Application for the inclusion of the cyclin-dependent kinase 4/6 inhibitors (palbociclib, ribociclib, abemaciclib) in the WHO Model list of ESSENTIAL MEDICINES for the treatment of patients with hormone receptor positive/ HER2-negative advanced breast cancer

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European Society of Medical Oncology (ESMO)

International Nonproprietary Name (INN/generic name) of the medicine

- *Palbociclib*
- *Ribociclib*
- *Abemaciclib*

Introduction

The Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors palbociclib, ribociclib and abemaciclib are US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved compounds for the treatment of patients with locally advanced unresectable or metastatic breast cancer, in combination with the standard hormone therapy.(1,2) The use of CDK4/6 inhibitors is approved in the first and second line setting, for patients with breast tumors positive to the estrogen receptor (ER) and negative to the human epidermal growth factor receptor 2 (HER2), who have experienced or not a previous response to hormone agents (treatment naïve, endocrine sensitive and endocrine-resistant diseases), variously combined to aromatase inhibitors, tamoxifen or fulvestrant.. The present application will address the use of CDK4/6 inhibitors only for the metastatic setting, where multiple confirmations across several trials have consolidated the role and value of these agents in cancer management. Emerging evidence

suggest a possible role in the early setting of care, with some recent positive reports on the incorporation in the adjuvant treatment.(3) However, for the present submission and the scope of the WHO EML as a policy tool and global reference to inform prioritization, procurement and/or reimbursement policies, the uncertainties for the use in the early setting of care may be still preponderant to suggest a global implementation of these medicines in the (neo-)adjuvant setting, as an "essential" component; therefore, more mature data and final reports from ongoing clinical trials are warranted, to understand better the magnitude of clinical benefit and population health benefits. The selection of the CDK4/6 inhibitors for consideration in the WHO EML aligns with the criteria settled by the WHO EML Cancer working group, that acknowledges the role of the **ESMO Magnitude of Clinical Benefit Scale (MCBS v1.1)** as a tool to screen potential compounds for the consideration of the expert committee; medicines scored >3 with the MCBS v.1.1 (in the advanced setting) or A-B (in the early setting) might be considered eligible for the consideration in the EML.(4,5). According to *WHO Selection of essential medicines at country level* Report (6), in fact, guiding principles for inclusion of cancer medicines on the WHO Model list must be given to the magnitude of clinical benefit (e.g., informed by MCBS v1.1) associated with treatment. The observed benefit must be clinically meaningful, patient-relevant and of public health relevance: a threshold for benefit of at least 4-6 months survival gain must be met for new cancer medicines to be considered for EML inclusion; MCBS scores should be taken into consideration for new cancer medicines. Accordingly, the European Society of Medical Oncology (ESMO) adopted the established criteria, and has developed the present application in support of the WHO work, as part of the societal commitment of the status of official WHO partner, to enhance the global dialogue on the global cancer control and inform with updated evidence, including in innovative areas of care or to technically support in more controversial situations.(7) **The present submission is not intended to endorse the use of fulvestrant as a single agent** in the management of advanced breast cancer, but only in the context of a combination regiment with CDK4/6 inhibitors, in the second-line setting. Based on the MCBS v.1.1, the use of fulvestrant in the first- and second-line settings is associated with a modest improvement of the progression- free survival. Based on the pivotal study in the first- line setting, the use of fulvestrant is associated with an improvement of the PFS of +2.8 months, with a hazard ratio of 0·797, 95% CI 0·637–0·999 (p=0·0486).(8)

Formulation proposed for inclusion, including adult and pediatric (if appropriate)

Palbociclib (trade name: Ibrance, company: Pfizer) Palbociclib is a highly selective, reversible inhibitor of CDK4 and 6.(9) It is available in the market as hard capsules, with a shell composed of Gelatin, Red iron oxide (E172), Yellow iron oxide (E172), Titanium dioxide (E171), at the formulations of 75mg, 100mg

and 125mg. Palbociclib 75 mg hard capsules are Opaque, with a light orange body (printed “PBC 75” in white) and a light orange cap (printed “Pfizer” in white). The capsule length is 18.0 ± 0.3 mm. Palbociclib 100 mg hard capsules are Opaque, hard capsule, with a light orange body (printed “PBC 100” in white) and a caramel cap (printed “Pfizer” in white). The capsule length is 19.4 ± 0.3 mm. Palbociclib 125 mg hard capsules are Opaque, hard capsule, with a caramel body (printed “PBC 125” in white) and a caramel cap (printed “Pfizer” in white). The capsule length is 21.7 ± 0.3 mm.

Ribociclib (Kisqali, Novartis) Ribociclib is a selective inhibitor of CDK 4 and 6.(10) It is available in the market as film-coated tablets, containing soya lecithin, at the formulation of 200mg. The tablets appear as light greyish violet, unscored, round, curved with bevelled edges (approximate diameter: 11.1 mm), debossed with “RIC” on one side and “NVR” on the other side.

