First-Line Treatment for Endocrine-Sensitive Bone-Only Metastatic Breast Cancer: Systematic Review and Meta-analysis

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Abstract

In the last decade, several clinical trials have investigated novel endocrine combinations for the first-line treatment of hormone receptor–positive metastatic breast cancer. Nevertheless, the use of combinations for the first-line treatment of bone-only disease is widely discussed as a result of its indolent natural history. We performed a comprehensive search of phase 3 randomized clinical trials published in the literature through September 2018. Our aim was to explore the role of the new endocrine approaches in bone-only metastatic breast cancer, suggesting a possible strategy for their selection. In particular, we evaluated the comparative risk of adverse event occurrence during these treatments. A total of 6 studies were deemed suitable for meta-analysis: the Monaleesa-2, Monaleesa-7, Monarch-3, Paloma-2, SWOG, and Alliance trials. Overall, the novel strategies were shown to improve progression-free survival in bone-only disease (hazard ratio = 0.65; 95% confidence interval, 0.49-0.86; $P = .003$). Combinations with cyclin-dependent kinase inhibitors improved progression-free survival (hazard ratio = 0.54; 95% confidence interval, 0.39-0.75; $P < .001$) with an acceptable toxicity profile. Abemaciclib was associated with increased anemia and gastrointestinal toxicity (especially diarrhea), whereas palbociclib was associated with increased leukopenia (but not neutropenia) compared to the other compounds. Increased aspartate aminotransferase levels were reported for both ribociclib and abemaciclib. The combination of cyclin-dependent kinase 4/6 inhibitors and endocrine therapy represents an effective and well-tolerated approach for first-line treatment in bone-only disease settings. Because no direct comparison between the 3 cyclin-dependent kinase 4/6 inhibitors is available, the selection of the most appropriate treatment should be based on toxicity profile as well as patient preference and copathologies.

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Introduction

The standard first-line treatment for hormone receptor (HR)-positive human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer was until quite recently represented by endocrine therapy, even in the presence of visceral disease, unless there is visceral crisis, or concern or proof of endocrine resistance.[1] In particular, the class of aromatase inhibitors (AI) represented the standard first-line endocrine strategy for postmenopausal patients, while tamoxifen (TAM) plus luteinizing hormone-releasing hormone (LHRH) analog was the first option for premenopausal women. In the last few years, new targeted and/or combined endocrine approaches have been studied in clinical trials, and some of them are now available for use in daily clinical practice.[2]

Novel strategies for the first-line treatment of metastatic HR-positive, HER2-negative disease currently investigated in phase 3 clinical trials include fulvestrant as monotherapy, the combination of fulvestrant and AI, the combination of bevacizumab and AI, and the combination of cyclin-dependent kinase (CDK) 4/6 inhibitors and AI/TAM + LHRH analog. Several randomized trials have shown that combining CDK4/6 inhibitors with endocrine therapy, either AI/TAM + LHRH analog or fulvestrant, improves outcomes in

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metastatic breast cancer patients. On this basis, several international guidelines have begun recommending their use in association with endocrine treatment in metastatic settings.[1,3] In particular, the US Food and Drug Administration has approved palbociclib and ribociclib in combination with letrozole, and abemaciclib in combination with an AI as a first-line treatment. In addition, palbociclib and abemaciclib have been approved in combination with fulvestrant after a first endocrine line, and abemaciclib has been approved as a single agent after endocrine therapy and previous chemotherapy.

Bones are the most common site of metastasis in HR-positive metastatic breast cancer patients.[4] However, bone-only disease (BoD) is not as common, and consequently it is often studied in combination with other nonbone or nonvisceral sites in clinical trials. Nevertheless, it is noteworthy that bone-only metastatic breast cancer presents a different natural history and a better prognosis than non-BoD.[5-7] In particular, a recent large pooled analysis confirmed that BoD has better progression-free survival (PFS) than the other subgroups, leading to the hypothesis that the BoD subset might respond differently to different types of therapy.[8] For all these reasons, the introduction of the combination in the first-line setting of BoD is widely discussed as a result of the indolent course of the disease. An alternative strategy in BoD might be the use of standard endocrine monotherapy followed only at progression by the combination approach in order to delay the major toxicity and increased costs associated with the combination.

We performed the present meta-analysis to improve our understanding of the role of the new endocrine approaches in patients with HR-positive bone-only metastatic breast cancer in order to suggest a possible strategy for their selection and introduction.

Methods

Study Objectives

The present study was a quantitative synthesis of randomized phase 3 trials. Its primary objective was to determine the improvement in PFS provided by the novel experimental endocrine approaches (fulvestrant plus AI, bevacizumab plus AI, CDK4/6 inhibitors plus AI/TAM + LHRH analog) compared to standard endocrine therapy alone as a first-line treatment for bone-only metastatic breast cancer. Moreover, the present meta-analysis evaluated the comparative risk of adverse event (AE) occurrence during these treatments compared to endocrine therapy alone in the overall study populations. For each treatment strategy, the following AEs were considered: overall incidence of grade 1-4 AEs, overall incidence of grade 3 and grade 4 AEs, and grade 1-4 AEs with an incidence $\geq$ 15% in each published trial. The National Cancer Institute Common Terminology for Adverse Events (NCI CTCAE) criteria were used to grade the AEs.

Data Sources and Search Strategy

A systematic literature search of the electronic databases Medline, Embase, and Cochrane Library was conducted. This identified phase 3 randomized controlled trials published as full-text articles that investigated novel endocrine strategies compared to standard AI/TAM + LHRH analog therapies for the first-line treatment of patients with HR-positive, HER2-negative metastatic breast cancer. No restrictions in terms of language or year of publication were applied. The final date for the database search was September 30, 2018.

The search strategy was developed using the patient, intervention, comparator and outcome (PICO) framework. The terms used for the search strategy were the following: "breast cancer," "endocrine therapy," and "first line therapy." Boolean operators were used to connect specific search keywords for each database and other free-text terms. The specific rules and vocabulary of the database were used. The search strategy was designed by two authors (A.T. and L.M.) and was discussed with all of the other authors.

Breatriz Finally, the references reported in all the identified publications were assessed to find any additional eligible study. The present analysis was conducted accordingly to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[9] This meta-analysis was registered under Prospero registration number CRD42018099762, and the full protocol is freely available on the Prospero website.

Article Selection

The eligible trials for this analysis were those with the following characteristics: (1) phase 3 randomized clinical trials with published and publicly available data; (2) trials conducted in patients with locally advanced inoperable/metastatic HR-positive HER2-negative breast cancer; (3) studies comparing the standard first-line endocrine therapy (AI/TAM + LHRH analog) to an experimental endocrine strategy; (4) studies with available information on PFS in the subgroup of BoD; and (5) studies with sufficient information to estimate the hazard ratio and 95% confidence interval (CI) for disease progression.

