Infectious Complications of Cyclin-Dependent Kinases 4 and 6 Inhibitors in Patients With Hormone Receptor-Positive Metastatic Breast Cancer: A Systematic Review and Meta-analysis

Onur Bas  
Hacettepe University: Hacettepe Universitesi

Enes Erul (eneserul@hotmail.com)  
Hacettepe University: Hacettepe Universitesi  https://orcid.org/0000-0002-2487-2087

Deniz Can Guven  
Hacettepe University: Hacettepe Universitesi

Sercan Aksoy  
Hacettepe University: Hacettepe Universitesi

Research Article

Keywords: cyclin-dependent kinase (CDK), 4/6 Inhibitors, Abemaciclib, Palbociclib infection, Ribociclib

Posted Date: March 2nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1270186/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

**Aim:** The combination of cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors plus endocrine therapy (ET) improved the survival outcomes and became standard of care in the treatment of metastatic hormone-positive breast cancer. However, these combinations increased the risk of neutropenia compared with ET alone. While the infection-related mortalities did not seem to be increased, the exact risk of infections with CDK 4/6 inhibitor and ET combinations is relatively understudied. Therefore, we performed a meta-analysis of CDK 4/6 inhibitor clinical trials to assess the infection risk of adding CDK4/6 inhibitors to ET.

**Material and Method:** We systematically searched the PubMed database for relevant clinical trials. For each study, all grades and grade 3 or higher infections, upper respiratory tract infections (URTIs), urinary tract infections (UTIs), pneumonia and febrile neutropenia rates were recorded, whenever available. The hazard ratios (HR) with %95 confidence intervals (CI) of infection risk were calculated via the generic inverse-variance method with a random-effects model.

**Results:** Nine eligible studies were included in the analyses (MONALEESA-2,3,7, MONARCH-2,3, MONARCH plus, PALOMA-1,2,3). In the meta-analysis of these studies, CDK 4/6 inhibitors plus ET arms were associated with increased all grades infections (HR: 1.77 95% CI: 1.56-2.01 p<0.00001), grade 3 or higher infections, (HR: 1.77, %95 CI:1.28-2.43 p=0.0005), UTIs (HR:1.59 %95 CI: 1.19-2.12 p=0.43), and febrile neutropenia (HR:4.28 %95 CI:1.73-10.62 p=0.002)

**Conclusion:** In this meta-analysis, we observed that adding CDK4/6 inhibitors to ET significantly increased all grades and grade 3 or higher infections, UTIs. We propose that a close vigilance for infections is required for metastatic breast cancer patients using CDK 4/6 inhibitors.

1. Introduction

Breast cancer is the most commonly diagnosed cancer in women and a leading cause of cancer mortality. Approximately 2.2 million people (11.7%) were diagnosed with breast cancer in 2020[1]. Hormone-receptor (HR) positive breast cancer constitutes the largest subgroup, with approximately 2/3 of all breast cancer.

The HR-positive breast cancer is an estrogen-dependent disease[2, 3]. Therefore, the treatment of HR-positive advanced breast cancer has been aimed on effective blocking the estrogen-receptor signaling pathway or decrease estrogen levels for many years. Accordingly, ET is the first-line treatment for HR positive and human epidermal growth factor receptor 2 (HER2) negative advanced breast cancer other than patients presenting with visceral crisis. However, resistance to hormonal blockade is inevitable over time and managing endocrine resistance is most important aspect of ET. New treatment approaches are needed to combat this endocrine-resistance.

Endocrine resistance in breast cancer is linked with alterations in the cycline-D–CDK 4/6–Rb pathway cause the loss of regulation of this critical Rb checkpoint that result in activation of growth factor pathways to bypass endocrine resistance. Considering the instrumental roles of CDK 4/6 in the cell cycle, the inhibition of this cell cycle control points came forward as a therapeutic option in the treatment of HR-positive advanced breast cancer. CDK4/6 inhibitors (ribociclib, palbociclib and abemaciclib) are oral selective inhibitors of CDK4 and CDK6 that inhibits DNA synthesis by blocking cell cycle at G1 to S phase. The addition of CDK4/6 inhibitors to standard ET has improved progression-free survival (PFS) and overall survival of (OS) by helping overcome endocrine resistance.