Abemaciclib (Verzenio, Eli Lilly) Abemaciclib is a potent and selective inhibitor of CDK 4 and 6.(11) It is available in the market as film-coated tablets containing lactose monohydrate in the formulations of 50mg, 100mg and 150mg. Abemaciclib 50 mg film-coated tablets Beige, oval tablet of 5.2 x 9.5 mm, debossed with “Lilly” on one side and “50” on the other. Abemaciclib 100 mg film-coated tablets White, oval tablet of 6.6 x 12.0 mm, debossed with “Lilly” on one side and “100” on the other. Abemaciclib 150 mg film-coated tablets Yellow, oval tablet of 7.5 x 13.7 mm debossed with “Lilly” on one side and “150” on the other.

The selection of patients eligible for treatment with CDK4/6 inhibitors (CDK4/6i) is not based on a **predictive biomarker or specific molecular profile** in the cell-cycle control disruption. Accordingly, the current practice is to escalate the endocrine treatment with one of these small molecules, in order to enhance the durability of response and prevent possibly the emergence of endocrine resistance or, in endocrine- resistant diseases, attempt to improve the control and re-establish the endocrine sensitivity (i.e., in combination with fulvestrant(12). For this reason, **no companion diagnostic** is assumed to be considered when CDK4/6i are included in the treatment of patients.

The safety and efficacy of palbociclib, ribociclib and abemaciclib in **children and adolescents** aged less than 18 years have not been established and the use should be considered on-label only for adult patients with breast cancer aged 18 or more. Therefore, **no pediatric formulation** is currently available on the market for this indication.(13)

The three molecules hereby considered are on-patent, hence there is no availability for generics. The patents that cover palbociclib will expire in January 2023, in both the United States and Europe; however, in both regions the patents may be extended up to 5 years (in 2028) under the statutes that provide for patent term extensions.(14,15) For ribociclib, the expiry is expected for November 2031. For abemaciclib, the expiry is estimated for December 2029.(14,15)

Approved clinical use, based on FDA and EMA labelling

Palbociclib is indicated to treat hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer.(9) Presently, this drug is indicated in combination with an aromatase inhibitor or fulvestrant in women (and men) who have received prior endocrine therapy, both pre- and post-menopausal women, both endocrine sensitive and endocrine resistant disease according to ESMO definition. In pre- or peri- menopausal women, the endocrine therapy should be combined with a LHRH agonist. Alternatively, pre- menopausal women who have received other types of ovarian ablation, including surgical bilateral ovariectomy or with radiotherapy, are eligible to receive palbociclib plus an aromatase inhibitor or fulvestrant, without LHRH agonist. The recommended dose is 125 mg of palbociclib once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days. The recommended starting dose is 125 mg, and dose modifications as clinically appropriate can be offered with 100mg or 75 mg daily dosage. Complete count blood (CBC) should be at least offered on the day 1 of every cycle and for the first 2 cycles, and an adjunctive CBC is recommended on day 15, to assess the tolerability and the hematological toxicity. When well- tolerated, CBC can be offered every 3 months, in the absence of concerning or major toxicities and good tolerability for at least 6 continuous cycles. At the recommended dose, no ECG monitoring is requested.

Ribociclib is indicated for the treatment of women with HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.(10) In pre- or perimenopausal women, the endocrine therapy should be combined with a LHRH agonist. Women who have received previous ovarian ablation when still in pre-menopausal status, are treated without LHRH agonist. The recommended dose is 600 mg (3 X 200 mg tablets) of ribociclib once daily for 21 consecutive days followed by 7 days off treatment, resulting in a complete cycle of 28 days. CBC should be ordered before the initiation of the treatment with ribociclib, and then used for clinical monitoring every 2 weeks for the first 2 cycles, then at day 1 for 4 cycles; eventually, if the therapy is tolerated, in the absence of

concerning or major toxicities, CBC is requested at the clinician's discretion. In addition, liver function tests should be performed at the day 1 of every cycle, following the same schedule of CBC. For the specific safety profile, ribociclib also requires a cardiac monitoring, to ensure no pathological treatment-induced elongation of the QT tract: ECG is mandated before the treatment start and repeated at 2 weeks of treatment, during the cycle 1 and at the beginning of the cycle 2; then, as clinically appropriate.