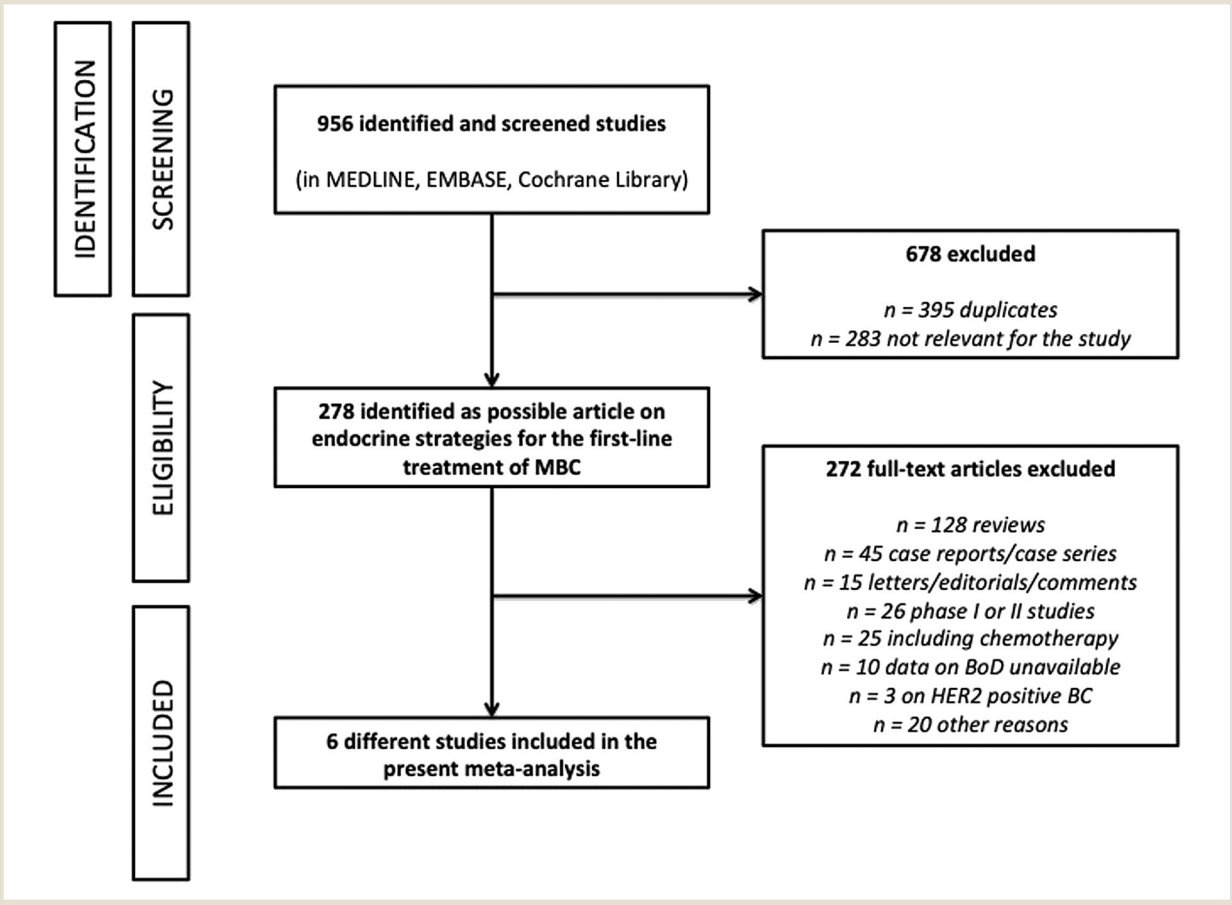
The studies excluded from this analysis were those with the following characteristics: (1) randomized trials evaluating the efficacy of new endocrine strategies but with no AI/TAM + LHRH analog control arm; (2) nonrandomized studies; (3) phase 1 and 2 clinical trials; and (4) studies currently ongoing but not yet published, and for which no and/or insufficient results were available at the time of the literature search.

Two investigators (E.M. and M.V.) independently extracted the data from all the included studies. In case of multiple reports relating to the same trial, the most recently published results were selected. The following variables were collected: first author, name of the trial, year of publication, overall sample size, description of standard and experimental treatments, number of patients included in the BoD subgroups, and number of patients who developed every specific AE.

Statistical Analysis

We compared treatments using hazard ratio and 95% CI. Heterogeneity was evaluated by χ^2 Q test and I^2 statistic.[10] For the Q test, $P < .05$ indicated significant heterogeneity; for the I^2 statistic, $I^2 > 50\%$ was considered significant. The pooled hazard ratio estimate was calculated using a random-effect model.[11] Our results are graphically displayed as forest plots, with hazard ratio < 1.0 indicating better outcome in the experimental arm. Publication bias was evaluated by visual inspection of funnel plots. Calculations were accomplished by Comprehensive Meta-analysis 2.0 software (CMA; Biostat, Englewood, NJ).

Figure 1 PRISMA Flowchart Summarizing Process to Identify Eligible Studies



Abbreviations: BC = breast cancer; BoD = bone-only disease; MBC = metastatic breast cancer; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Results

With the terms used for the search strategy, 956 publications were identified for initial eligibility screening. On the basis of the information found in their titles and/or abstracts, 395 were excluded because they were duplicates, and 283 were deemed not relevant to the study (Figure 1). Of the remaining 278 entries, an additional 272 articles were excluded because they did not meet all the inclusion criteria: 128 were reviews, 45 case reports, 15 letters and editorials, and 26 phase 1 or 2 studies, and 25 studies included chemotherapy in the experimental arm. Moreover, for 10 studies, data on BoD were unavailable, 3 studies included HER2-positive tumors, and 20 full-text articles were excluded for other reasons.

A total of 6 studies were identified and deemed suitable for our meta-analysis. The characteristics of these 6 studies are listed in Table 1. Three trials—Monaleesa-2,[13] Monarch-3,[16] and Paloma-2[12]—explored the role of CDK4/6 inhibitors in association with AI in postmenopausal patients. In particular, the Monaleesa-2 and Paloma-2 trials respectively compared ribociclib and palbociclib in association with letrozole to letrozole alone. The Monarch-3 trial, however, compared abemaciclib along with nonsteroidal AI (eg, letrozole or anastrozole) to the same AI alone. Additionally, one trial, Monaleesa-7,[15] assessed the efficacy and safety of ribociclib plus AI/TAM + LHRH analog in premenopausal women. The SWOG trial[17] compared the combination of anastrozole and fulvestrant to anastrozole alone or sequential anastrozole and fulvestrant in postmenopausal women. Finally, the Alliance trial[18] evaluated the addition of bevacizumab to letrozole in patients who were postmenopausal or receiving ovarian suppression with an LHRH agonist.

The 6 studies selected included 801 patients diagnosed with HR-positive, HER2-negative bone-only metastatic breast cancer and treated with a first-line endocrine-based treatment. In all studies, the hazard ratio and 95% CIs for disease progression were presented, and the NCI CTCAE were used to grade the AEs. The first results of the Monaleesa-2 trial were first published in 2016[14] and reported the AEs occurring in at least 15% of patients in either treatment arm. In the subsequent updated analysis,[13] the one included in our meta-analyses, only AEs occurring in $\geq$ 20% of patients were included. As regards AEs occurring in 15% to 20% of patients and the total incidence of any AEs, we therefore considered the data previously published in 2016.[14] Furthermore, the Monarch-3 trial[16] described grade 1-4 AEs reported in at least 15% of the patients in any group, while the Paloma-2 trial[12] presented grade 1-4 AEs that

Table 1 Study Characteristics

Trial ID	Reference	Treatment Arms	Overall Population	BoD	Method of AE Assessment	Version
PALOMA 2	Finn[12]	Palbociclib + letrozole; letrozole	444; 222	103; 48	NCI CTCAE	3.0
MONALEESA 2	Hortobagyi[13,14]	Ribociclib + letrozole; letrozole	334; 334	69; 78	NCI CTCAE	4.0
MONALEESA 7	Tripathy[15]	Ribociclib + AI/TAM + LHRH; AI/TAM + LHRH	335; 337	81; 78	NCI CTCAE	4.03
MONARCH 3	Goetz[16]	Abemaciclib + NSAI; NSAI	328; 165	70; 39	NCI CTCAE	4.0
SWOG	Mehta[17]	Anastrozole + fulvestrant; anastrozole	349; 345	75; 76	NCI CTCAE	3.0
ALLIANCE	Dickler[18]	Bevacizumab + letrozole; letrozole	173; 170	41; 43	NCI CTCAE	3.0

