

Prognostic Significance of Low HER2 Expression in Patients With Metastatic Hormone Receptor-positive Breast Cancer Treated With First Line CDK4/6 Inhibitors: A Greek Multicenter Real-world Data Analysis

GEORGE DOUGANIOTIS¹, GEORGE KESISIS², EFTHALIA LALLA¹,
IPPOKRATIS KORANTZIS², IOANNIS BOUKOVINAS³ and KONSTANTINOS PAPAZISIS⁴

¹3rd Department of Medical Oncology, Theageneion Cancer Hospital, Thessaloniki, Greece;

²Oncology Department, Saint Luke Private Hospital, Thessaloniki, Greece;

³Oncology Department, BioClinic Thessaloniki, Thessaloniki, Greece;

⁴Medical Oncology Department, Euromedica General Clinic, Thessaloniki, Greece

Abstract. *Background/Aim:* Low expression of HER2 has defined a new “HER2-low” subgroup of breast cancer with distinct clinicopathological characteristics and both prognostic and predictive implications. The impact of low HER2 expression in metastatic hormone receptor-positive HER2-negative breast cancer treated with first-line CDK4/6 inhibitors has not been studied. Using real-world patient data, we aimed to identify prognostic differences in this patient population according to HER2 expression with immunohistochemistry. *Patients and Methods:* We retrospectively analyzed 191 patients from 5 Oncology Department databases in Thessaloniki, Greece, with hormone receptor-positive HER2-negative metastatic breast cancer treated with CDK4/6 inhibitors in the first line, for whom detailed immunohistochemical HER2 data could be retrieved. *Results:* Median progression-free survival was numerically different among the different HER2 subgroups (3.35 years for HER2 0 tumors, 2.18 years for HER2 +1 tumors, 1.74 years for HER2 +2/ISH-negative tumors), but this difference

was not statistically significant ($p=0.477$). Median PFS was statistically significantly longer in patients without visceral metastases (5.45 years) compared to patients with visceral metastases (1.61 years) ($p=0.017$). Median PFS was also statistically significantly longer in patients taking an aromatase inhibitor (2.99 years) compared to patients taking fulvestrant (1.33 years) ($p<0.0001$). There were no statistically significant differences in the other subgroups examined. *Conclusion:* CDK4/6 inhibitors are equally effective as first-line treatment agents, regardless of the exact level of HER2 expression. Numerical differences, however, do exist among the different HER2 subgroups, and merit further evaluation in future studies to better study this phenomenon.

The standard-of-care first line treatment for patients with metastatic hormone receptor (HR) positive, HER2-negative breast cancer is the combination of a CDK4/6 inhibitor (CDKI) with endocrine therapy (an aromatase inhibitor, tamoxifen, or fulvestrant), except for cases of imminent organ failure, where chemotherapy is indicated (1). The incorporation of CDKIs in clinical practice has been one of the major advancements in the field of breast cancer; however, despite the significant added benefit offered by these drugs, metastatic breast cancer remains an incurable disease, and its treatment a significant unmet need. Today, there is evidence for disease-free survival benefit from all three approved CDKIs both in first and in second-line treatment (2-7). The addition of ribociclib to hormonal therapy has shown statistically significant prolongation of overall survival (OS) in the first line of treatment, both in premenopausal and postmenopausal women in combination with aromatase inhibitors (8, 9), and in combination with fulvestrant (10). Abemaciclib has shown statistically

Correspondence to: Konstantinos Papazisis, Euromedica General Clinic, Gravias 2 & Maria Kallas 11 Street, 54645, Thessaloniki, Greece. Tel: +30 2310895362, Fax: +30 2310895363, e-mail: k.papazisis@oncomedicare.com

Key Words: Breast cancer, HER2-low, CDK 4/6 inhibitors, hormone receptor positive.

©2022 International Institute of Anticancer Research
www.iiar-anticancer.org



This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY-NC-ND) 4.0 international license (<https://creativecommons.org/licenses/by-nc-nd/4.0>).

significant prolongation of OS in the second line of treatment (11), and palbociclib has shown trends for OS improvement in the second line (12, 13). A recent meta-analysis from FDA of Monaleesa-3, Monarch-2, and Paloma-3 trials concluded that the addition of CDKIs to fulvestrant resulted in a consistent OS benefit (14).

Extensive research is taking place globally to identify new potential targets for therapy. For HR-positive, HER2-negative breast cancer, drugs targeting the PI3K pathway, and the PARP enzymes involved in DNA repair have been approved for use in clinical practice (15, 16), and drugs targeting other surface receptors, the apoptotic machinery or boosting the immune response are in development (17). One of these new fields is the field of HER2-low breast cancer. HER2 expression is currently assessed by immunohistochemistry (IHC) as per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, with IHC 0, +1 or +2 with a negative result in in situ hybridization (ISH) being classified as “HER2-negative”, and IHC +2/ISH-positive or +3 being classified as “HER2-positive” (18). However, an emerging body of evidence in recent years suggests that tumors which are currently classified as HER2-negative may differ in characteristics and prognosis based on their exact level of HER2 expression.