Abemaciclib is indicated for the treatment of women with HR-positive, HER2 negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.(11) In pre- or perimenopausal women, the endocrine therapy should be combined with a LHRH agonist. Women who have received previous ovarian ablation when still in pre-menopausal status, are treated without LHRH agonist. The recommended dose of abemaciclib is 150 mg twice daily continuously when used in combination with endocrine therapy. In USA, abemaciclib is also approved as a single agent, at the dose of 200 mg twice daily on a continuous schedule, in women pretreated with chemotherapy and hormone therapy in the advanced setting. However, as not validated in controlled randomized clinical trials, and being this specific indication for late lines of therapy, the submitters consider abemaciclib 200mg as a single agent outside the primary scope of this submission and will not be further commented.(16) Patients receiving abemaciclib should be monitored with CBC at the day 1 of every cycle and at day 15, for the first 2 cycles. Thereafter, CBC should be ordered at day 1 for other 2 cycles, and eventually as clinically appropriate. In addition, liver function test should be monitored before the treatment start, then every 2 weeks for the first 2 months, monthly for other 2 months ad then as appropriate, based on the clinical judgement. At the recommended dose, no ECG monitoring is requested.

The CDK4/6 inhibitors are intended to be used as **oral medicines**, in the approved schedules, 3 ON/ 1 OFF for palbociclib and ribociclib and continuously for abemaciclib, in combination with hormone agents. Aromatase inhibitors (i.e., anastrozole, letrozole and exemestane) or tamoxifen are used continuously, with no pause. Of notice, aromatase inhibitors and tamoxifen are already listed in the WHO EML for breast cancer; however, Fulvestrant is not yet, and its inclusion is endorsed in the present submission in combination with the CDK4/6 inhibitors. Fulvestrant is used at the approved high-dose schedule, as a large-volume (i.e., more than 3ml) intramuscular injection on days 1, 15, and 29, then once monthly at doses of 500 mg (2 syringe of 250 mg/5 ml with 21-gauge, 1.5-inch general purpose hypodermic needles). Fulvestrant is commonly administered by (cancer) nurses or doctors, who inject intramuscularly two 250mg-syringes, each per gluteus.

The therapeutic position and value of CDK4/6 inhibitors in the treatment of breast cancer, based on the *2020 ESMO/ESO guidelines (17) for the management of patients with advanced breast cancer*.

The use of CDK4/6 inhibitors in the management of patients with advanced breast cancer has consolidated in the clinical practice, based on pivotal clinical trials showing an improvement of the progression- free survival (PFS) and/or overall- survival (OS), along with improvement in the quality of life. Nowadays, the clinical guidelines for the management of breast cancer all acknowledge the role of CDK4/6 inhibitors in this setting, both for the pre- and post- menopausal women and largely by extrapolation and few real-world reports, for men.(18-22) In addition, the adjunctive toxicity related to the incorporation of these novel molecules to the standard hormone therapy is generally modest, and more often clinically manageable with delays and dose reductions. In fact, the chief toxicity related to CDK4/6 inhibitors, a class-effect derived from the cell cycle blockade, is hematological, expressed by a numerical reduction of the neutrophil with no increased risk for infections, nor febrile neutropenia. The **ESMO/ESO guidelines for the management of advanced breast cancer** have been developed as a consensus, with statements voted by an international expert panel. The panel acknowledged that there is a small group of patients who can be treated with endocrine therapy alone, when CDK4/6 are affordably accessible; although clear identification of these patients is not possible at this time, in the absence of controlled evidence and conclusive reports, some factors such as limited burden of metastatic disease and features of less aggressive biology may help with this identification. There are currently no biomarkers to enable accurate identification of these patients and the previous attempts to identify prospectively predictive markers did not translate into clinical evidence of an advantage for biomarker- selected patients.(12, 23) The ESMO guidelines have recently adopted the inclusion of the scores calculated with the MCBS tool.(24) **Table 1.**

Table 1. MCBS score for the three EMA and FDA approved CDK4/6 inhibitors for the treatment of patients with ER-positive and HER2-negative advanced breast cancer.

CDK4/6 inhibitor (combined hormone agent)	Clinical Setting	MCBS v1.1 score (range: 1-5)
Palbociclib (+aromatase inhibitor)	First line therapy	3
Palbociclib (+Fulvestrant)	Second line therapy	4
Ribociclib (+aromatase inhibitor)	First line therapy (postmenopausal women)	3
Ribociclib (+endocrine therapy)	First line therapy (premenopausal women)	5
Ribociclib (+Fulvestrant)	First and Second line therapy	4
Abemaciclib (+aromatase inhibitor)	First line therapy	3
Abemaciclib (+Fulvestrant)	Second line therapy	4

CDK4/6, Cyclin-dependent kinase 4/6. MCBS, Magnitude of Clinical Benefit Scale.

Of note, the three CDK4/6 inhibitors have not been compared head-to-head within a clinical trial nor in trials of sequence (i.e., use in first Vs use in second line). It remains still unclear if CDK4/6 inhibitors should be preferably administered in the first- or second-line setting, as a meaningful clinical benefit has variously been observed in both settings. In general, the clinical preference expressed in the *ESMO/ESO guidelines (17)* is to provide the CDK4/6i medicines in the first- line setting for the majority of the patients. Currently, no data support the use of these compounds in the maintenance setting after chemotherapy, as an intensification of the standard hormone therapy.