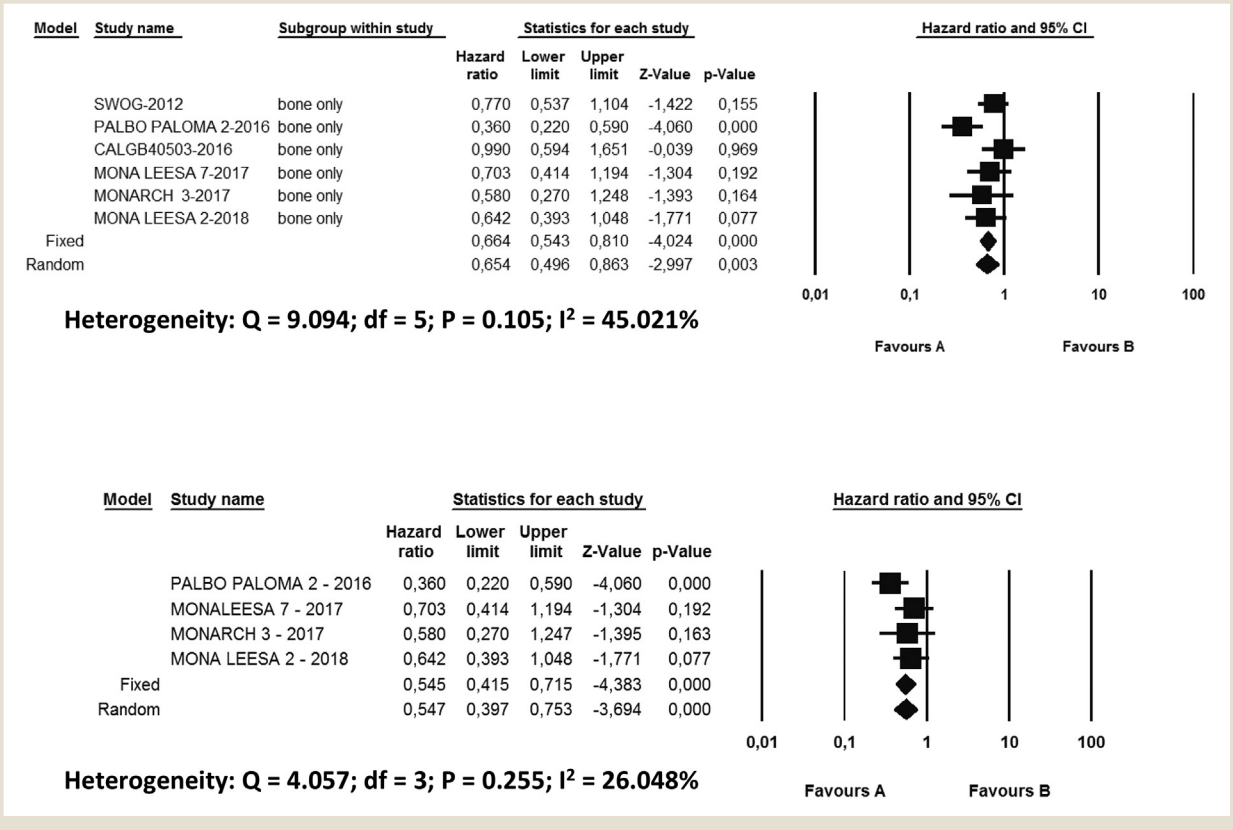
Abbreviations: AE = adverse event; AI = aromatase inhibitor; BoD = bone-only disease; LHRH = luteinizing hormone-releasing hormone; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAI = nonsteroidal anti-inflammatory drug; TAM = tamoxifen.

occurred in at least 10% of patients in either study group. In addition, the Monaleesa-7 study[15] presented grade 1-4 AEs occurring in at least 5% of patients in either study group. Finally, the SWOG trial reported all grade 1-4 AEs developed,[17] whereas the Alliance trial[18] reported only grade 3/4 AEs. All studies used NCI CTCAE version 3.0 or 4.0 (Table 1).

Comparison Between Experimental and Control Arms

Overall, the meta-analysis showed a PFS advantage of the experimental arms compared to the control arms (hazard ratio = 0.65; 95% CI, 0.49-0.86; $P = .003$), with a low/moderate nonsignificant heterogeneity ($I^2 = 45.02\%$; $P = .105$) (Figure 2). Notably, the meta-analyses restricted to the trials investigating combinations with CDK inhibitors confirmed the PFS advantage compared to the control arms (hazard ratio = 0.54; 95% CI, 0.39-0.75; $P < .001$), with a low nonsignificant heterogeneity ($I^2 = 26.04\%$; $P = .255$) (Figure 2). Nevertheless, taken individually, only the Paloma-2 trial showed a statistically significant improvement in PFS for palbociclib + letrozole (hazard ratio = 0.36; 95% CI, 0.22-0.59; $P < .001$) compared to letrozole alone.

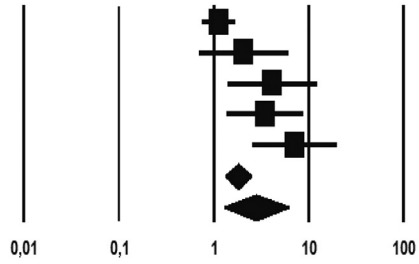
Figure 2 Meta-analysis of HR for Subgroup "Bone-Only Disease" of 6 Studies Included and in 4 Trials Investigating CDKi Combinations



Abbreviations: CDKi = cyclin-dependent kinase inhibitor; HR = hazard ratio.

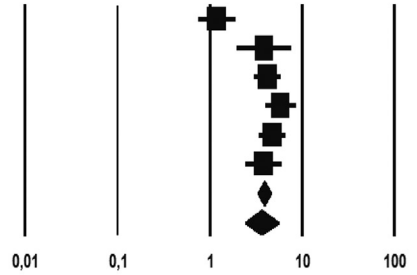
Figure 3 Overall AE Comparative Risk Overview. Overall AEs are Shown for Grades 1-4, Grade 3, and Grade 4

Model	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	SWOG -2012	Any adverse event	1,119	0,749	1,672	0,550	0,582
	MONA LEESA 2-2016	Any adverse event	2,056	0,695	6,082	1,303	0,193
	PALBO PALOMA 2-2016	Any adverse event	4,142	1,398	12,268	2,565	0,010
	MONA LEESA 7-2017	Any adverse event	3,460	1,371	8,727	2,629	0,009
	MONARCH 3-2017	Any adverse event	7,106	2,554	19,769	3,757	0,000
Fixed			1,790	1,305	2,454	3,614	0,000
Random			2,783	1,285	6,026	2,597	0,009



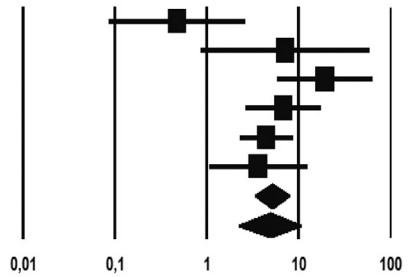
Heterogeneity: Q = 16.540; df = 4; P = 0.002; I^2 = 75.817%

Model	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	SWOG -2012	Any adverse event (G3)	1,186	0,750	1,877	0,730	0,465
	CALGB40503-2016	Any adverse event (G3)	3,872	1,993	7,521	3,997	0,000
	MONA LEESA 2-2016	Any adverse event (G3)	4,191	3,031	5,795	8,666	0,000
	PALBO PALOMA 2-2016	Any adverse event (G3)	5,800	4,004	8,403	9,295	0,000
	MONA LEESA 7-2017	Any adverse event (G3)	4,754	3,422	6,604	9,293	0,000
	MONARCH 3-2017	Any adverse event (G3)	3,815	2,448	5,946	5,915	0,000
Fixed			3,862	3,284	4,540	16,356	0,000
Random			3,597	2,362	5,479	5,965	0,000