The most frequent adverse events of CDK 4/6 inhibitors are neutropenia, nausea, diarrhea, and fatigue[4]. The neutropenia is especially frequent, and reported in more than half of the patients in the pivotal (MONARCH-3, PALOMA-3 and MONALEESA-3) clinical trials[5-7]. However, febrile neutropenia rates are surprisingly low in these trials (1 patient, 3 patients, 5 patients respectively), possibly due to reversibility of neutrophil maturation arrest with these agents rather than a true myelotoxicity[8]

Nine randomized controlled trials (MONALEESA-2,3,7, MONARCH-2,3, MONARCH plus, PALOMA-1,2,3)[5-7, 9-19] showed that combination of CDK 4/6 inhibitors plus ET increased neutropenia risk compared with placebo plus ET and several meta-analyses evaluated the pooled neutropenia risk in these studies. However, the risk of infections other than febrile neutropenia, is relatively understudied. Based on the preliminary literature review, we hypothesized that infection rates might be increased. Therefore, we performed a meta-analysis of pivotal clinical trials to assess the magnitude of infection risk of adding CDK4/6 inhibitors to ET.

2. Methods

2.1. Data Sources

We have searched the Pubmed (articles published between January 1st 2015 and March 31st 2021) for relevant clinical trials evaluating the addition of CDK4/6 inhibitors to endocrine therapy in HR-positive HER-2 negative metastatic breast cancers. Search terms included "Abemaciclib" OR "Ribociclib"OR "Palbociclib"AND "Adverse events" OR "Infections" as well as combinations of these terms.

2.2. Study selection and data extraction

Randomized controlled trials testing the addition of CDK 4/6 inhibitors to ET in HR-positive HER-2 negative metastatic breast cancers are included. When more than one report of the same trial was available, the most recent information was considered in the analysis. Irrelevant trials (n=863), trials include chemotherapy arm (MonarchHER[20] trial), trials conducted in the neoadjuvant settings (PALLET[21] trial) and trials without a placebo arm (TREnd[22] trial) were excluded. The flow diagram of the study selection process is shown in Figure 1. Only studies written English were included and analyzed. Two reviewers
(O.B. and E.E) independently extracted data from the studies. Any disagreement was resolved by discussion with senior author. Number of patients, all grades and grade 3 or higher infection, URTIs, UTIs, pneumonia and febrile neutropenia rates are extracted from each study.

2.3 Statistics

The risk of bias was assessed with risk of bias tool by OB and EE. The meta-analysis was performed using the generic inverse-variance method with a random-effects model. The principal summary measure used was the hazard ratios with 95% two-sided confidence intervals. All analyses were done using the Review Manager software, version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). The heterogeneity within each subgroup is reported using the I-square statistics. The p values below 0.05 were considered statistically significant.

3. Results

Nine eligible studies were included in the analyses (MONALEESA-2,3,7, MONARCH-2,3, MONARCH plus, PALOMA-1,2,3). A total of 4555 patients were enrolled in these studies, with 1763 (38.7%) being in the placebo plus ET arm and 2792 (61.3%) in the CDK4/6 inhibitors plus ET arm. A total of 8 studies reported separate data for the all-grade infection and grade 3 or higher infection rates. The infections rates were significantly increased in CDK4/6 inhibitors plus ET arm. (All grade infections HR= 1.77 95% CI: 1.56-2.01 p<0.00001; grade 3 or higher infections HR: 1.77, 95% CI:1.28-2.43 p=0.0005) (Figure 2).