Data from pivotal clinical trials on the role and value of CDK4/6 inhibitors for the treatment of patients with advanced breast cancer

An overview of the comparative effectiveness and safety across the pivotal clinical trials. We searched PubMed and Google Scholar and reviewed the data from the pivotal trials of CDK4/6i in the treatment of patients with advanced breast cancer. For the initial scoping review on the topic, utilized a simplified standard research strategy, run on 10 November 2020: *((palbociclib OR ribociclib OR abemaciclib) AND (advanced breast cancer OR metastatic breast cancer)) [N=596 records],* as a scoping research. Then, we searched the clinical trial repository of the US National Library of Medicine at *clinicaltrial.gov, the EU Clinical Trials Register at clinicaltrialsregister.eu,* the WHO International Clinical Trials Registry Platform at *apps.who.int/trialsearch* and eventually navigated the FDA and EMA online resources (1,2), to cross-reference with the original search and the pivotal studies in support of the regulatory decisions for approval, providing the most updated references. We refined the work with a manual research of the abstract submitted and/or presented at the ESMO Breast and ESMO annual meeting 2020. While

abstracts are not eligible to update the MCBS scores, and inform definitely the ESMO guidelines recommendations, for the objective limits of their nature against peer-reviewed material, we touched the information from them to support the evidence in literature, provide very recent updates (e.g., survival data at longer follow-up) and address some controversial areas, when appropriate. The principal characteristics of the pivotal clinical trials are reported in **table 2.**

Table 2. Synoptic table of the principal characteristics of the pivotal clinical trials enrolling patients with advanced breast cancer to receive CDK4/6 inhibitors plus endocrine therapy.

Clinical Trial (NCT identifier)	**Eligible population**	**Intervention**	**Sample size (randomization ratio)**	**Survival Endpoints** [primary; secondary]
PALOMA 2 (NCT01740427)	Treatment- naïve for ABC Post- menopausal DFI >12 mo	Palbociclib +letrozole	666 (2:1)	iPFS; OS
PALOMA 3 (NCT01942135)	PD after ET Pre- and post- menopausal women	Palbociclib + Fulvestrant	521 (2:1)	iPFS; OS
MONALEESA 2 (NCT01958021)	Treatment- naïve for ABC Post-menopausal women DFI >12 mo	Ribociclib + letrozole	668 (1:1)	iPFS; OS
MONALEESA 7 (NCT02278120)	Treatment- naïve for ABC Pre- and peri-menopausal women **	Ribociclib + endocrine therapy	672 (1:1)	iPFS; OS
MONALEESA 3 (NCT02422615)	Treatment- naïve for ABC OR PD after ET AND/ OR DFI <12 mo ^^	Ribociclib + Fulvestrant	726 (2:1)	iPFS; OS
MONARCH 3 (NCT02246621)	Treatment- naïve for ABC Post- menopausal DFI >12 mo	Abemaciclib + aromatase inhibitor	493 (2:1)	iPFS; OS
MONARCH 2 (NCT02107703)	PD after ET Pre- and post- menopausal women	Abemaciclib + Fulvestrant	669 (2:1)	iPFS; OS

All the studies are randomized phase 3, double-blind, placebo-controlled clinical trials. The schedules for the treatment within the clinical trials are the same approved for the clinical use. All the studies were designed for patients with ER-positive, HER2-negative advanced breast

cancer. All the studies had safety and objective response rates as secondary endpoints. OS was a protocol- specified secondary endpoint in all the trials. ABC, advanced breast cancer. DFI, disease-free interval from the completion of the adjuvant endocrine treatment. Mo, months. iPFS, investigator-assessed progression-free survival. OS, overall survival. NCT identifier, ClinicalTrials.gov number. PD, disease progression. ET, endocrine therapy in first- line setting. ** *Eligible women were 18 to 59 years of age, premenopausal or perimenopausal at the time of trial entry.* ^^ *MONALEESA3 enrolled women with either endocrine naïve, endocrine sensitive and endocrine resistant breast cancer. Patients with endocrine naïve (139 treated in the ribociclib and 74 in the placebo arm), sensitive (289 and 140) and resistant tumors, (53 and 25) were included. The benefit of OS was demonstrated in the overall population and regardless the baseline endocrine sensitivity or previous exposure to ET.*

The use of CDK4/6 inhibitors showed a significant improvement of the survival outcome and for some of them, of the quality of life, in the settings of interest. **Table 3**. When combined with the endocrine treatments, the three CDK4/6 inhibitors provided a benefit on the disease control, with an improvement of the PFS, consistently across the several clinical trials. In the first- line setting, both for pre- and post-menopausal women, the escalated regimen improved the PFS of 9.3 to 12.5 months, corresponding to a relative increase of PFS of 42% to 46%. However, mature data of OS in the first line use have only been provided for one of these drugs, that is ribociclib – in the context of the clinical trial MONALEESA 7 (i.e., premenopausal women). For the second- line therapy, in patients exposed to the endocrine therapy in the advanced setting and progressing thereafter, the CDK4/6i combined with fulvestrant showed PFS benefit, with a gain of 4.9 to 7.7 months, corresponding to a relative PFS improvement of 41% to 54%. In addition, for two molecules, mature data of OS have been positively reported. The use of ribociclib and abemaciclib in the second- line setting with fulvestrant demonstrated to provide an improvement of the OS of 15.6 and 9.4 months, respectively, corresponding to a relative gain of 28% and 24%, respectively.