Studies have reported differences both in clinical characteristics, with HER2+2/ISH-negative tumors more frequently being of larger diameter, higher Ki-67 score, grade and axillary lymph node involvement compared to HER2 0 and +1 tumors (19), and in biological characteristics, with distinct PAM50 gene expression features expressed in individual HER2-low subtypes (20). Regarding prognosis, no solid evidence yet exists to support HER2-low status (IHC +1 or +2/ISH-negative) as an independent prognostic factor (21). Multiple analyses have been conducted, but results have been conflicting, with authors reporting both survival differences among different HER2-low subgroups (19, 22, 23), and a lack thereof (24-26). Even though the prognostic significance of low HER2 expression is still being investigated, its predictive role has now been firmly elucidated; the novel antibody-drug conjugate trastuzumab deruxtecan has been shown to increase both progression-free survival and OS in patients with HER2-low metastatic breast cancer in the phase III clinical trial Destiny-Breast 04 (27).

The discovery that low HER2 expression is a valid therapeutic target and renders tumors responsive to anti-HER2 targeted therapies is expected to radically change the treatment landscape for metastatic breast cancer. Even moving beyond sequencing dilemmas, however, it is also paramount to analyze the extent to which low HER2 expression impacts response to currently available therapeutic options. Patients with metastatic HR-positive HER2-negative breast cancer are treated as standard practice

with combination treatments including a CDKI, but the impact of low HER2 expression on the real-world effectiveness of these drugs has not yet been studied. A post-hoc analysis of pooled Monaleesa phase III trials evaluated the intrinsic subtype distribution across all three trials (89.2% of tumor samples) based on PAM50 analysis (28). A 12.7% of the samples were characterized as HER2-enriched. Ribociclib treatment maintained the overall benefit in the HER2-enriched population as well (HR=0.39, $p<0.0001$) (28). However, PAM50 is a relatively expensive test and is not widely available to all patients in need of treatment. Furthermore, a similar analysis has not been performed for palbociclib or abemaciclib in this setting.

Immunohistochemistry is a simpler, widely-performed method, available for virtually all patients who are candidates for first-line hormonal therapy with a CDKI. There are currently no available data to evaluate the benefit of the addition of CDKIs to the hormonal treatment according to HER2 expression by immunohistochemistry. Therefore, we retrospectively evaluated the outcomes of patients with metastatic and/or unresectable HR-positive and HER2-negative breast cancer that received hormonal treatment with CDKIs as the first line of treatment.

Patients and Methods

This retrospective study was registered with the Euromedica General Clinic Ethics Committee with the registration number 1556/27-04-22. Data were collected from patients treated at four Oncology Centers in Thessaloniki, Greece: “Euromedica” General Clinic, Theageneion Cancer Hospital, Saint Luke Private Hospital, and BioClinic Thessaloniki. Patients were included provided they a) had a diagnosis of metastatic breast cancer, either *de novo* or relapsed as unresectable/metastatic disease, b) had HR-positive and HER2-negative tumors for whom the exact HER2 status on immunohistochemistry was recorded (0, +1, +2/ISH-negative), c) had received a CDK4/6 inhibitor as the first line of their treatment for metastatic disease. The HER2 status was recorded from the most recent biopsy performed.

The primary endpoint of the study was the assessment of progression-free survival (PFS), defined as the time elapsed between treatment initiation and first documentation of objective disease progression or death, according to HER2 status. Survival data were also recorded. Additional analysis was performed by the extent of disease (absence vs. presence of visceral metastases), the CDKI used, the type of concomitant endocrine therapy used (aromatase inhibitors or SERDs – Selective Estrogen Receptor Degraders), patient age, and histological tumor type.

All data were collected from May 2016 to March 2022 (database lock). The Kaplan–Meier method was used to estimate the median PFS and OS. Log-rank tests were used to test the equality of survivor functions across groups. According to the methodological features of an observational non-interventional study, all analyses were descriptive, and the results presented should be interpreted as such. All statistical analyses were performed using GraphPad by Dotmatics Prism 9.3.1 software (graphpad.com/scientific-software/prism).

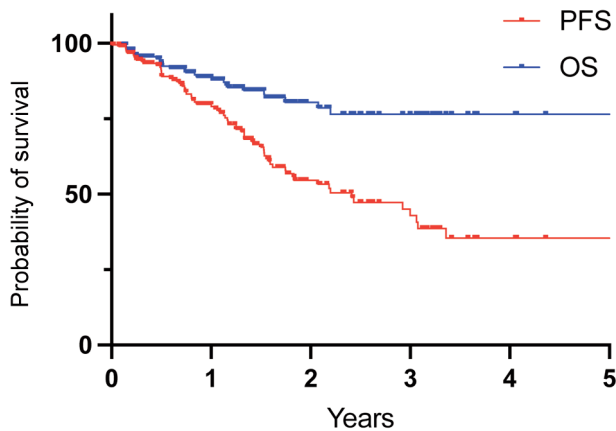


Figure 1. Progression-free survival (PFS) and overall survival (OS) for all patients ($n=191$).