A total of 6 studies reported separate data for the URTIs. 3975 patients were enrolled in the studies, with 1544 (38.8%) being in the placebo plus ET arm and 2431 (61.2%) in the CDK 4/6 inhibitor plus ET arm. Although there was trend towards increased URTI rate in CDK4/6 inhibitors plus ET arm, magnitude of risk increase was lower and did not reach statistical significance (HR= 1.22 95% CI:0.99-1.49 p=0.06) (Figure 3-a). Moderate degree of heterogeneity was noted in the studies (I²: 40%)

A total of 4 studies reported separate data for the UTIs. 2668 patients were enrolled in the studies, with 1004 (37.6%) being in the placebo plus ET arm and 1664 (62.4%) in the CDK 4/6 inhibitors plus ET arm. UTIs are increased in CDK4/6 inhibitors plus ET arm (HR:1.59%95 CI: 1.19-2.12 p=0.43) (Figure 3-b)

A total of 7 studies reported separate data for febrile neutropenia, a total of 4395 patients were enrolled in the studies, with 1686 (38.4%) being in the placebo plus ET arm and 2709 (61.6%) in the CDK 4/6 inhibitors plus ET arm. Febrile neutropenia is increased in CDK4/6 inhibitors plus ET arm (HR:4.28%95 CI:1.73-10.62 p=0.002) (Figure 4).

Although a total of three studies reported separate data for pneumonia, the definition of the respiratory event had a broad term that may encompass a variegated spectrum of lung diseases, with different clinical phenotypes except for underlying infective complications (bronchiolitis, pneumonia). Therefore, pneumonia was not noted in this study due to data on pneumonia being scant.

Despite increased rate of all grade and grade 3 infections, the risk of infection-related deaths was not significantly increased in the pooled analysis of the studies and event rates were very low (7 vs. 3 deaths in the CDK 4/6+ET and ET arms, respectively. HR: 1.00, 95% CI: 0.30-3.32, p>0.99).

4. Discussion

CDK4/6 are standard of care options with significantly better progression-free survivals, objective response rates and overall survivals in patients with advanced breast cancer [23] (Table 1). Despite this great efficacy, the questions are still present about whether they increase infection risks related to myelosuppression.

Table 1.

This meta-analysis showed that CDK 4/6 inhibitors plus ET significantly increased infection rates in patients with HR+/HER2- advanced breast cancer. The increased risk of infections was consistent throughout the infection types and grades and the increased risk of all grades and grade 3 or higher infections, UTIs, pneumonia and febrile neutropenia was observed. Additionally, we observed significantly increased infections rates in patients treated with CDK 4/6 inhibitors both in first- and second-line treatment. To the best of our knowledge, this is the first meta-analysis assessing infection rates in patients receiving CDK 4/6 inhibitors.

Neutropenia was the most common toxicity reported with CDK 4/6 inhibitors, particularly in patients treated with palbociclib and ribociclib. In contrast to chemotherapy which causes DNA damage and induces apoptosis of proliferating neutrophil precursors, the CDK 4/6 inhibitors prevent progression through G1 to S checkpoint which causes to cell cycle arrest. Therefore, CDK 4/6 inhibitors, as an important mechanism difference from chemotherapy, reflecting a cytostatic effect on the bone marrow by cell cycle arrest in hematopoietic precursor cells and cause quiescence without apoptosis[24]. The white blood cells may continue to their function after withdrawal of CDK 4/6 inhibitors and also rapid recovery of the marrow may occur without long-term detrimental effect. Although there was higher incidence of neutropenia in the CDK 4/6 inhibitor arms, it was not led to serious clinical outcomes. 33 (1.2%) patients showed febrile neutropenia in CDK 4/6 inhibitors’ arm. Even so, the monitoring of complete blood count and infection parameters may still be necessary to prevent further neutropenic fever. (Table 2)

There are three main limitations of our meta-analysis. First, we used the data from the published articles instead of individual patient data. Second, the data on the specific infection types was not available all studies. Therefore, the interpretation of the results on the several infection types needs to be taken cautiously. Third, the moderate heterogeneity between the studies limited the generability. Additionally, we could not be able to conduct additional analyses on the impact of infections on the quality of life due to lack of data. However, despite these limitations we were able to take a snapshot of the infection risk in patients treated with CDK 4/6 inhibitors in a large body of data collected from well-constructed clinical trials.
5. Conclusion

In this meta-analysis, we observed that adding CDK4/6 inhibitors to ET significantly increased infection rates. We propose that a close vigilance for infections is required for metastatic breast cancer patients using CDK 4/6 inhibitors. Further research is needed to delineate the effects of infections on quality of life in patients treated with CDK 4/6 inhibitors.