Table 3. Randomized phase 3 clinical trials testing the addition of a CDK4/6 inhibitor to the endocrine therapy for patients with advanced breast cancer, ER-positive/ HER2- negative.

CDK4/6 inhibitor (combined hormone agent)	Clinical Setting	PFS gain (months); HR (95%CI)	OS gain (months); HR 95%CI	Clinical Trial
Palbociclib (+letrozole)	First line therapy	10.3; 0.58 (0.46-0.72)	NA	PALOMA 2 (25-27)
Palbociclib (+Fulvestrant)	Second line therapy	4.9; 0.46 (0.36-0.59)	6.9; NS	PALOMA 3 (28-30)
Ribociclib (+letrozole)	First line therapy (postmenopausal women)	9.3; 0.57 (0.46-0.70)	NA	MONALEESA 2 (31)
Ribociclib (+endocrine therapy#)	First line therapy (premenopausal women)	10.8; 0.55 (0.44-0.69)	16**; 0.71 (0.54-0.95)	MONALEESA 7 (32-34)
Ribociclib (+Fulvestrant)	First and Second line therapy	7.7; 0.59 (0.48-0.73)	15.6‡; 0.72 (0.57-0.92)	MONALEESA 3 (35,36)
Abemaciclib (+aromatase inhibitor)	First line therapy	12.5; 0.54 (0.41-0.72)	NA	MONARCH 3 (37,38)
Abemaciclib (+Fulvestrant)	Second line therapy	7.1; 0.55 (0.45-0.68)	9.4; 0.76 (0.61-0.95)	MONARCH 2 (39,40)

CI, confidence interval. SoC, standard of care (control arm). PFS, progression- free survival. OS, overall- survival. NS, not statistically significant. NA, not available. ***The absolute gain in OS in this trial has been calculated based on point estimate HR 0.7; in the original report, the median OS values were not reported and the authors estimated overall survival at 42 months was 70.2% (63.5 to 76.0) in the ribociclib group and 46.0% (32.0 to 58.9) in the placebo group. #anatrozole, letrozole or tamoxifen. ‡ Calculated estimate of gain based on point estimate HR 0.72; in the original report, the estimated overall survival at 42 months was 57.8% (52.0 to 63.2) in the ribociclib group and 45.9% (36.9 to 54.5) in the placebo group.*

The pooled analysis from trial- based metanalysis of clinical trials essentially confirmed the findings from the single studies, and remarked some limits related to the heterogeneous trial populations and unavailability of mature data in some of these trials, especially for the OS. Adding a CDK4/6 inhibitor to endocrine therapy appeared to be beneficial in terms of PFS, irrespective of the presence or not of visceral metastases, the number of metastatic sites, and the length of the treatment-free interval. The addition of CDK4/6 inhibitors produces a significant OS improvement, both in aromatase inhibitor sensitive and resistant patients.(41)

The **safety profile** of the CDK4/6 inhibitors is quite peculiar. The principal class effect regards the hematological toxicity. The use of CDK4/6i, in fact, is associated with a predictable, reversible, and generally not infection- prone neutropenia – related to the cell cycle effects on the hematopoiesis of the cell cycle blockade.(42) This toxicity seems to affect mostly the neutrophil cellular maturation and