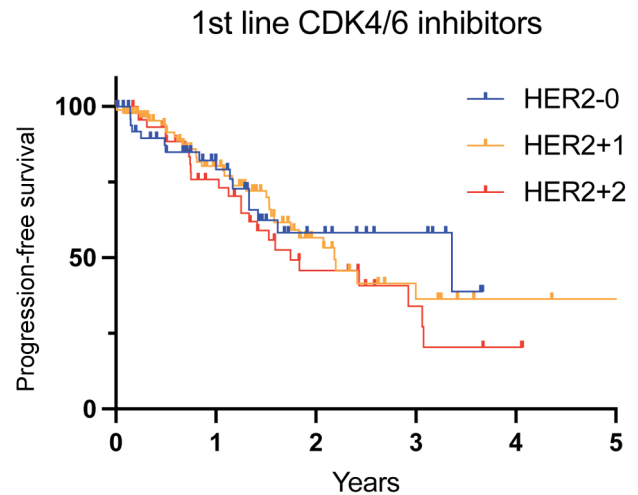


Figure 2. Progression-free survival according to human epidermal growth factor receptor-2 (HER2) expression.

Results

A total of 191 patients from 5 centers were included. The median age at presentation of metastatic disease was 60 years (range=24-91 years). Median follow-up was 1.25 years. Seventy-four of the patients presented with *de novo* metastatic disease, and 117 relapsed with unresectable/ metastatic cancer. Eighty-eight of the patients presented with non-visceral disease, and 113 with visceral disease. The most common CDKI used was ribociclib (103 patients), followed by palbociclib (81 patients), and abemaciclib (7 patients). Three patients who started on ribociclib switched to palbociclib due to poor compliance, and a further two stopped CDKI due to side-effects and continued on the same hormonal treatment. All data were analyzed by the intention-to treat (by the CDKI they started treatment on). Regarding the endocrine therapy used in combination with the CDKI, 135 patients were treated with an aromatase inhibitor (38 of whom together with a gonadotropin-releasing hormone agonist – GnRHa – and 97 without one), 52 patients were treated with fulvestrant, of whom 8 in combination with a GnRHa, 2 were treated with tamoxifen and a GnRHa, and 2 were enrolled in a clinical trial (SERD vs. aromatase inhibitor). HER2 status was recorded in all patients, as follows: 52 patients HER2 0, 90 patients HER2 +1, 47 patients HER2 +2/ISH-negative, and 2 patients unknown but HER2 negative.

Median PFS was 2.41 years and median OS was not reached (Figure 1). Since a median OS was not reached, further subgroup analyses regarding survival were not performed. Median PFS was numerically different among the different HER2 subgroups; 3.35 years for HER2 0 patients, 2.18 years for HER2 +1 patients, and 1.74 years for HER2 +2/ISH-negative patients, but this difference did not reach statistical significance ($p=0.477$) (Figure 2). Median PFS

was significantly longer in patients without visceral metastases (5.45 years) compared to patients with visceral metastases (1.61 years) ($HR=2.088$ for presence of visceral metastases, 95%CI=1.318-3.308, $p=0.017$) (Figure 3). Median PFS was significantly longer in patients taking an aromatase inhibitor (2.99 years) *versus* SERD (Fulvestrant) (1.33 years) ($HR=0.41$, 95%CI= $p<0.0001$) (Figure 4).

When analyzed by HER2 status, there was no difference in patients that received ribociclib ($HR=1.022$, 95%CI=0.4963-2.103), in concert with the Monaleesa trials' data (28). However, HER2-low patients on palbociclib had a numerically worse outcome than HER2-0 patients, but this was not a statistically significant difference ($HR=1.701$, 95%CI=0.7624-3.797). There were no statistically significant differences in PFS in the other subgroups examined, with the exemption of patients treated with fulvestrant, where HER2-low patients performed less well than HER2-0 ($HR=2.958$, 95%CI=1.334-6.56) (Figure 5).

Discussion

This study was designed to assess the impact of different levels of immunohistochemical HER2 expression on the PFS of HR-positive, HER2-negative metastatic breast cancer patients treated with first-line CDK4/6 inhibitors. There is strong biologic rationale for the contribution of the EGFR/HER2 signalling pathway, however limited, to endocrine resistance (29, 30), but data examining this phenomenon in real-world clinical practice are lacking.

The retrospective analysis of data showed numerical but not statistically significant differences in PFS according to HER2 status. Such a result is encouraging, considering that

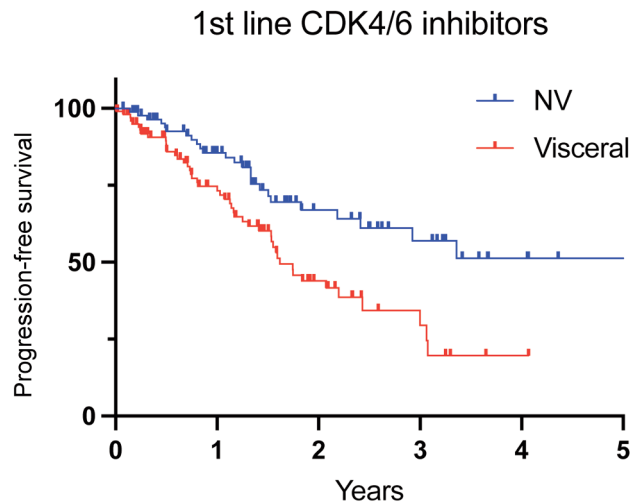


Figure 3. Progression-free survival according to extent of disease. NV: Non-visceral.