Declarations

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interests The authors have no relevant financial or non-financial interests to disclose.

Author Contributions All authors contributed to the study conception and design. All authors, namely DCG, OB, EE and SA have made significant and substantive contributions to the reporting of the work. All authors have participated in the review of relevant literature, drafting of the manuscript, and review and revisions of the final draft. Material preparation, data collection and analysis were performed by DCG, OB and EE. The first draft of the manuscript was written by OB and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability The data supporting the conclusions of this article are included within the article and its additional file.

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable (no informed consent required).

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians 2021. https://doi.org/10.3322/caac.21660
2. Masood S: Estrogen and progesterone receptors in cytology: A comprehensive review. Diagnostic Cytopathology 1992, 8(5):475-491. https://doi.org/10.1002/dc.2840080508
3. Mohibi S, Mirza S, Band H, Band V: Mouse models of estrogen receptor-positive breast cancer. J Carcinog 2011, 10:35. https://doi.org/10.4103/1477-3163.91116
4. Shah M, Nunes MR, Steams V: CDK4/6 Inhibitors: Game Changers in the Management of Hormone Receptor–Positive Advanced Breast Cancer? Oncology (Williston Park, NY) 2018, 32(5):216-222.
5. Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, Park IH, Trédan Q, Chen SC, Manso L et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2017, 35(32):3638-3646. https://doi.org/10.1200/jco.2017.75.6155
6. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, Colleoni M, DeMichele A, Loi S, Verma S et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016, 17(4):425-439. https://doi.org/10.1016/s1470-2045(15)00613-0
7. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, Petrakova K, Bianchi GV, Esteva FJ, Martin M et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2018, 36(24):2465-2472. https://doi.org/10.1200/jco.2018.78.9909
8. Asghar U, Witkiewicz AK, Turner NC, Knudsen ES: The history and future of targeting cyclin-dependent kinases in cancer therapy. Nat Rev Drug Discov 2015, 14(2):130-146. DOI: 10.1038/nrd4504
9. Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, Harbeck N, Loibl S, Huang Bartlett C, Zhang K et al: Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med 2015, 373(3):209-219. https://doi.org/10.1038/nrd4504
10. Finn RS, Crown JP, Ettl J, Schmidt M, Bondarenko IM, Lang I, Pinter T, Boer K, Patel R, Randolph S et al. Efficacy and safety of palbociclib in combination with letrozole as first-line treatment of ER-positive, HER2-negative, advanced breast cancer: expanded analyses of subgroups from the randomized pivotal trial PALOMA-1/TRIO-18. Breast cancer research : BCR 2016, 18(1):67. https://doi.org/10.1186/s13058-016-0721-5
11. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, Campone M, Blackwell KL, André F, Winer EP et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med 2016, 375(18):1738-1748. https://doi.org/10.1056/nejmoa1609709
12. Sledge GW, Jr, Toi M, Neven P, Sohn J, Inoue K, Pivott X, Burdaeva O, Okera M, Masuda N, Kaufman PA et al: The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. JAMA oncology 2019, 6(1):116-124. https://doi.org/10.1001/jamaoncol.2019.4782
13. Sledge GW, Jr, Toi M, Neven P, Sohn J, Inoue K, Pivott X, Burdaeva O, Okera M, Masuda N, Kaufman PA et al: MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2017, 35(25):2875-2884. https://doi.org/10.1200/jco.2017.73.7585
14. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, Petrakova K, Bianchi GV, Esteva FJ, Martín M et al: Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. *N Engl J Med* 2020, 382(6):514-524. https://doi.org/10.1056/nejmoa1911149

15. Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N, Hurvitz SA, Chow L, Sohn J, Lee KS et al: Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol* 2018, 19(7):904-915. https://doi.org/10.1016/s1470-2045(18)30292-4

16. Im SA, Lu YS, Bardia A, Harbeck N, Colleoni M, Franke F, Chow L, Sohn J, Lee KS, Campos-Gomez S et al: Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. *N Engl J Med* 2019, 381(4):307-316. https://doi.org/10.1056/nejmoa1903765