Heterogeneity: Q = 31.834; df = 5; P = 0.000; I^2 = 84.293%

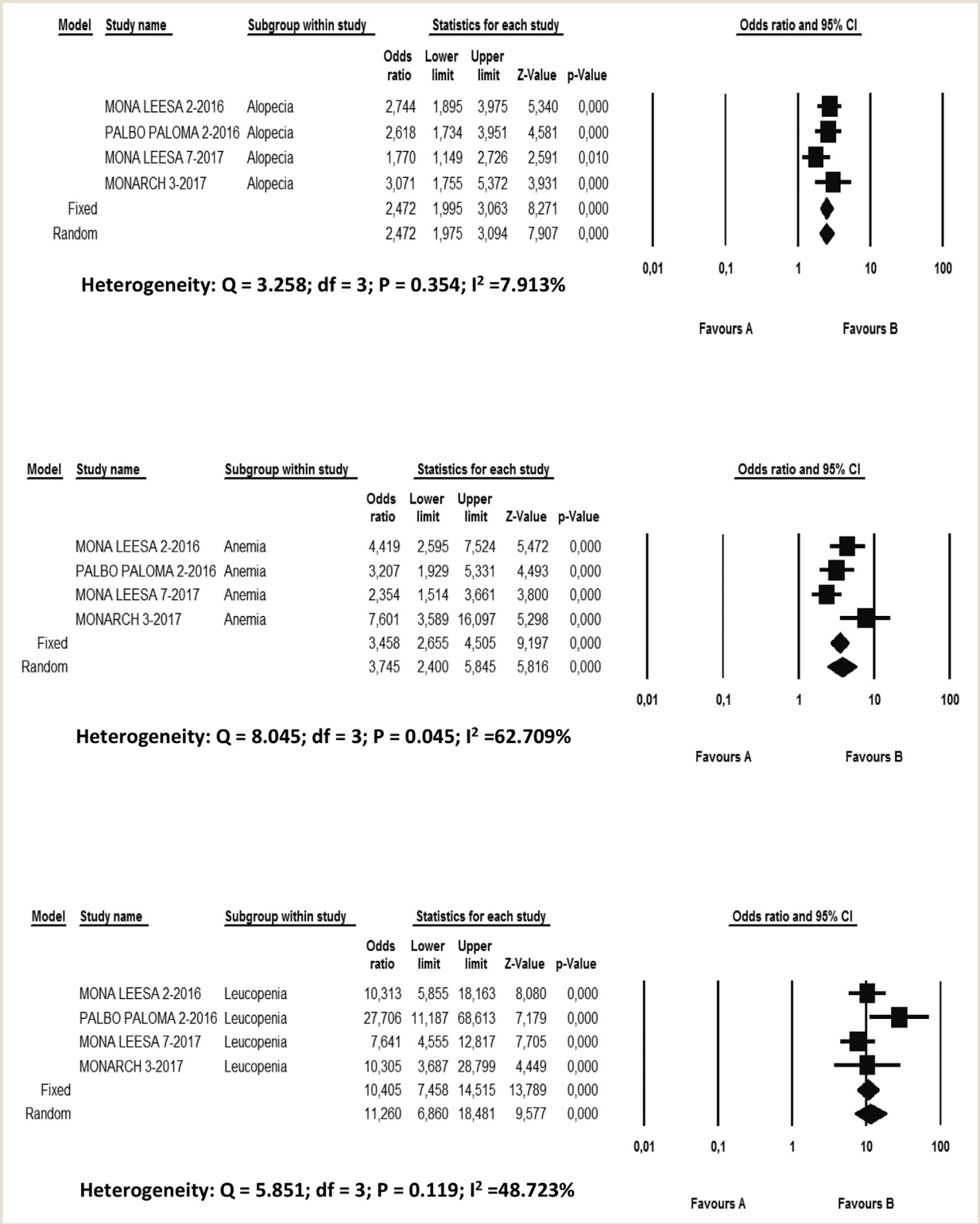
Model	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	SWOG -2012	Any adverse event (G4)	0,477	0,087	2,620	-0,852	0,394
	CALGB40503-2016	Any adverse event (G4)	7,127	0,867	58,559	1,827	0,068
	MONA LEESA 2-2016	Any adverse event (G4)	19,190	5,921	62,192	4,925	0,000
	PALBO PALOMA 2-2016	Any adverse event (G4)	6,781	2,683	17,142	4,045	0,000
	MONA LEESA 7-2017	Any adverse event (G4)	4,420	2,299	8,496	4,457	0,000
	MONARCH 3-2017	Any adverse event (G4)	3,614	1,062	12,302	2,056	0,040
Fixed			5,085	3,315	7,800	7,451	0,000
Random			4,810	2,219	10,428	3,979	0,000



Heterogeneity: Q = 13.257; df = 5; P = 0.021; I^2 = 62.283%

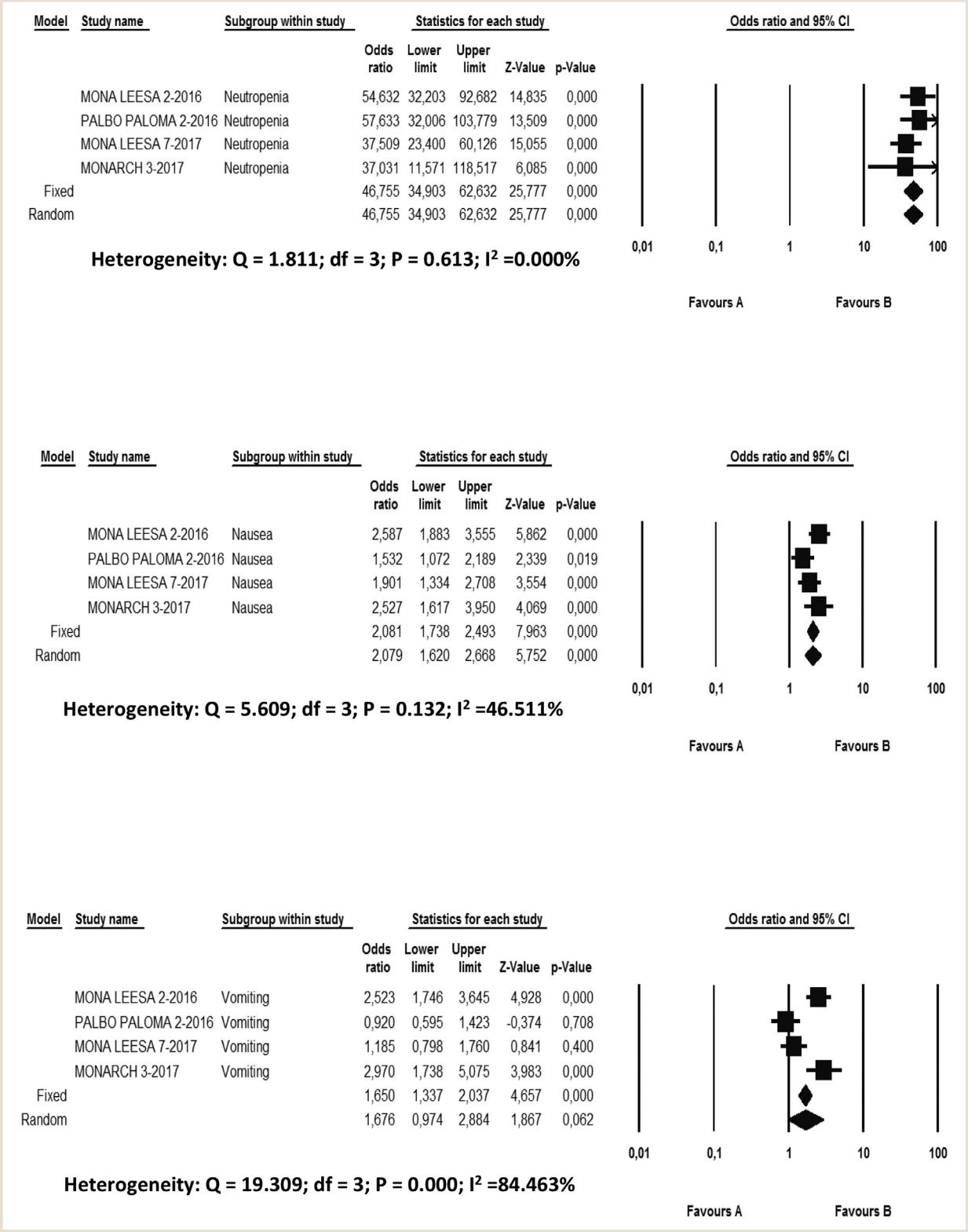
Abbreviation: AE = adverse event.