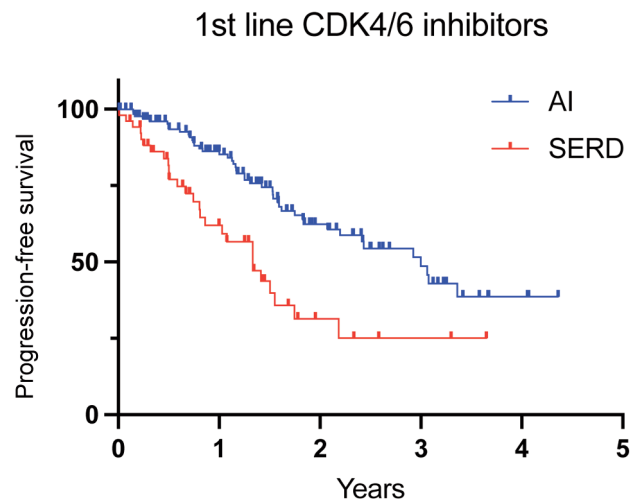


Figure 4. Progression-free survival according to endocrine therapy used. AI: Aromatase inhibitor.

CDKIs are routinely used in clinical practice in HER2-negative patients regardless of the exact level of HER2 expression. However, it should be noted that numerical differences did exist among the different subgroups, and that the differences were associated with a progressively higher expression of HER2 in a linear fashion, with HER2 0 patients having the numerically best PFS at 3.35 years, HER2 +1 patients having a median PFS at 2.18 years, and HER2 +2/ISH-negative patients having the numerically worst PFS at 1.74 years. The only other study in the literature to specifically examine the relationship between different levels of HER2 expression and CDK4/6 inhibitors reported similar results, with HER2-low patients being associated with a shorter PFS compared to HER2 0 patients (31). Other studies have shown that HER2 +1 tumors exhibit characteristics between HER2 0 and HER2 +2 tumors and suggested a possible linear correlation between HER2 expression and tumor behavior (23). A similar correlation has been established between HER2 expression and response to anti-HER2 targeted therapy, as was evident by the results of the Destiny-Breast 04 trial, which showed that anti-HER2 therapy is effective also in HER2-low tumors (27). These data further solidify the notion that individual HER2 subgroups should be examined separately in upcoming clinical trials, in order to effectively identify any such differences and their clinical significance. A trend of HR-positive, HER2 0 tumors behaving differently from HR-positive, HER2-low tumors would have far-reaching implications for clinical practice. Considering that molecular profiling using PAM50 signatures would not be routinely feasible, the level of HER2 expression assessed by immunohistochemistry is the best surrogate marker available to assess this relationship in future research.

Our study also examined other prognostic parameters in patients treated with first-line CDKIs. The presence of visceral metastases was associated with a significantly lower PFS. This is in concordance with the results reported from the large, randomized trials of CDKIs, in which the presence of visceral metastases has been established as an adverse prognostic factor (32). Furthermore, the use of an aromatase inhibitor as a concomitant hormonal therapy was associated with a significantly higher PFS compared to the use of fulvestrant. However, an important selection bias should be identified in this case. Aromatase inhibitors are the first choice of hormonal therapy in this patient population, therefore the patients who would receive fulvestrant in the first line together with a CDKIs are generally those who would not be eligible for aromatase inhibitor use due to secondary hormonal resistance; these patients have more biologically aggressive tumors and belong to a worse prognostic category (32). To support the abovementioned, we analyzed the distribution of hormonal treatment by endocrine responsiveness. Fulvestrant was used in 4.05% of patients who presented with *de novo* metastatic disease, in 28.2% of patients who relapsed after at least 5 years of adjuvant endocrine treatment and in 51.1% of patients that relapsed within the first 5 years of adjuvant endocrine treatment. Median PFS was 3.06 years for patients who presented with *de novo* metastatic disease or relapsed after 5 years vs. 1.55 years for patients who relapsed earlier (HR=1.974, $p=0.0035$).

