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Special article

Abemaciclib as adjuvant treatment for high-risk early breast cancer

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A B S T R A C T

Objective: To adapt the GHEMA report of abemaciclib, an inhibitor of cyclin-dependent kinases 4 and 6. European Medicines Agency authorization (April 2022) includes, in combination with endocrine therapy, the adjuvant treatment of adult patients with hormone receptor positive, human epidermal growth factor receptor 2 negative, node-positive, early breast cancer at high risk of recurrence.
Method: The efficacy and safety of abemaciclib were evaluated in a randomized, open-label, and multicenter phase III study. A total of 5637 patients diagnosed with early breast cancer with hormone receptor positive, human epidermal growth factor receptor 2 negative, node positive, and high risk of recurrence were included. High risk was defined as patients with 4 or more positive axillary lymph nodes, or 1–3 positive axillary lymph nodes and at least one of the following: tumor size ≥5 cm, histologic grade 3, or Ki-67≥20%. Patients were randomized (1:1) to receive adjuvant abemaciclib + endocrine therapy (n = 2808) or endocrine therapy alone (n = 2829) for 2 years, with endocrine therapy prescribed for at least 5 years.
Results: With a median follow-up of 15.5 months, abemaciclib + endocrine therapy demonstrated a statistically significant improvement in invasive disease-free survival versus endocrine therapy alone [HR = 0.747 (95% CI 0.598–0.932), $P = 0.0096$]; achieving an absolute improvement of 3.5% invasive disease-free survival rate at 2-years. These results were maintained, with a median follow-up of 27.7 months: absolute improvement of 2.7% and 5.4% in invasive disease-free survival rate at 2 and 3 years, respectively. All-causality grade 3 or 4 adverse events were 45.9% for abemaciclib and 12.9% for endocrine therapy, and included neutropenia (19.6% vs. 0.8%), leukopenia (11.4% vs. 0.4%), and diarrhea (7.8% vs. 0.2%).
Conclusions: The results of the pivotal trial are sufficient to consider abemaciclib as adjuvant treatment for high-risk early breast cancer in highly selected patients. However, in order to the efficacy results present less uncertainty, we must wait for a evaluation later, in which we can have a mature determination at 3 years (with more patients at risk).

Abemaciclib en adyuvancia para el tratamiento del cáncer de mama precoz de alto riesgo

Palabras clave:
abemaciclib
hormonoterapia
adyuvante
cáncer de mama precoz
alto riesgo
tasa de supervivencia libre de enfermedad invasiva

R E S U M E N

Objetivo: Adaptar el informe GHEMA de abemaciclib, un inhibidor de quinasas dependientes de ciclinas 4 y 6, con autorización de la Agencia Europea del Medicamento en abril de 2022 para el tratamiento adyuvante de pacientes adultos con cáncer de mama precoz, receptor hormonal positivo, receptor del factor de crecimiento epidérmico negativo, con afectación ganglionar y riesgo elevado de recaída; en combinación con hormonoterapia.
Método: La eficacia y seguridad de abemaciclib se evaluó en un estudio fase III multicéntrico, aleatorizado y abierto. Se incluyeron 5.637 pacientes diagnosticados de cáncer de mama precoz con ganglios positivos, receptor hormonal positivo, receptor del factor de crecimiento epidérmico negativo y alto riesgo de recaída. El criterio de alto riesgo se definió como la presencia de ≥ 4 ganglios positivos, o de 1–3 ganglios y al menos una de las siguientes características: tamaño del tumor ≥5 cm, grado histológico 3 o Ki-67 ≥ 20%. Los pacientes fueron aleatorizados (1:1) a recibir durante 2 años abemaciclib + hormonoterapia (n = 2.808) u hormonoterapia sola (n = 2.829). En ambos brazos el tratamiento con hormonoterapia se mantuvo mínimo 5 años.

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Resultados: Con una mediana de seguimiento de 15,5 meses, abemaciclib + hormonoterapia mostró beneficio significativo frente a la hormonoterapia sola [HR = 0,747 (IC95% 0,598-0,932), p = 0,0096], con una mejora absoluta del 3,5% en la tasa de supervivencia libre de enfermedad invasiva a 2 los años. Este beneficio se mantuvo con una mediana de seguimiento de 27,7 meses, logrando una mejora en la tasa de supervivencia libre de enfermedad invasiva del 2,7% y del 5,4% a los 2 y 3 años, respectivamente. La incidencia de efectos adversos grado 3–4 fue superior en el brazo de abemaciclib (45,9% vs. 12,9%); e incluía neutropenia (19,6% vs. 0,8%), leucopenia (11,4% vs. 0,4%) y diarrea (7,8% vs. 0,2%).