Figure 4 Grade 3/4 Comparative Risk AEs for Alopecia, Anemia, and Leukopenia



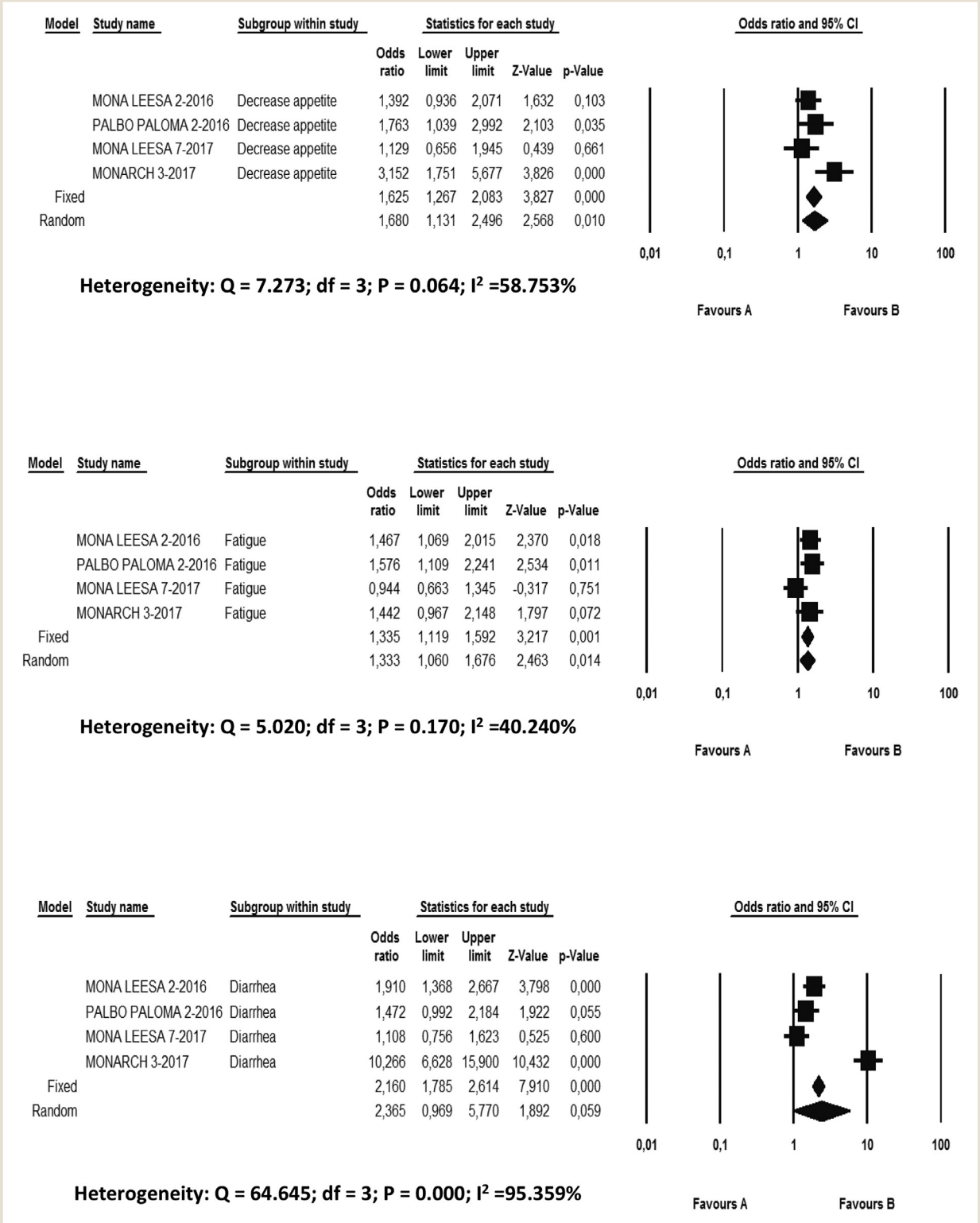
Abbreviation: AE = adverse event.

Figure 5 Grade 3/4 Comparative Risk AEs for Neutropenia, Nausea, and Vomiting



Abbreviation: AE = adverse event.

Figure 6 Grade 3/4 Comparative Risk AEs for Decreased Appetite, Fatigue, and Diarrhea



Abbreviation: AE = adverse event.

Overall Incidence of AEs

In 2 of 5 studies (Monaleesa-2 and SWOG), the overall incidence of grade 1-4 AEs did not significantly differ across the experimental and control arms (Figure 3). In particular, overall grade 3 AEs were increased in incidence in all the trials except SWOG, while overall grade 4 AEs were increased in all the trials except SWOG and Alliance (Figure 3).

Grade 1-4 AEs With Incidence ≥ 15% in Each Trial

Grade 1-4 AEs were available for all the studies except for the Alliance trial. Nevertheless, the AEs in the SWOG study were reported with a different classification, and they therefore could not be compared to other trials. Thus, only the 4 studies investigating the 3 CDK inhibitors were included in the meta-analyses.

The incidence of alopecia, anemia, leukopenia, neutropenia, and nausea was significantly increased in all of the 4 studies (Figures 4 and 5). Nonetheless, anemia was significantly more frequent in the Monarch-3 study and leukopenia significantly more frequent in the Paloma-2 study than in the other studies.

Headache and constipation did not significantly differ between the two treatment arms in all 4 studies (Supplemental Figures in the online version). However, the incidence of decreased appetite was significantly increased in the experimental arm of the Monarch-3 study (Figure 6), fatigue was significantly increased in the Monaleesa-2 and Paloma-2 studies (Figure 6), and the incidence of vomiting and diarrhea was significantly increased in the experimental arm of the Monaleesa-2 and Monarch-3 studies (Figures 5 and 6). In particular, decreased appetite, vomiting, and diarrhea were significantly more frequent in the Monarch-3 study than in the other studies.

Other grade 1-4 AEs with an incidence of ≥ 15% in at least one published trial but not reported in all of the 4 studies were as follows: abdominal pain, asthenia, cough, arthralgia, back pain, pain in the extremities, pyrexia, stomatitis, hot flushing, increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST), rash, and thrombocytopenia. More specifically, pyrexia, stomatitis, and thrombocytopenia were reported with an incidence of ≥ 15% only in the Paloma-2 and Monaleesa-7 studies. The incidence of pyrexia was significantly increased in the experimental arm of the Monaleesa-7 study and stomatitis in the experimental arm of the Paloma-2 study, whereas thrombocytopenia was significantly increased in the experimental arms of both studies. Interestingly, ALT was significantly increased in the experimental arm of the Monaleesa-2, Monaleesa-7, and Monarch-3 studies, AST in the Monaleesa-2 study, abdominal pain in the Paloma-2 and the Monarch-3 studies, and rash in the Monaleesa-2 and the Paloma-2 studies, whereas hot flushing was significantly reduced in the Paloma-2 study. The results of meta-analyses regarding these AEs are reported in the Supplemental Figures in the online version.

Discussion

Patients with bone-only metastatic breast cancer have previously been shown to have unique characteristics, including improved survival, compared to patients with nonosseous metastases.[5-7,19,20] Nevertheless, despite the better survival rates, bone metastases are often complicated by bone pain and skeleton-related events, such as pathologic fractures, spinal cord compression, the need for surgery or radiotherapy to bone, and hypercalcemia. These skeleton-related events strongly affect mobility[4,21] and have been correlated with reduced quality of life (QoL).[22] Multiple bone metastases and lytic bone metastases are associated with increased pain. Additionally, several risk factors, including multiple bone metastases, axial and appendicular skeleton involvement, $HR^-/HER2^+$ and $HR^-/HER2^-$ subtypes, and de novo bone-only metastasis, are associated with decreased overall survival.[23,24] For all these reasons, bone-only metastatic breast cancer should not be considered an indolent and less relevant condition; it warrants therapy as appropriate and thoughtful as visceral disease does.