There were no statistically significant differences in PFS in the additional subgroups examined (Figure 5). In our analysis, CDKIs appear to be equally effective regardless of patient age and histologic tumor type. There were also no statistically significant differences among different CDKIs across different levels of HER2 expression. It must be noted,

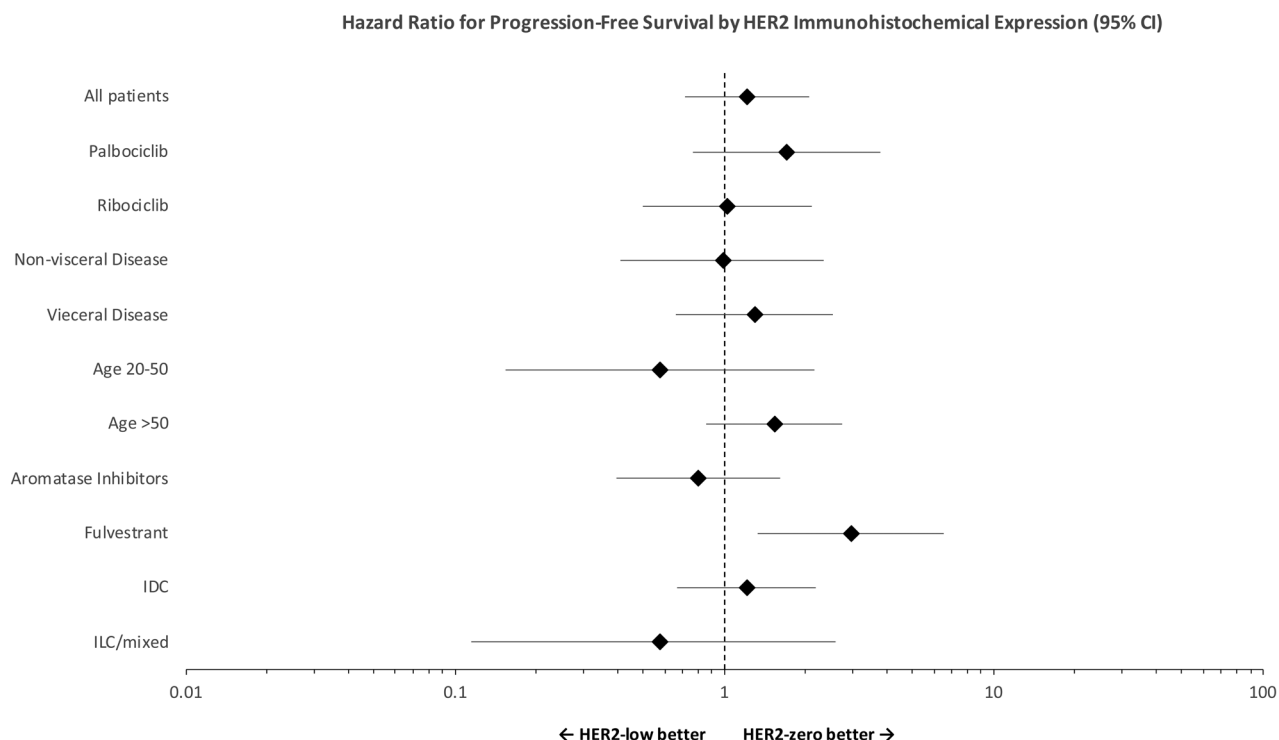


Figure 5. Hazard ratio for progression-free survival by HER2 immunohistochemical expression (95%CI). IDC: Invasive ductal carcinoma; ILC: invasive lobular carcinoma.

however, that abemaciclib has a distinct clinical profile compared to palbociclib and ribociclib due to its unique pharmacological characteristics (33), which has led to trials investigating abemaciclib use after progression on prior CDKIs (34), but the sample size for abemaciclib in this study was not large enough to draw any conclusions (n=7 patients).

The main limitation of our study is its retrospective nature. Other potential limitations include the use of multiple centers without centralized review of HER2 expression, and a relatively small sample size. However, this is a multicenter study and one of the only studies to date to examine this phenomenon. Further prospective studies with patient stratification at baseline would shed further light in this promising new field of cancer research.

Conclusion

In this retrospective multicenter analysis of real-world data, CDKIs were shown to be equally effective as first-line treatment of metastatic HR-positive HER2-negative patients regardless of the exact level of HER2 expression. There were numerical differences in PFS among the different HER2 subgroups, which did not reach statistical significance, but merit evaluation in future, larger prospective trials.

Conflicts of Interest

GD declares no relevant conflict of interest. GK has received honoraria and consultancy fees from Amgen, Avaviosis, Astellas, AstraZeneca, Boehringer, BMS, Demo, Galenica, Ipsen, LEO Pharma, Merck, MSD, Novartis, Pfizer, Roche, and Sanofi. EL has received honoraria and consultancy fees from AstraZeneca, Genesis Pharma, Novartis, Pfizer, Roche, and Amgen. IK has received honoraria and consultancy fees from Boehringer, Sandoz, Amgen, Roche, AstraZeneca, Pfizer, Novartis, Sanofi, MSD, Merck and BMS. IB has received honoraria and consultancy fees from Sandoz, Amgen, Roche, AstraZeneca, Ipsen, Pfizer, Novartis, Sanofi, Genesis Pharma, MSD, LEO pharma, Merck, Servier and BMS and Research Funding from Boehringer, Regeneron, Eli Lilly, Pfizer, Novartis, BMS, MSD and Roche. KP has received honoraria and consultancy fees from MSD, Gilead, AstraZeneca, Novartis, Eli Lilly, Roche and GSK and Research Funding from Roche, Novartis, Daiichi Sankyo, Eli Lilly, AstraZeneca, BMS, Boehringer and Eisai.