Conclusiones: Los resultados del ensayo pivotal son suficientes para considerar abemaciclib como tratamiento adyuvante del cáncer de mama precoz con alto riesgo de recaída en pacientes muy seleccionados. Sin embargo, para que los resultados de eficacia presenten menos incertidumbre, debemos esperar a una evaluación posterior en la que podamos tener una determinación más madura a los 3 años (con más pacientes a riesgo).

Introduction

Breast cancer, which originates within the ducts (85%) or lobules (15%) of the mammary glandular tissue, is a major health problem due to its high incidence, prevalence, and mortality. Worldwide, there were about 2.1 million new cases of female breast cancer diagnosed in 2018. This cancer type in males is rare, contributing to 1% of cases. The incidence has increased since the introduction of mammography screening and continues to rise with the aging of the population (less than 5% occur before the age of 35). The most important risk factors are: genetic predisposition, exposure to estrogen, ionizing radiation, low parity, high breast density, and a history of atypical hyperplasia.[1]

Breast cancer is a heterogeneous disease with multiple intrinsic tumor subtypes. Luminal A-like (hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-)) are the most common subtypes, with the best prognosis. Luminal B-like (HR-positive and HER2-positive/negative) has higher proliferative index and is more aggressive than the A-like subtype. All luminal cancers should be treated with endocrine therapy (ET). The use of chemotherapy (ChT) in HER2-negative luminal type A and luminal type B patients depends on high disease burden and individual risk of recurrence, respectively. HER2-positive luminal B breast cancer should be treated with ChT, ET, and anti-HER2 therapy.[1]

Many patients with luminal A-like early breast cancer (EBC) will not experience recurrence or distant recurrence with currently available standard therapies. However, up to 30% of patients with high-risk clinical and/or pathologic features may experience distant recurrence, many of them within the first 10 years. Superior treatment options are needed to prevent early recurrence and the development of metastases for this group of patients.[2] Abemaciclib, an oral small-molecule inhibitor of cyclin-dependent kinases (CDKs), has recently been approved in combination with ET for adjuvant treatment of adult patients with HR+, HER2-, node positive, and EBC with high risk of recurrence, showing an absolute improvement in invasive disease-free survival (IDFS) rates.[3] In this paper, an adaptation of the GHEMA report is made. We reviewed abemaciclib plus ET compared with ET alone for adjuvant treatment of patients with high-risk luminal A EBC based on a phase III trial.

Efficacy

The results of the monarchE (NCT03155997) are presented below. This is an open-label, global, randomized, and phase III trial comparing standard-of-care adjuvant ET for at least 5 years with or without abemaciclib for 2 years, was conducted in patients with HR+, HER2-, node positive, and high-risk EBC.[2] Patients were assigned to cohort 1 or cohort 2. Cohort 1 included patients with 4 or more positive axillary lymph nodes (ALNs) or 1–3 positive ALNs and at least: tumor size ≥5 cm or histologic grade 3. Cohort 2, according to Food and Drug Administration (FDA) criteria, began enrolling 1 year after cohort 1 and included patients with 1–3 positive ALNs and Ki-67 index ≥20%. Patients were randomized (in a 1:1 ratio) to receive adjuvant abemaciclib plus ET or ET alone for 2 years, with ET prescribed for at least 5 years. Cohort 1, initially planned in the protocol and regardless of Ki-67 index, accounted for 91% of the total study population. However, cohort 2, introduced later and with a reduced population (9% of patients included),[4] changed the primary objective and raised questions of external validity and applicability. Furthermore, analysis of the results of cohort 2 in isolation did not show a significant benefit. For this reason, only the results of cohort 1 will be shown.