With the aim to evaluate the best approach in the first-line setting for endocrine-sensitive bone-only metastatic breast cancer, we carried out a systematic review of randomized phase 3 trials studying novel experimental endocrine approaches compared to standard endocrine monotherapy (AI/TAM + LHRH analog). A total of 6 studies were identified and deemed suitable for our meta-analysis. In the overall study population, the combination of CDK4/6 inhibitors and AI/TAM + LHRH analog demonstrated better PFS than standard endocrine monotherapy.[12,13,15,16] The combination of fulvestrant and anastrozole showed a small PFS advantage compared to the standard anastrozole[17]—a finding also confirmed in the recent update.[25] Finally, one trial showed an improved PFS with the addition of bevacizumab to letrozole monotherapy.[18] In the overall study population, the addition of fulvestrant to anastrozole adds no significant toxicity, but at the same time, it adds only a 1.5-month advantage to standard endocrine monotherapy. However, the addition of bevacizumab to letrozole improves the outcome but also markedly increases the risk of grade 3 toxicities. On these grounds, only the combination of CDK4/6 inhibitors and AI/TAM + LHRH analog seems to represent an effective step forward for the first-line treatment of patients with HR-positive, HER2-negative metastatic breast cancer.

Considering the subgroup of BoD, the meta-analysis showed a significant PFS advantage in the combinations with CDK inhibitors compared to the control arms. If taken individually, however, only the Paloma-2 trial showed a statistically significant improvement in PFS for palbociclib + letrozole compared to letrozole alone. Nevertheless, it is noteworthy that the included studies do not report any information regarding the characteristics of bone involvement, such as tumor burden, axial and appendicular skeleton involvement, characteristics of bone lesion (lytic or blastic), and the presence of skeleton-related events. Moreover, no direct comparison of the three CDK4/6 inhibitors in these patients is yet available. Therefore, the selection of the best treatment in this setting could be based on the toxicity profile of each compound as well as patient preferences, needs, and copathologies, with the aim of preserving QoL. In particular, abemaciclib seems to be associated with increased anemia and gastrointestinal toxicity (especially diarrhea), while palbociclib seems to be associated with increased leukopenia (but not neutropenia) compared to the other compounds. Notably, increased AST levels were reported for both ribociclib and abemaciclib. Interestingly, ribociclib in the Monaleesa-2 study did not increase the incidence of overall grade 1-4 AEs compared to the control arm, but rather showed an increased incidence of grade 3/4 AEs. Moreover, ribociclib showed a slightly different toxicity profile in the postmenopausal women in the Monaleesa-2 study and the premenopausal women in the Monaleesa-7 study (ie, incidence of

rash and increased ALT), likely as a result of the iatrogenic anticipation of menopause and patient age. However, it should be noted that it is always difficult to compare one agent to another by looking at the toxicity data of single trials. In fact, excluding measurable toxicities, constitutional symptoms (eg, appetite, fatigue, and diarrhea, but also hot flushes, rash, and pain) are difficult to evaluate because their severity is influenced by patients' interpretation.

Moreover, the maintenance of QoL observed in all the trials exploring the three CDK4/6 inhibitors is an important concern that adds value to the benefit of the brand new regimens. In fact, although different definitions of time to deterioration were used in the 4 main studies, QoL was maintained in the Paloma-2 trial[26] with no differences between visceral and nonvisceral metastases,[27] and was associated with improved in the Monaleesa-2 and -7 trials.[15,28] However, data have not yet been made available for the Monarch-3 trial. Regarding the global effect on QoL, we should look into the single items that comprise the QoL questionnaires. Pain represents a common symptom in the presence of bone disease. In the trials mentioned above, a significantly greater improvement from baseline was observed in the scores of items assessing pain in body parts. This emphasizes the efficacy of the CDK4/6-based regimen as well as the possible greater clinical effect in the presence of pain derived from bone disease.

Conclusion

The combination of CDK4/6 inhibitors and endocrine therapy represents an effective and well-tolerated approach for the first-line treatment of metastatic breast cancer in the BoD setting. Because no direct comparison of the three CDK4/6 inhibitors is available yet, the selection of the most appropriate treatment could be based on the toxicity profile of each compound and patient preferences, needs, and copathologies.

In clinical trials, BoD is often included in the nonvisceral disease subgroup. The design of future clinical trials should take into account differences in terms of the natural history of the disease and the better prognosis of BoD in order to define the best approach to this particular subset of patients.

Disclosure

A.T. reports financial relationships with Roche, Eli Lilly, and Eisai. F.P. reports financial relationships with AstraZeneca, Novartis, and Eisai. C.O. reports financial relationships with Eisai. L.C. reports financial relationships with AstraZeneca and Pfizer. S.C. reports financial relationships with Eli Lilly and Bayer. L.M. reports financial relationships with Pfizer, Roche, Novartis, Eli Lilly, and Eisai. The other authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2019.06.011.

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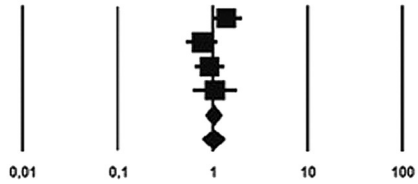
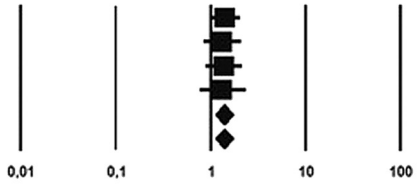
Supplemental Figure 1 Grade 3/4 Adverse Event Comparative Risk, Headache and Constipation

Model	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	MONA LEESA 2-2016	Headache	1,395	0,974	1,998	1,819	0,069
	PALBO PALOMA 2-2016	Headache	0,770	0,529	1,121	-1,366	0,172
	MONA LEESA 7-2017	Headache	0,928	0,650	1,325	-0,411	0,681
	MONARCH 3-2017	Headache	1,055	0,623	1,786	0,199	0,843
Fixed			1,013	0,833	1,231	0,127	0,899
Random			1,012	0,776	1,318	0,086	0,931



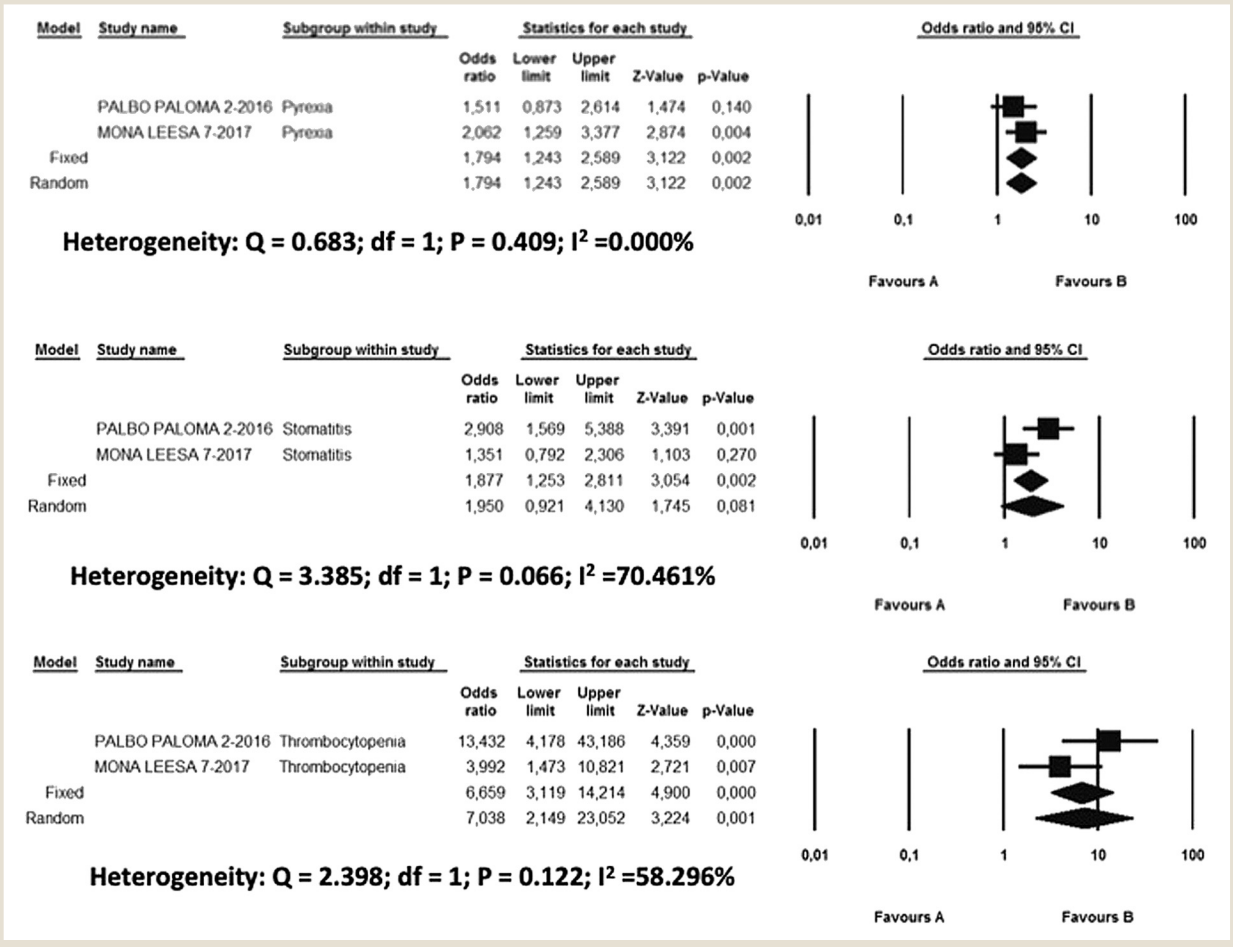
Heterogeneity: Q = 5.365; df = 3; P = 0.147; I^2 =44.087%