Authors' Contributions

GD and KP prepared the manuscript. KP performed all the analyses on the database. GK, EL, IK, IB and KP treated the patients, collected the data, and helped in the formation of the final manuscript. All Authors approved the final manuscript.

References

- Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, Dent R, Fenlon D, Gligorov J, Hurvitz SA, Im SA, Krug D, Kunz WG, Loi S, Penault-Llorca F, Ricke J, Robson M, Rugo HS, Saura C, Schmid P, Singer CF, Spanic T, Tolaney SM, Turner NC, Curigliano G, Loibl S, Paluch-Shimon S, Harbeck N and ESMO Guidelines Committee: ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol* 32(12): 1475-1495, 2021. PMID: 34678411. DOI: 10.1016/j.annonc.2021.09.019
- Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, Campone M, Blackwell KL, André F, Winer EP, Janni W, Verma S, Conte P, Arteaga CL, Cameron DA, Petrakova K, Hart LL, Villanueva C, Chan A, Jakobsen E, Nusch A, Burdaeva O, Grischke EM, Alba E, Wist E, Marschner N, Favret AM, Yardley D, Bachelot T, Tseng LM, Blau S, Xuan F, Souami F, Miller M, Germa C, Hirawat S and O'Shaughnessy J: Ribociclib as First-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* 375(18): 1738-1748, 2016. PMID: 27717303. DOI: 10.1056/NEJMoa1609709
- Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, Harbeck N, Lipatov ON, Walshe JM, Moulder S, Gauthier E, Lu DR, Randolph S, Diéras V and Slamon DJ: Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 375(20): 1925-1936, 2016. PMID: 27959613. DOI: 10.1056/NEJMoa1607303
- Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, Park IH, Trédan O, Chen SC, Manso L, Freedman OC, Garnica Jaliffe G, Forrester T, Frenzel M, Barriga S, Smith IC, Bourayou N and Di Leo A: MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol* 35(32): 3638-3646, 2017. PMID: 28968163. DOI: 10.1200/JCO.2017.75.6155
- Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, Petrakova K, Bianchi GV, Esteva FJ, Martín M, Nusch A, Sonke GS, De la Cruz-Merino L, Beck JT, Pivot X, Vidam G, Wang Y, Rodriguez Lorenc K, Miller M, Taran T and Jerusalem G: Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol* 36(24): 2465-2472, 2018. PMID: 29860922. DOI: 10.1200/JCO.2018.78.9909
- Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, Colleoni M, DeMichele A, Loi S, Verma S, Iwata H, Harbeck N, Zhang K, Theall KP, Jiang Y, Bartlett CH, Koehler M and Slamon D: 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* 17(4): 425-439, 2016. PMID: 26947331. DOI: 10.1016/S1470-2045(15)00613-0
- Sledge GW Jr, Toi M, Neven P, Sohn J, Inoue K, Pivot X, Burdaeva O, Okera M, Masuda N, Kaufman PA, Koh H, Grischke EM, Frenzel M, Lin Y, Barriga S, Smith IC, Bourayou N and Llombart-Cussac A: MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2-advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol* 35(25): 2875-2884, 2017. PMID: 28580882. DOI: 10.1200/JCO.2017.73.7585
- Im SA, Lu YS, Bardia A, Harbeck N, Colleoni M, Franke F, Chow L, Sohn J, Lee KS, Campos-Gomez S, Villanueva-Vazquez R, Jung KH, Chakravarty A, Hughes G, Gounaris I, Rodriguez-Lorenc K, Taran T, Hurvitz S and Tripathy D: Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med* 381(4): 307-316, 2019. PMID: 31166679. DOI: 10.1056/NEJMoa1903765
- Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Hart L, Campone M, Petrakova K, Winer EP, Janni W, Conte P, Cameron DA, André F, Arteaga CL, Zarate JP, Chakravarty A, Taran T, Le Gac F, Serra P and O'Shaughnessy J: Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med* 386(10): 942-950, 2022. PMID: 35263519. DOI: 10.1056/NEJMoa2114663
- Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, Petrakova K, Bianchi GV, Esteva FJ, Martín M, Nusch A, Sonke GS, De la Cruz-Merino L, Beck JT, Pivot X, Sondhi M, Wang Y, Chakravarty A, Rodriguez-Lorenc K, Taran T and Jerusalem G: Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med* 382(6): 514-524, 2020. PMID: 31826360. DOI: 10.1056/NEJMoa1911149
- Sledge GW Jr, Toi M, Neven P, Sohn J, Inoue K, Pivot X, Burdaeva O, Okera M, Masuda N, Kaufman PA, Koh H, Grischke EM, Conte P, Lu Y, Barriga S, Hurt K, Frenzel M, Johnston S and Llombart-Cussac A: 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 Oncol* 6(1): 116-124, 2020. PMID: 31563959. DOI: 10.1001/jamaoncol.2019.4782
- Turner NC, Slamon DJ, Ro J, Bondarenko I, Im SA, Masuda N, Colleoni M, DeMichele A, Loi S, Verma S, Iwata H, Harbeck N, Loibl S, André F, Puyana Theall K, Huang X, Giorgetti C, Huang Bartlett C and Cristofanilli M: Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med* 379(20): 1926-1936, 2018. PMID: 30345905. DOI: 10.1056/NEJMoa1810527
- Cristofanilli M, Rugo HS, Im S-A, Slamon DJ, Harbeck N, Bondarenko I, Masuda N, Colleoni M, DeMichele A, Loi S, Iwata H, O'Leary B, Bananis E, Liu Y, Huang X, Kim S, Lechuga M and Turner NC: Overall survival (OS) with palbociclib (PAL) + fulvestrant (FUL) in women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC): Updated analyses from PALOMA-3. *Journal of Clinical Oncology* 39(15_suppl): 1000-1000, 2021. DOI: 10.1200/JCO.2021.39.15_SUPPL.1000
- Gao JJ, Cheng J, Prowell TM, Bloomquist E, Tang S, Wedam SB, Royce M, Krol D, Osgood C, Ison G, Sridhara R, Pazdur R, Beaver JA and Amiri-Kordestani L: Overall survival in patients with hormone receptor-positive, HER2-negative, advanced or metastatic breast cancer treated with a cyclin-dependent kinase 4/6 inhibitor plus fulvestrant: a US Food and Drug Administration pooled analysis. *Lancet Oncol* 22(11): 1573-1581, 2021. PMID: 34656225. DOI: 10.1016/S1470-2045(21)00472-1
- André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, Iwata H, Conte P, Mayer IA, Kaufman B, Yamashita T, Lu YS, Inoue K, Takahashi M, Pápai Z, Longin AS, Mills D, Wilke C, Hirawat S, Juric D and SOLAR-1 Study Group: Alpelisib for *PIK3CA*-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med* 380(20): 1929-1940, 2019. PMID: 31091374. DOI: 10.1056/NEJMoa1813904

