tests showed I² values less than 40%, suggesting mild to moderate heterogeneity. The fixed-effects model result interpretations for the comparison of palbociclib plus fulvestrant 500 mg against the other treatment comparators did not change in any of the sensitivity analyses performed.

DISCUSSION AND LIMITATIONS

- A comprehensive SLR and a robust MTC meta-analysis were conducted to obtain indirect comparisons between palbociclib plus letrozole and first-line endocrine therapies (ie, tamoxifen) and between palbociclib plus fulvestrant and second-line endocrine therapies for postmenopausal women with ER+/HER2– advanced breast cancer.

- The network for the second-line MTC was expansive with the number of nodes between comparators ranging from 1 to 6, as a consequence wider CIs were seen for indirect comparisons with longer distances (eg, exemestane plus letrozole).

- An implication of the network geometry was that no sensitivity analyses or heterogeneity tests could be performed for first-line treatment, and only a limited number of sensitivity analyses were performed for second-line treatment.

CONCLUSIONS

- These results suggest that palbociclib plus letrozole and palbociclib plus fulvestrant are associated with significantly improved PFS compared with all first-line and most second-line endocrine treatments evaluated in this MTC for advanced and metastatic breast cancers.

REFERENCES

4. The Design and Conduct of a Randomized Phase II/III Study of Palbociclib Plus Letrozole in Postmenopausal Women with HR+ER+ HER2- Advanced Breast Cancer, ClinicalTrials.gov; Identifier: NCT01774155; First updated: 2016-02-05.

For questions or more information, please contact drph@rti.org

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