17. Rugo HS, Finn RS, Gelmon K, Joy AA, Harbeck N, Castrellon A, Mukai H, Walshe JM, Mori A, Gauthier E et al: Progression-free Survival Outcome Is Independent of Objective Response in Patients With Estrogen Receptor-positive, Human Epidermal Growth Factor Receptor 2-negative Advanced Breast Cancer Treated With Palbociclib Plus Letrozole Compared With Letrozole: Analysis From PALOMA-2. *Clinical breast cancer* 2020, 20(2):e173-e180. https://doi.org/10.1016/j.clbc.2019.08.009

18. Rugo HS, Finn RS, Diéras V, Ettl J, Lipatov O, Joy AA, Harbeck N, Castrellon A, Iyer S, Lu DR et al: Palbociclib plus letrozole as first-line therapy in estrogen-receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. *Breast cancer research and treatment* 2019, 174(3):719-729. https://doi.org/10.1007/s10549-018-05125-4

19. Zhang QY, Sun T, Yin YM, Li HP, Yan M, Tong ZS, Oppermann CP, Liu YP, Costa R, Li M et al: MONARCH plus: abemaciclib plus endocrine therapy in women with HR+/HER2- advanced breast cancer: the multinational randomized phase III study. *Therapeutic advances in medical oncology* 2020, 12:1758835920963925. https://doi.org/10.1177/1758835920963925

20. Tolaney SM, Wardley AM, Zambelli S, Hilton JF, Troso-Sandoval TA, Ricci F, Im SA, Kim SB, Johnston SR, Chan A et al: Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarchHER): a randomised, open-label, phase 2 trial. *Lancet Oncol* 2020, 21(6):763-775. https://doi.org/10.1016/s1470-2045(20)30112-1

21. Johnston S, Puhalla S, Wheatley D, Ring A, Barry P, Holcombe C, Boileau JF, Provence L, Robidoux A, Rimawi M et al: Randomized Phase II Study Evaluating Palbociclib in Addition to Letrozole as Neoadjuvant Therapy in Estrogen Receptor-Positive Early Breast Cancer: PALLET Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2019, 37(3):178-189. https://doi.org/10.1200/jco.18.01624

22. Malorni L, Curigliano G, Minisini AM, Cinieri S, Tondini CA, D’Hollander K, Arpino G, Bernardo A, Martignetti A, Criscitiello C et al: Palbociclib as single agent or in combination with the endocrine therapy received before disease progression for estrogen receptor-positive, HER2-negative metastatic breast cancer: TREnd trial. *Ann Oncol* 2018, 29(8):1748-1754. https://doi.org/10.1093/annonc/mdy214

23. Piezzo M, Chiodini P, Riemma M, Cocco S, Caputo R, Cianniello D, Di Gioia G, Di Lauro V, Rella FD, Fusco G et al: Progression-Free Survival and Overall Survival of CDK 4/6 Inhibitors Plus Endocrine Therapy in Metastatic Breast Cancer: A Systematic Review and Meta-Analysis. *Int J Mol Sci* 2020, 21(17):6400. https://doi.org/10.3390/ijms21176400

24. Hu W, Sung T, Jessen BA, Thibault S, Finkelstein MB, Khan NK, Sacaan AI: Mechanistic Investigation of Bone Marrow Suppression Associated with Palbociclib and its Differentiation from Cytotoxic Chemotherapies. *Clinical Cancer Research* 2016, 22(8):2000-2008. https://doi.org/10.1158/1078-0432.ccr-15-1421

Tables

Table 1.
### Table 2.