In addition, ambiguity has been detected in the approved indications. The FDA is restrictive and only includes patients with elevated Ki-67 index. However, the indication approved by the European Medicines Agency (EMA) could be applied to both cohorts 1 and 2 and to other patients, including populations that are not represented in the pivotal study. Due to the uncertainty in the results of cohort 2 mentioned above, the ambiguity of the approval can be interpreted in a restrictive sense, selecting cohort 1, which is the only one whose results appear in the efficacy section of the data sheet. Reporting data exclusively from cohort 1 is in line with the Committee for Medicinal Products for Human Use (CHMP) recommendation in the European Public Assessment Report (EPAR). Therefore, it is considered that the demonstrated benefit of abemaciclib as adjuvant treatment would apply exclusively to patients at high risk of recurrence included in cohort 1.

Eligible patients were women aged 18 years or older diagnosed with HR+, HER2-, and high-risk EBC. High risk was defined as patients with 4 or more positive ALNs, or 1–3positive ALNs and at least one of the following: tumor size ≥5 cm, histologic grade 3, or Ki-67≥20%. The number of patients included was 5637 but only 5591 patients were randomized to receive treatment (2794 to the abemaciclib + ET arm and 2797 to the ET alone arm). Results were analyzed on an intention-to-treat basis, considering all patients included in the trial.[2]

Abemaciclib was administered orally at 150 mg twice daily and ET (anti-estrogen agents or aromatase inhibitors) was administered according to the physician's choice, with or without a gonadotropin-releasing hormone agonist.[4] Patients were treated for 2 years (period with higher recurrence rate) or until they met discontinuation criteria (unacceptable toxicity, discontinuation, or death). After treatment period, patients continued to receive ET for 5–10 years. No cross-over was allowed. In general, demographics and baseline characteristics were balanced between treatment groups.[2]

The primary endpoint was IDFS according to the Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials (STEEP) criteria[5] defined as the interval between the dates of randomization and the first documentation of disease progression (as assessed by the investigator) or death from any cause. Secondary endpoints were distant relapse-free survival (DRFS), defined as the time from randomization to distant recurrence or death from any cause; overall survival (OS) and safety. Routine safety assessments were performed and grades of severity of adverse events were assessed by the investigator.[2]

Table 1
Efficacy results from the pivotal trial.

Outcome	Abemaciclib + ET (N = 2808) rate	ET alone (N = 2829) rate	Hazard ratio	Rate difference[a]	NNT
Main outcome:					
IDFS-15.5 months of follow-up (2° intermediate analysis, becomes final analysis)	92.2% at 2 years	88.7% at 2 years	HR = 0.75 (IC 95%: 0.60–0.93) $P = .01$	3.5%	29
IDFS-27 months of follow-up	92.7% at 2 years	90.0% at 2 years	HR = 0.70 (IC 95%: 0.59–0.82) $P < .0001$	2.7%	37
(was the final analysis specified initially)	88.8% at 3 years	83.4% at 3 years		5.4%	19
Secondary outcomes of interest:					
DRFS-27 months of follow-up	94.1% at 2 years	91.6% at 2 years	HR = 0.69 (IC 95%: 0.57–0.83) $P < .0001$	2.5%	40

Abbreviations: Endocrine Therapy (ET), Invasive Disease-Free Survival (IDFS), Distant Relapse-Free Survival (DRFS), Hazard Ratio (HR), Number Needed to Treat (NNT).
[a] Rates difference obtained from the Kaplan–Meier curves. The significance in HR does not imply significance in rates difference.

The results obtained in cohort 1 are shown in Table 1. At the second interim efficacy analysis, median follow-up time was approximately 15.5 months in both arms, abemaciclib plus ET demonstrated a statistically significant improvement in IDFS versus ET alone (P = .01; HR = 0.75, 95% CI: 0.60–0.93), with 2-year IDFS rates of 92.2% (abemaciclib arm) versus 88.7% (control arm).[2] With an additional 8 months of median follow-up, the benefit of abemaciclib versus ET was maintained for IDFS ($P < .0001$; HR = 0.70, 95% CI: 0.59–0.82). The Kaplan–Meier curves continued to show the benefit of abemaciclib, even beyond the 2-year treatment period of the study. With more patients at risk of recurrence at 3 years, the data demonstrated a 5.4% absolute improvement in 3-year IDFS rates (abemaciclib plus ET 88.8% vs. ET alone 83.4%).[4]

Subgroup analysis showed consistent results across all patient subgroups. Two subgroups with statistical interaction were detected: primary tumor size and patient performance status-1.[2] However, the difference found in both subgroups was unreliable when assessing complementary aspects and should not be considered in clinical practice.