Model	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	MONA LEESA 2-2016	Constipation	1,408	0,987	2,008	1,887	0,059
	PALBO PALOMA 2-2016	Constipation	1,328	0,860	2,051	1,281	0,200
	MONA LEESA 7-2017	Constipation	1,380	0,894	2,129	1,455	0,146
	MONARCH 3-2017	Constipation	1,333	0,766	2,320	1,017	0,309
Fixed			1,370	1,106	1,697	2,880	0,004
Random			1,370	1,106	1,697	2,880	0,004

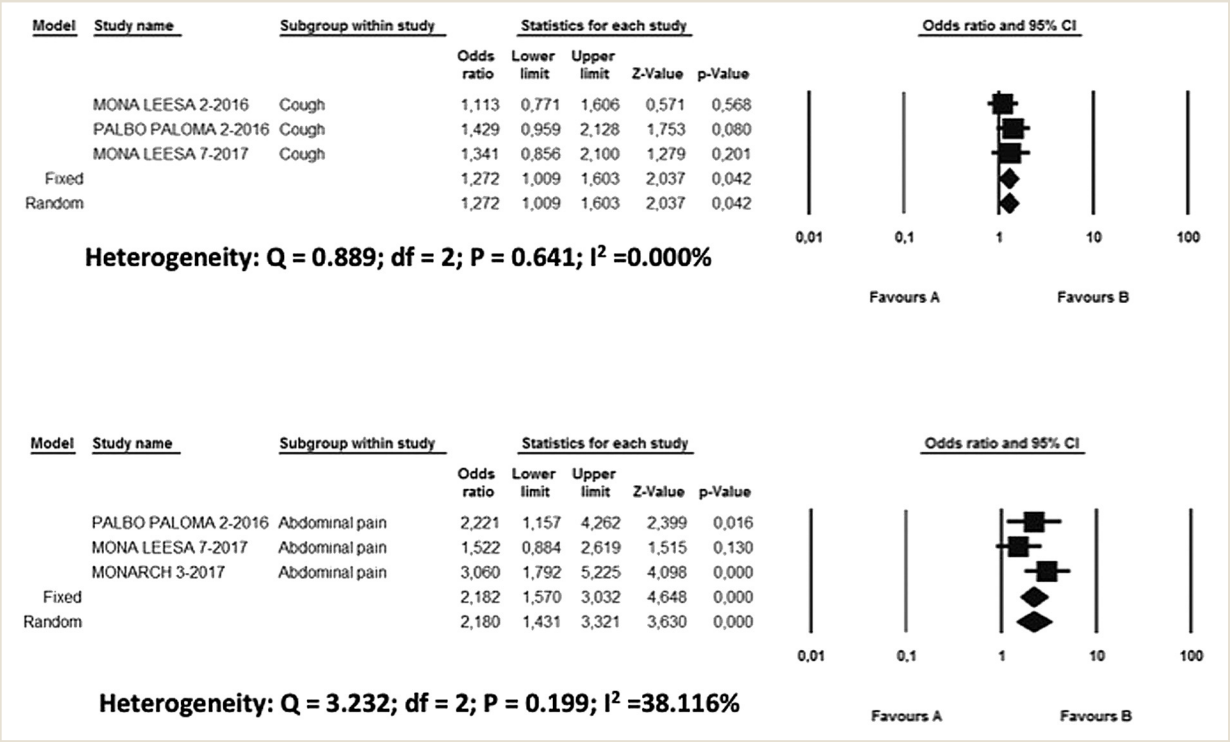


Heterogeneity: Q = 0.052; df = 3; P = 0.997; I^2 =0.000%

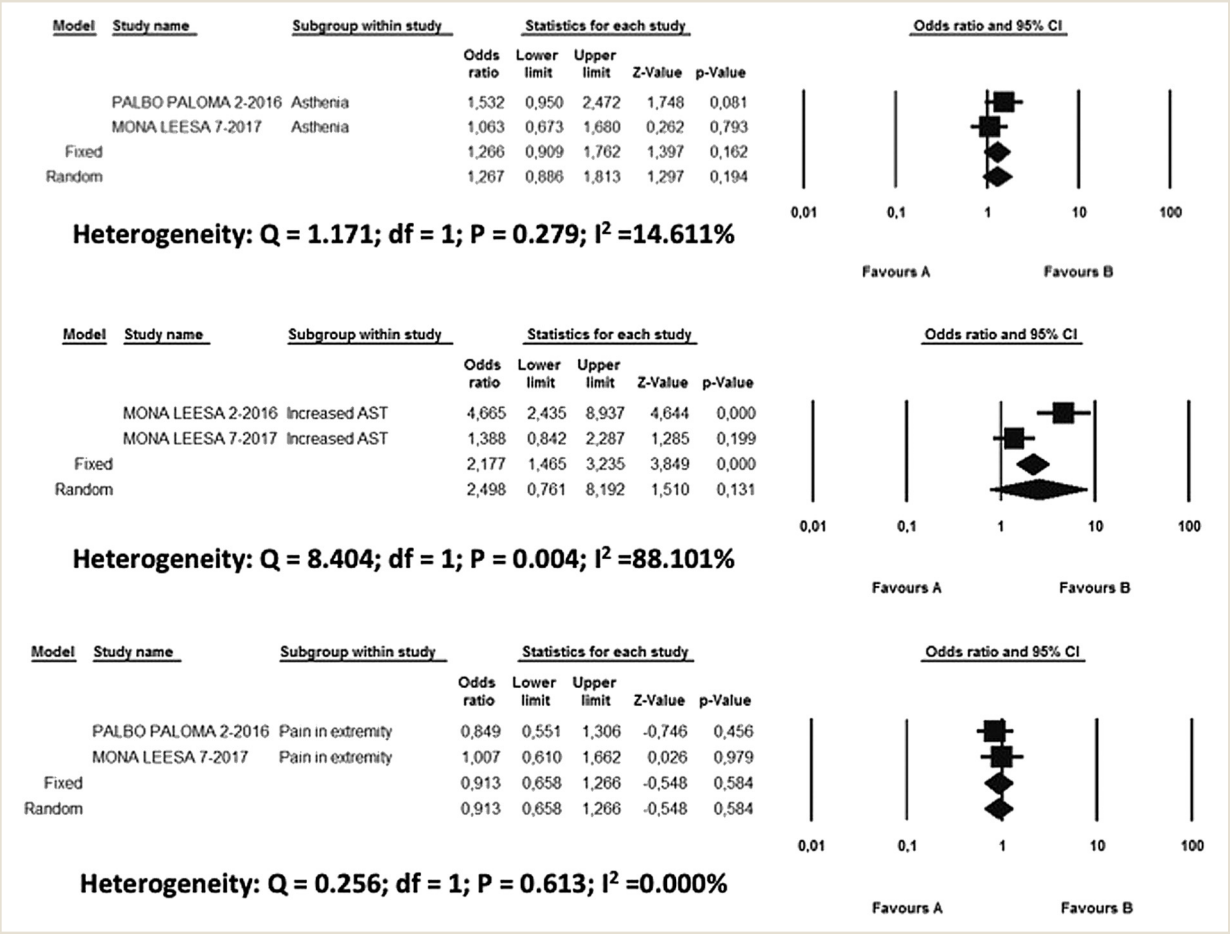
Supplemental Figure 2 Grade 3/4 Adverse Event Comparative Risk, Pyrexia, Stomatitis, and Thrombocytopenia