| Trial          | Regimen                | Phase | Total | ET | ET+ CDK 4/6 inh. | Median follow-up | Et | ET+ CDK 4/6 inh. | PFS, mo (p < 0.00001) | ORR, % (p < 0.0001) | Neutropenia |
|----------------|------------------------|-------|-------|----|-----------------|------------------|----|-----------------|----------------------|---------------------|--------------|
|                |                        |       |       |    |                 |                   |    |                 |                      |                     | Grade 1-2 | Grade 3 | Grade 4 |
| PALOMA-1       | Letrozole ± palbociclib| II    | 165   | 81 | 84              | 27.9/29.6         | 39 | 55              | 10.2                 | 20.2               | 3           | 17       | 1       | 41       | 0         | 5         |
| PALOMA-2       | Letrozole ± palbociclib| III   | 666   | 222 | 444             | 23.0              | 44 | 55              | 14.5                 | 24.8               | 11          | 58       | 2       | 249      | 1         | 46        |
| PALOMA-3       | Fulvestrant ± palbociclib| III  | 521   | 174 | 347             | 44.8              | 10 | 6               | 4.6                  | 11.2               | 6           | 50       | 0       | 200      | 0         | 40        |
| MONALEESA-2   | Letrozole ± ribociclib | III   | 668   | 334 | 334             | 15.3              | 39 | 55              | 16                   | 25.3               | 15          | 50       | 4       | 175      | 0         | 32        |
| MONALEESA-7   | ET + OS ± ribociclib   | III   | 672   | 337 | 335             | 19.2              | 36 | 51              | 13                   | 23.8               | 14          | 46       | 12      | 174      | 3         | 39        |
| MONALEESA-3   | Fulvestrant ± ribociclib| III  | 726   | 242 | 484             | 39.4              | 36 | 51              | 12.8                 | 20.5               | 5           | 78       | 0       | 225      | 0         | 33        |
| MONARCH-3      | NSAI ± abemaciclib     | III   | 493   | 165 | 328             | 17.8              | 44 | 59              | 14.7                 | NE                 | 1           | 66       | 1       | 64       | 1         | 5         |
| MONARCH-2      | Fulvestrant ± abemaciclib| III  | 669   | 223 | 446             | 19.5              | 21 | 48              | 9.3                  | 16.4               | 5           | 86       | 3       | 104      | 1         | 13        |
| MONARCH-PLUS   | Fulvestrant/NSAI± abemaciclib | III | 463   | 152 | 311             | 16/12.2           | *36.1          | 10.5   | 65.9                    | 14.7                | NE              | 22         | 163      | 7       | 83       | 1         | 2         |

### Figures

| Trial          | Febrile neutropenia | Any grade infection | URTI | UTI |
|----------------|---------------------|---------------------|------|-----|
|                | ET                  | ET+ CDK 4/6 inh.    | ET+ CDK 4/6 inh. | ET+ CDK 4/6 inh. |
| PALOMA-1       | 0                   | 0                   | 4     | 23  |
|                | 0                   | 0                   | 2     | 9   |
|                |                     |                     | N/A   | N/A |
| PALOMA-2       | 0                   | 9                   | 100   | 278 |
|                | 0                   | 9                   | 25    | 59  |
|                |                     |                     | 17    | 53  |
| PALOMA-3       | 1                   | 3                   | 52    | 144 |
|                | 1                   | 3                   | 28    | 67  |
|                |                     |                     | N/A   | N/A |
| MONALEESA-2    | 0                   | 5                   | 140   | 168 |
|                | 0                   | 5                   | 35    | 35  |
|                |                     |                     | N/A   | N/A |
| MONALEESA-7    | 2                   | 7                   | 140   | 180 |
|                | 2                   | 7                   | 42    | 57  |
|                |                     |                     | 27    | 30  |
| MONALEESA-3    | 0                   | 5                   | 107   | 279 |
|                | 0                   | 5                   | N/A   | N/A |
|                |                     |                     | N/A   | N/A |
| MONARCH-3      | 0                   | 1                   | 46    | 128 |
|                | 0                   | 1                   | N/A   | N/A |
| MONARCH-2      | 0                   | 4                   | 55    | 188 |
|                | 0                   | 4                   | 17    | 82  |
|                |                     |                     | 10    | 44  |
| MONARCH-PLUS   | 0                   | 1                   | N/A   | N/A |
|                | 0                   | 1                   | 27    | 45  |
|                |                     |                     | N/A   | N/A |
Figure 1
Flow diagram of study selection process

Figure 2
All grade infection rates (a) and Grade 3 or higher infection rates (b).

Figure 3
Upper respiratory tract infections’ rates (a) and Urinary tract infection rates (b)
Figure 4

Febrile neutropenia rates