Clinical guidelines

The following are the latest recommendations from the most important guidelines used in our daily clinical practice for the treatment of EBC:

-ASCO Guideline 2022: Based on a predefined secondary analysis conducted by the FDA, 2 years of abemaciclib (150 mg twice daily) plus ET may be offered to patients with RH+, HER2, Node+ EBC with a high risk of recurrence, and Ki-67 score of ≥20%. The panel also recommends, based on the analyses reported by Harbeck et al,[4] that abemaciclib for 2 years plus ET for ≥5 years may be offered to the broader intention-to-treat population of patients with resected, RH+, HER2-, node-positive, and high risk of recurrence.[6]

-NCCN Guideline version 4.2022: In patients with HR+/HER2-, high-risk breast cancer, 2 years of adjuvant abemaciclib *in combination with ET*[7] may be considered.

-CADTH Guideline 2022: Abemaciclib is indicated in combination with ET for the adjuvant treatment of adult patients with HR+, HER2-, node-positive, and early breast cancer at high risk of disease recurrence based on clinicopathological features and a Ki-67 score ≥20%.[8]

Safety and/or adverse effects studies

The incidence of grade ≥3 adverse events (AEs) was 45.9% in the abemaciclib arm and 12.9% in the control arm. The most common grade ≥3 AEs with abemaciclib were neutropenia (19.6%), leukopenia (11.3%), diarrhea (7.8%), and lymphopenia (5.4%); with ET alone, they were neutropenia (0.8%), alanine aminotransferase increased (0.7%), and lymphopenia (0.5%).[4] Serious adverse events (SAEs) occurred in 12.3% of patients in the abemaciclib arm and 7.2% of patients in the control arm, with pneumonia being the most frequently reported SAE in both arms (0.8% and 0.5%, respectively). A total of 1901 patients (68.1%) treated with abemaciclib underwent dose reductions. The rate of treatment discontinuation due to adverse events was as follows: 16.6% discontinued abemaciclib, 6.2% discontinued both treatments, and 0.8% discontinued ET alone.[2]

Economic analysis

Cost-effectiveness estimates for abemaciclib compared to current treatment are uncertain. A brief study of costs is presented below. It would be necessary to carry out a more complete economic evaluation, including the costs of treatment after relapse and modeling the IDFS curves to project them considering a longer time horizon.

Tables 2 and 3 include the results of the preliminary economic evaluations of abemaciclib compared to the reference therapy in our country. For the incremental cost-efficacy, data from the follow-up period of the pivotal trial were used, yielding an estimated additional cost of 2,752,412.83 € at 2 years and 1,446,463.20 € at 3 years, for each additional patient who avoids disease recurrence.

Discussion and positioning

Regarding the efficacy results obtained in the pivotal trial, abemaciclib plus ET demonstrated significant and clinically relevant improvements in IDFS rate versus ET alone in the adjuvant treatment of patients with HR+, HER2-, node-positive, and high-risk EBC. After applying form 1 of the ESMO-MCBS v1.123 clinical benefit scale, a category B was obtained. Besides, the primary endpoint, IDFS, is considered a sufficiently valid intermediate endpoint to assess the efficacy because the selected patients have a very high overall survival that is difficult to measure.

However, the trial has certain limitations. The results of efficacy at 3 years are immature (few patients at risk). Furthermore, it is an open-label study without an independent evaluation committee. For this reason, IDFS, a subjective variable, must be interpreted with caution since the investigator's bias. Other trials on adjuvant treatment in breast

Table 2
Abemaciclib costs compared to other alternatives.

	Abemaciclib + ET	ET alone
	Verzenios® 50, 100 y 150 mg	Tamoxifen/Aromatase Inhibitor
Unit price (PVL + VAT)[a]	61.50 €	ET cost
Posology	150 mg twice a day	–
Daily cost	123.00 €	–
Cost/month	3443.96 €	–
Treatment duration (months)[b]	24 months	–
Complete treatment cost	82,655.04 € + ET cost	ET cost
Incremental cost respect to reference therapy[c]	+ 82,655.04 €	Reference drug

Abbreviations: Endocrine Therapy (ET).
[a] Included 7.5% rebate, according to the Spanish Royal Decree-Law 8/2010.
[b] Treatment period.
[c] Pending price reduction with the new indication.

Table 3
Incremental efficacy-cost.