differentiation, with an on-target/ off-tumor treatment- related drop of the absolute neutrophil count. One meta-analysis (43) on the toxicity of the CDK4/6 inhibitors has reported an onset of neutropenia in 65%, 58% and 26% of grade 3 and 4 (namely, a count below 1000 cells/ mm3) with the use of palbociclib, ribociclib and abemaciclib, respectively. However, the occurrence of febrile neutropenia has been registered in less than 1% of the trial population, with any of these compounds. **Table 4.** In general, the onset of moderate to severe neutropenia prompts a delay, temporary interruption or dose reduction of the CDK4/6 inhibitor, but less likely requires other interventions: for the functional and reversable nature of this effect, no use of the granulocyte- stimulating factors and/ or antibiotic prophylaxis is commonly requested, as the febrile neutropenia occurs quite rarely.(44) The only precaution requested with the use of this class of agents, therefore, is the CBC control at the begin of each cycle and, precautionarily after 2 weeks for the first 2 cycles, to check the bone marrow reserve. Moreover, the anti-CDK4/6 agents are associated with a unique safety profile, that gives a specific clinical profile that informs mostly the decision of the clinicians to use one compound over another one, along with the patient preference. The different safety profile, in fact, is presently the most important factor to account in the treatment decision for patients with ER-positive/ HER2- negative advanced breast cancer in the first or second line of therapy, in the absence of head-to-head comparisons. In particular, compared to palbociclib, ribociclib and abemaciclib showed significantly lower grade 3-4 neutropenia, but significantly higher gastrointestinal toxicity. Moreover, treatment discontinuation was higher with abemaciclib than other drugs, in part related to the higher rates of treatment- related diarrhea.(45) Of note, the use of ribociclib has been associated with a prolongation of the QT interval. An ECG finding of a QT interval corrected for heart rate according to Friderica's formula (QTcF) greater than 450 m has been observed in 7% of the patients treated with ribociclib, and 1% in the patients enrolled in the placebo arm.(32-34) Moreover, 10% of patients receiving ribociclib experienced a QTcF prolongation of +60msec or more in at least one post-baseline ECG assessment, versus 2% in the placebo arm. Of them, QT prolongation was more commonly observed when tamoxifen was the endocrine agent in association (16%) than aromatase inhibitor (7%). While no clinical symptoms or arrhythmias (e.g,, ventricular tachycardia or Torsades de Pointes) were reported related to the QTcF prolongation, the treatment was interrupted or reduced in 4% of the population in the experimental arm, based on the protocol indications, owing to such an adverse effect.(32-24) Accordingly, as aforementioned, the EMA and FDA recommend an initial ECG monitoring for patients receiving ribociclib, to ensure the safest conditions of treatment. No clinically relevant cardiotoxicity has been reported with abemaciclib and palbociclib and commonly an ECG monitoring is not required. This warning is also included in the *ESMO/ESO guidelines.* (17)

The principal differences in the safety profile of these molecules are presented in the **table 4.**

Table 4. Safety Profile of the approved CDK4/6 inhibitors based on the results from the pivotal clinical trials.

	Palbociclib	Ribociclib	Abemaciclib
Any Grade 3 and 4 AEs	74%	79%	58%
Neutropenia G3 and G4	65%	58%	26%
Neutropenic fever	<1%	<1%	<1%
Anemia	24% (5.5% G3/4)	19%	30% (7% G3)
Increased AST or ALT	All grade <10%	25% (G3/4/ in 9%)	All grade <10%
GI toxicity	25% diarrhea 35% nausea	52% nausea 35% diarrhea	87% diarrhea (13% G3) 45% nausea (3% G3)

The grading system used to assess and score the toxicity is the CTCAE, the Common Terminology Criteria for Adverse Events developed by the US National Cancer Institute. The scores (G) range between 1 (mild) to 4 (severe); a score of 5 equals a fatal event. *AST, aspartate aminotransferase. ALT, alanine aminotransferase. GI, gastrointestinal.*

Many discussions are ongoing about the true difference of the CDK4/6 inhibitors, and the variegated results across the clinical trials. Some experts would propose that there are biological differences, for example in the kinome of the molecules and the possible target promiscuity (46), reflected by the different safety profile and could impact on the overall clinical benefit. However, some other experts are more prone to argue that the clinical trial populations enrolled in the studies are not completely superimposable, and that in the absence of more mature data, longer follow-up and head-to-head comparisons, possible major divergencies are a matter of speculation.(47) For the purpose of the present submission, based on the current clinical guidelines for the management of breast cancer, including the *ESMO/ESO guidelines*, the submitters consider the three molecules comparable per clinical efficacy and different for the safety profile. A gain in overall survival has been reported with some CDK4/6 inhibitors, and in some settings, there is large uncertainty on the designs of the trials and follow-up terms.(48) Thereforethe submitters align with the general assumptions stated in the *ESMO/ESO Guidelines* and the current best practice, to tailor the molecule to the patients' features and preference, based on the local availability and affordable accessibility, without a preference for one over another CDK4/6 inhibitor. Of course, this statement should be considered conditional, pending final results from ongoing clinical trials.