Supplemental Figure 3 Grade 3/4 Adverse Event Comparative Risk, Cough and Abdominal Pain

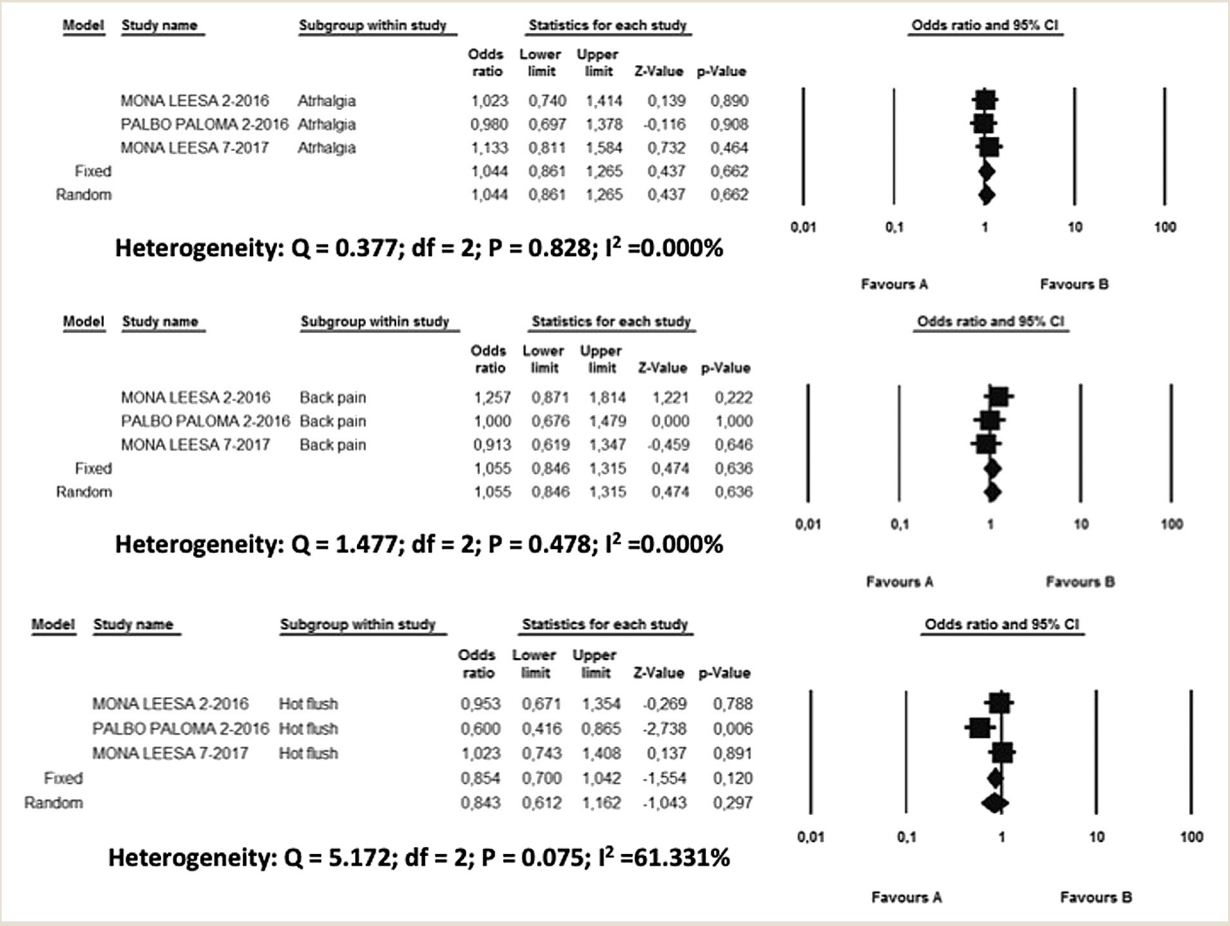


Supplemental Figure 4 Grade 3/4 Adverse Event Comparative Risk, Asthenia, Increased AST, Pain in Extremities

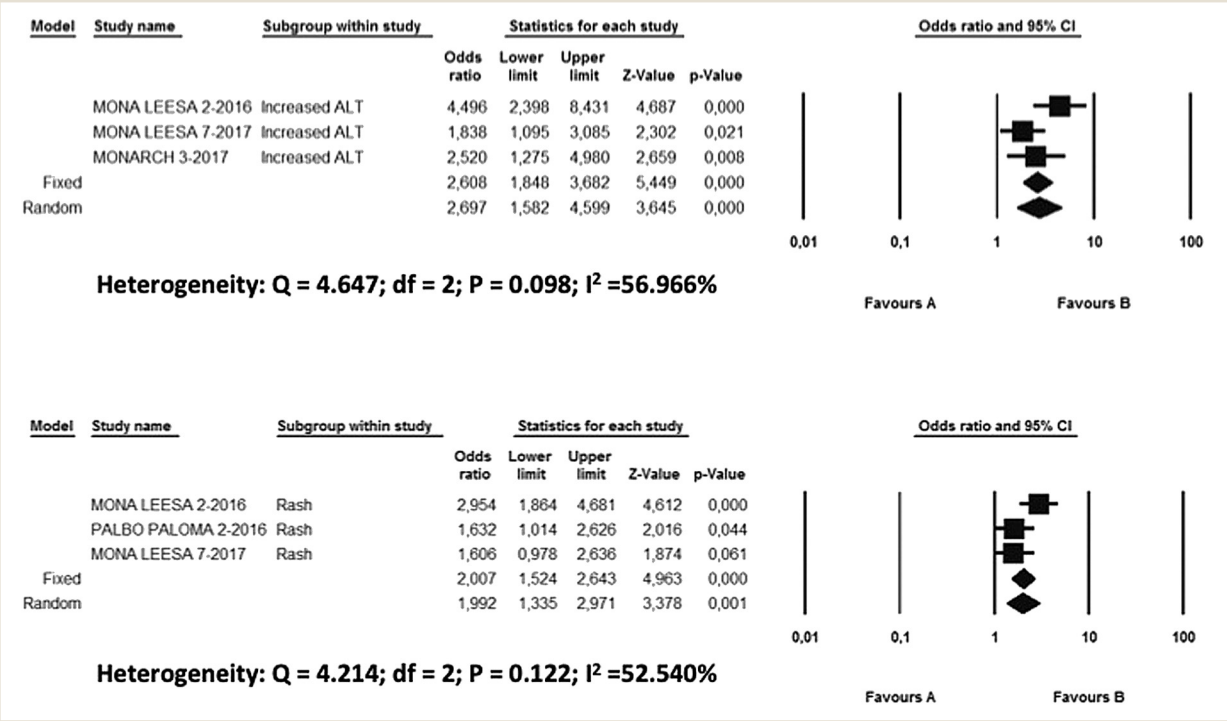


Abbreviation: AST = aspartate aminotransferase.

Supplemental Figure 5 Grade 3/4 Adverse Event Comparative Risk, Arthralgia, Back Pain, and Hot Flush



Supplemental Figure 6 Grade 3/4 Adverse Event Comparative Risk, Increased ALT and Rash



Abbreviation: ALT = alanine aminotransferase.