	Evaluated outcome	NNT	Incremental cost	IEC
Abemaciclib + ET versus ET alone (pivotal trial)	IDFS 2 years	33,3	82,655.04 €	2,752,412.83 €/patient without disease recurrence
	IDFS 3 years	17,5		1,446,463.20 €/year without disease recurrence

Abbreviations: Incremental efficacy-cost (IEC), Number Needed to Treat (NNT), Endocrine therapy (ET), Invasive Disease-Free Survival (IDFS).

cancer have already been published with the same limitation: KATHERINE9 of trastuzumab-emtansine and HERA10 of trastuzumab. On the other hand, the cohort 2 was introduced later than cohort 1, changed the initial protocol and raised questions of external validity and applicability: cohort 2 included a reduced population (9% of patients included) and IDFS results (HR = 0.986; 95% CI: 0.475–2.048) cannot be affirmed without high uncertainty.

Abemaciclib administered as adjuvant treatment reduces the number of patients who relapse by one-third, but for the remaining two-thirds who relapse anyway, abemaciclib probably implies the loss of a therapeutic option in advanced or metastatic cancer. In any case, the positive balance of clinical benefit seems assured.

An adjusted indirect treatment comparison (ITC) was carried out to establish whether abemaciclib and palbociclib, both inhibitors of CDKs, could be considered equivalent therapeutic alternatives (ETA). Two trials were included: monarchE2 (abemaciclib) and Penélope-B11 (palbociclib). Both of them were phase III trials, randomized, in patients with HER2-negative, high risk, and luminal EBC. Differences were found in the trial design (abemaciclib open-label vs. palbociblib double-blind), number of patients included (abemaciclib N = 5637 vs. palbociclib N = 1250), treatment duration (abemaciclib 2 years vs. palbociclib 1 year) and percentage of patients pretreated with taxane, anthracycline, or both (abemaciclib 37% vs. palbociclib 99%). Clinical trials were not similar due to these differences. Abemaciclib was effective in HER2-negative, high risk, and luminal EBC. However, palbociclib was not. IDFS abemaciclib group was statistically significant (HR = 0.70; 95% CI: 0.59–0.82; $P < .0001$) with a median follow-up of 27 months (90% patients completed treatment). In contrast, IDFS palbociclib group was not statistically significant (HR = 0.93; 95% CI: 0.74–1.17; $P = .525$) with a median follow-up of 43 months (92% patients completed treatment). Regarding consist results, 2-year IDFS rate was different too: abemaciclib 93% versus palpociclib 88%. In short, relevant methodological limitations were detected so adjusted ITC was not possible.

Despite short median follow-up (15 months for the interim analysis and 27 months for the final analysis), the results of the monarchE study at 2 years are sufficient to consider abemaciclib plus ET as first-line adjuvant treatment in highly selected patients with EBC at high risk of recurrence, even though longer follow-up time is needed to support its inclusion.

The safety data were consistent with the previously known safety profile of abemaciclib. 33% of patients (difference between arms) experienced grade 3–4 AEs with abemaciclib, and 16% had to discontinue treatment due to AEs. Diarrhea, neutropenia, and leukopenia were the most common grade 3–4 AEs associated with abemaciclib.

Regarding the cost of treatment, it is necessary to know the final price after the new indication and the evaluation carried out by the Spanish Agency of Medicines and Health Products published in its Therapeutic Positioning Report in order to issue an appropriate therapeutic positioning.

Contribution to scientific literature

Abemaciclib may be considered for the adjuvant treatment of early breast cancer at high risk of relapse in highly selected patients based on the results of the pivotal trial. For the efficacy results to present less uncertainty, we must wait for a more mature subsequent evaluation.

The selection of a pharmacological alternative must be supported by criteria of scientific evidence and efficiency. The evaluation and selection of drugs, carried out according to their therapeutic value and incremental clinical benefit, allows their positioning in the therapeutic care guidelines and protocols so that patients receive the most appropriate treatments taking into account the available resources.

Declaration of authorship

All authors have contributed to the design of the paper and the analysis of the information, the drafting and writing of the article and its subsequent approval for publication. Likewise, no person who has participated in the aforementioned is excluded.

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Conflict of interest

The authors declare that they have no conflict of interest.

Data confidentiality

The authors declare that they have followed the protocols established by their respective health centres for accessing the data in the medical records in order to be able to carry out this type of publication for research/dissemination purposes for the scientific community.

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