- 16 Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, Delaloge S, Li W, Tung N, Armstrong A, Wu W, Goessl C, Runswick S and Conte P: Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med* 377(6): 523-533, 2017. PMID: 28578601. DOI: 10.1056/NEJMoa1706450
- 17 Stravodimou A and Voutsadakis IA: The future of ER+/HER2-metastatic breast cancer therapy: Beyond PI3K inhibitors. *Anticancer Res* 40(9): 4829-4841, 2020. PMID: 32878771. DOI: 10.21873/anticancer.14486
- 18 Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, Bilous M, Ellis IO, Fitzgibbons P, Hanna W, Jenkins RB, Press MF, Spears PA, Vance GH, Viale G, McShane LM and Dowsett M: Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline focused update. *Arch Pathol Lab Med* 142(11): 1364-1382, 2018. PMID: 29846104. DOI: 10.5858/arpa.2018-0902-SA
- 19 Rossi V, Sarotto I, Maggiorotto F, Berchialla P, Kubatzki F, Tomasi N, Redana S, Martinello R, Valabrega G, Aglietta M, Ponzzone R and Montemurro F: Moderate immunohistochemical expression of HER-2 (2+) without HER-2 gene amplification is a negative prognostic factor in early breast cancer. *Oncologist* 17(11): 1418-1425, 2012. PMID: 22951668. DOI: 10.1634/theoncologist.2012-0194
- 20 Schettini F, Chic N, Brasó-Maristany F, Paré L, Pascual T, Conte B, Martínez-Sáez O, Adamo B, Vidal M, Barnadas E, Fernández-Martínez A, González-Farre B, Sanfeliu E, Cejalvo JM, Perrone G, Sabarese G, Zalfa F, Peg V, Fasani R, Villagrasa P, Gavilá J, Barrios CH, Lluch A, Martín M, Locci M, De Placido S and Prat A: Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. *NPJ Breast Cancer* 7(1): 1, 2021. PMID: 33397968. DOI: 10.1038/s41523-020-00208-2
- 21 Tarantino P, Hamilton E, Tolane SM, Cortes J, Morganti S, Ferraro E, Marra A, Viale G, Trapani D, Cardoso F, Penault-Llorca F, Viale G, André F and Curigliano G: HER2-low breast cancer: Pathological and clinical landscape. *J Clin Oncol* 38(17): 1951-1962, 2020. PMID: 32330069. DOI: 10.1200/JCO.19.02488
- 22 Denkert C, Seither F, Schneeweiss A, Link T, Blohmer JU, Just M, Wimberger P, Forberger A, Tesch H, Jackisch C, Schmatloch S, Reinisch M, Solomayer EF, Schmitt WD, Hansch C, Fasching PA, Lübke K, Solbach C, Huober J, Rhiem K, Marmé F, Reimer T, Schmidt M, Sinn BV, Janni W, Stickeler E, Michel L, Stötzer O, Hahnen E, Furlanetto J, Seiler S, Nekljudova V, Untch M and Loibl S: Clinical and molecular characteristics of HER2-low-positive breast cancer: pooled analysis of individual patient data from four prospective, neoadjuvant clinical trials. *Lancet Oncol* 22(8): 1151-1161, 2021. PMID: 34252375. DOI: 10.1016/S1470-2045(21)00301-6
- 23 Eggemann H, Ignatov T, Burger E, Kantelhardt EJ, Fettke F, Thomssen C, Costa SD and Ignatov A: Moderate HER2 expression as a prognostic factor in hormone receptor positive breast cancer. *Endocr Relat Cancer* 22(5): 725-733, 2015. PMID: 26187126. DOI: 10.1530/ERC-15-0335
- 24 Agostinetti E, Rediti M, Fimereli D, Debieu V, Piccart M, Aftimos P, Sotiriou C and de Azambuja E: HER2-low breast cancer: Molecular characteristics and prognosis. *Cancers (Basel)* 13(11): 2824, 2021. PMID: 34198891. DOI: 10.3390/cancers13112824