We collected other integrative data to the pivotal clinical trials and other possibly useful information from the scoping review, based on a systematic research of the literature- as previously outlined. We collected a number of papers from our research to provide an **external validation of the findings from**

the pivotal clinical trials across diverse ethnical groups and settings. Real- world data and ad-hoc designed clinical trials in specific ethnic groups seem to reproduce the findings from controlled clinical trials. A **real-world** study from Europe (n=1017 patients, 5 countries) showed a PFS rate at 12- and 24-months of 88.2% and 62.2% in first- line and 81.1% and 55.2% in second- line, respectively (IRIS study, ESMO meeting 2020, #269P). OS rates at 12- and 24-months were 97.7% and 93.2% in the first line and 96.8% and 85.2% in the second line, respectively. Dose reductions in patients from Europe are observed with palbociclib in 11%-17% of the patients in the first- and second- line, respectively mostly related to the neutropenia. The phase 3b study CompLEEment1 (n=3246; 38 countries; multiple Regions) moreover, assessed the benefit of ribociclib and letrozole in selected subgroup of patients treated in the first line setting, less likely included in the pivotal trials (ESMO meeting 2020, #333P). Patients with a poorer performance status, namely scored ECOG 2, largely underrepresented in clinical trials, showed a comparative benefit to patients scored ECOG 0 or 1 (better performance status). In particular, the median time to progression was 19.5 months (95% CI 13.5-Not reached months) in the ECOG2 patients. Neutropenia was confirmed as the most common side effect, not dissimilar in ECOG2 patient subgroup, ranging between 62.3% and 74.7%, resulting in a treatment discontinuation of 11.6%-12.4%, mostly for neutropenia. Some other studies addressed the **possible ethnical differences in the safety and response**. A prospective experience has been reported from Latin America, in patients with breast cancer. An analysis of real-world use of palbociclib with endocrine therapy in patients with ER+/HER2- advanced breast cancer between October 2015 and August 2019 in Buenos Aires, Argentina was reported in the context of the study RENATA. The study included 128 patients, to receive palbociclib, in the approved indications and standard schedule. The investigators reported an overall PFS of 36.7 months in the first- and 24.2 months in the second- line; only 2% had to interrupt the treatment for drug- related toxicities. Neutropenia was the main moderate to severe adverse event, of which 7% febrile neutropenia, that is higher than in the pivotal trials. Overall, the data on survival were consistent with the pivotal PALOMA trials.(49) Another study analyzed the outcomes of patients with breast cancer receiving letrozole or fulvestrant plus palbociclib in South Korea, providing the data of safety and activity in an Asian population (April 2017 to November 2019; n=169). The authors showed a median PFS with letrozole plus palbociclib and fulvestrant plus palbociclib of 25.6 (95% confidence interval [CI]; 19.1 to not reached) and 6.37 months (95% CI; 5.33 to not reached) in the first- and second-line, respectively. Neutropenia was observed in 88.3% of the patients, most commonly grade 3 and 4.(50) In Japan, a phase 2 single- arm and open- label clinical trial was designed to investigate the efficacy and safety of palbociclib plus letrozole as first-line treatment in 42 postmenopausal patients with advanced breast cancer.(51) The first analysis showed a probability of PFS at 1 year of 75.6% (90%

confidence interval, 62.4-84.7), with a median PFS of 35.7 months (95% confidence interval, 21.7-46.7). The safety profile in the Japanese population was consistent with the one reported in non-Asian patients; neutropenia was the most common adverse effect, up to 93% of grade 3 and 4; however, only one patient experienced febrile neutropenia. While the pivotal clinical trials formally did not exclude Black American patients, no study has been conducted specifically in the Black ethnicity, and no data provided in one African population. Such a gap represents a priority area of the research, and is the object of investigation of a study – the PALINA trial (NCT02692755), a phase 2 clinical trial of palbociclib in combination with letrozole or fulvestrant in African American women with HR positive HER2 negative advanced breast cancer. There is evidence that Black- American women have a reduced absolute neutrophil count; probably related to some polymorphisms of the chemokine signaling that is specific to people of African descent.(52,53) Accordingly, the definition of restrictive enrollment criteria (e.g., an absolute neutrophil count of 1500/mm3 or more) in the pivotal clinical trial may have impacted on the likelihood of eligibility and screening success of these women, thus representing a structural barrier derived from a less inclusive conceptualization and design of the studies. For this, the current use of CDK4/6 inhibitors in the Black American women is essentially extrapolated from the pivotal trials, where these women were under-represented.

Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group.

The rapid development and significant improvement of the patient outcomes with the CDK4/6 inhibitors has stimulated a brisk discussion on the economic impact, in relation to the population health benefits (cost- effectiveness) and resource utilization and prioritization (budget impact). Currently, no international database or reference source exist to understand how the costs of CDK4/6 inhibitors are negotiated at the country level. This information is variable across the institutions in some low- and middle- income countries, especially when prices are not negotiated at the national level, and are a matter of agreements between single institutions, intermediate procurement mechanisms and companies. The average cost for a course of one month of treatment with palbociclib in Europe can range between 5000 and 13,000 US dollars, for ribociclib 8900 US dollars and for abemaciclib 3500-12,000 US dollars.(54) In comparison, while the total costs per year for letrozole and palbociclib has been estimated around 52,400 US dollars, letrozole alone is 252 US dollars.(55) Our research of the literature retrieved multiple exercises for the assessment of cost- effectiveness and other metrics of economic impact at country level. One study from Singapore evaluated the cost-effectiveness of adding ribociclib to goserelin and a nonsteroidal aromatase inhibitor or tamoxifen as initial therapy for