- 25 Horisawa N, Adachi Y, Takatsuka D, Nozawa K, Endo Y, Ozaki Y, Sugino K, Kataoka A, Kotani H, Yoshimura A, Hattori M, Sawaki M and Iwata H: The frequency of low HER2 expression in breast cancer and a comparison of prognosis between patients with HER2-low and HER2-negative breast cancer by HR status. *Breast Cancer* 29(2): 234-241, 2022. PMID: 34622383. DOI: 10.1007/s12282-021-01303-3
- 26 Douganiotis G, Kontovinis L, Markopoulou E, Ainali A, Zarampoukas T, Natsiopoulos I and Papazisis K: Prognostic significance of low HER2 expression in patients with early hormone receptor positive breast cancer. *Cancer Diagn Progn* 2(3): 316-323, 2022. PMID: 35530657. DOI: 10.21873/cdp.10111
- 27 Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, Tsurutani J, Ueno NT, Prat A, Chae YS, Lee KS, Niikura N, Park YH, Xu B, Wang X, Gil-Gil M, Li W, Pierga JY, Im SA, Moore HCF, Rugo HS, Yerushalmi R, Zagouri F, Gombos A, Kim SB, Liu Q, Luo T, Saura C, Schmid P, Sun T, Gambhire D, Yung L, Wang Y, Singh J, Vitazka P, Meinhardt G, Harbeck N, Cameron DA and DESTINY-Breast04 Trial Investigators: Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med* 387(1): 9-20, 2022. PMID: 35665782. DOI: 10.1056/NEJMoa2203690
- 28 Prat A, Chaudhury A, Solovieff N, Paré L, Martínez D, Chic N, Martínez-Sáez O, Brasó-Maristany F, Lteif A, Taran T, Babbar N and Su F: Correlative biomarker analysis of intrinsic subtypes and efficacy across the MONALEESA Phase III studies. *J Clin Oncol* 39(13): 1458-1467, 2021. PMID: 33769862. DOI: 10.1200/JCO.20.02977
- 29 Osborne CK and Schiff R: Mechanisms of endocrine resistance in breast cancer. *Annu Rev Med* 62: 233-247, 2011. PMID: 20887199. DOI: 10.1146/annurev-med-070909-182917
- 30 Mazumder A, Shiao S and Haricharan S: HER2 activation and endocrine treatment resistance in HER2-negative breast cancer. *Endocrinology* 162(10): bqab153, 2021. PMID: 34320193. DOI: 10.1210/endo/bqab153
- 31 Bao KKH, Soutanto L, Tse SSW, Man Cheung K and Chan JCH: The association of ERBB2-low expression with the efficacy of cyclin-dependent kinase 4/6 inhibitor in hormone receptor-positive, ERBB2-negative metastatic breast cancer. *JAMA Netw Open* 4(11): e2133132, 2021. PMID: 34739066. DOI: 10.1001/jamanetworkopen.2021.33132
- 32 Piezzo M, Chiodini P, Riemma M, Cocco S, Caputo R, Cianniello D, Di Gioia G, Di Lauro V, Rella FD, Fusco G, Iodice G, Nuzzo F, Pacilio C, Pensabene M and De Laurentiis M: 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* 21(17): 6400, 2020. PMID: 32899139. DOI: 10.3390/ijms21176400
- 33 Torres-Guzmán R, Ganado MP, Pérez CM, Marugán C, Baquero C, Yang Y, Du J, de Dios A, Puig O and Lallena M-J: Abemaciclib, a CDK4 and 6 inhibitor with unique pharmacological properties for breast cancer therapy. *J Clin Oncol* 39(15 suppl): e12506, 2021. DOI: 10.1200/JCO.2021.39.15_SUPPL.E12506
- 34 Seki H, Sakurai T, Sakurada A, Kinoshita T and Shimizu K: Subsequent-abemaciclib treatment after disease progression on palbociclib in patients with ER-positive HER2-negative metastatic breast cancer. *Anticancer Res* 42(2): 1099-1106, 2022. PMID: 35093912. DOI: 10.21873/anticancer.15572

Received June 25, 2022

Revised July 12, 2022

Accepted July 13, 2022