premenopausal women with breast cancer, using a partitioned survival model based on the MONALEESA-7 trial.(56) The base-case analysis resulted in an incremental cost-effectiveness ratio (ICER) of 197,667 Singaporean dollars (equal to 147,000 USD) per quality-adjusted life-year (QALY). The authors concluded for an unlikely cost- effectiveness of ribociclib in this setting, for the approved indication. In USA, a cost-effectiveness exercise for palbociclib plus letrozole and ribociclib plus letrozole estimated an ICER of $634,000 per QALY gained and of ICER of $440,000 per QALY gained, respectively.(57) The last report from the pan-Canadian oncology drug review on ribociclib reported an ICER of178,872 CAD/ QALY . The authors, in addition, posed some concerns on the certainty of the cost- effectiveness estimations for the use of CDK4/6 inhibitors in first- line in pre-menopausal women, as it was based mostly on the predicted clinical benefit beyond the actual trial follow-up, leaving significant margins of uncertainties.(58) Another simulation from high-income countries was reported for Italy. The authors aimed to estimate pharmacological costs of CDK4/6-inhibitors.(59) When abemaciclib was used frontline, the cost estimated was 2246 € per month of PFS-gained, that was more convenient than ribociclib and palbociclib at full dose. In the second line setting, with fulvestrant, the most convenient drug was ribociclib, with an estimated 2070 € per PFS-gained month. An exercise from China, which is a transitioning economy country, was developed via a Markov model, to estimate the lifetime costs and cost- effectiveness metrics of palbociclib-containing regimens in second line of therapy.(60) The authors estimated that the incremental cost-effectiveness ratio in China was 182,779 USD QALY. When palbociclib cost was reduced at 30%, 20%, and 10% of the current price, the ICERs were 79,558, 64,812, and 50,066 USD/QALY, respectively. To meet 50% probability of cost-effectiveness, the estimated price would have to be 32.52 USD/100 mg at a willingness-to-pay threshold of 58,480 USD/QALY (3 × per-capita domestic product of Beijing). The authors concluded that adding palbociclib to a fulvestrant regimen is unlikely to be cost-effective as second-line endocrine therapy for patients with ER-positive/HER2-negative metastatic breast cancer, at the current price in China.

Is listing requested as an individual medicine or as an example of a therapeutic group?

Therapeutic group: "*Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors palbociclib, ribociclib and abemaciclib in combination with endocrine treatment for the management of patients with advanced breast cancer positive to the hormone receptor(s) and negative to HER2*"; , **square- boxed** as palbociclib (ribociclib, abemaciclib).

Information supporting the public health relevance

Breast cancer is the leading cause of morbidity, disability, and mortality in women, worldwide.(61) Based on the global estimates of the **International Agency for the Research on Cancer** (IARC), the WHO

specialized research agency, 2.1 million newly diagnoses of breast cancer occurred in 2018, accounting for 25% of all tumors in women. Breast cancer is the most diagnosed malignancy in women in more than 80% of the countries in the world, and main cause of women's' mortality in a half. Countries at transitioning economies, that include essentially low- and middle- income countries, have contributed to an increase of the incidence rates of breast cancer in the last decades. These evolving epidemiological conditions are related to the increase of known risk factors. (62) Of relevance, some of the most rapid increases have occurred in countries where breast cancer rates used to be historically relatively low, in transitioning countries in South America, Africa, and Asia. In 2018, 60% of the breast cancer incident cases and two-third of the related mortality occurred in low- and middle-income countries.

In low- and middle- income countries, the impaired timely access to cancer services is an obstacle for the curative management of the early disease, with most of the patients presenting with locally-advanced and/or non-resectable diseases or metastatic cancer. For instance, the proportion of women presenting with stage III or IV TNM in sub-Saharan Africa ranges between 30% to 100% and is pertinent to more than three-fourth of the women with this disease.(63) Overall, more than a half of women with breast cancer present with a disease that is ER- positive and HER2- negative, both in the early and advanced setting, which is the object of the present submission.

Conclusion. Breast cancer is a public health problem of global proportion. The existence of structural barriers and the chronic neglection of cancer control resulted in stark inequalities in cancer- related outcomes, including patients with breast cancer. Assuring a comprehensive cancer control planning means providing care for all the patients in need, and prioritizing the most valuable interventions by pursuing value for money while assuring the most valuable health interventions. ESMO has committed to provide technical support to enhance the realization of Universal Health Coverage for cancer care andhas developed tools and guidance to serve rational cancer care such as ESMO MCBS. Based on the WHO methodology, ESMO provides the submission for CDK4/6 inhibitors for consideration of the WHO EML to improve the current armamentarium of essential medicines for the management of advanced breast cancer addressing a priority area of health care, for a global public health problem.

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