BJMO clinic

Belgian Journal of Medical Oncology

VOLUME 14 | ISSUE 5
SEPTEMBER 2020

REPRINT

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THE BELGIAN JOURNAL OF MEDICAL ONCOLOGY IS THE OFFICIAL JOURNAL OF THE BELGIAN SOCIETY OF MEDICAL ONCOLOGY (BSMO) AND THE BELGIAN ASSOCIATION FOR CANCER RESEARCH (BACR)

Adding abemaciclib to fulvestrant delays disease progression and prolongs the survival of women with HR+/HER2 negative advanced breast cancer across treatment lines, with a particularly pronounced survival benefit in patients with poor prognostic features

Professor Patrick Neven (University Hospitals Leuven)

Abemaciclib is an oral, selective inhibitor of cyclin-dependent kinase (CDK) 4 and 6 that is indicated for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer.[1] In previous reports of the phase III MONARCH 2 trial, the addition of abemaciclib to fulvestrant was shown to result in a significant improvement of the progression-free (PFS) and overall survival (OS) of women with HR+/HER2- advanced breast cancer and significantly delayed the time to the initiation of chemotherapy.[2-4] In recent months, *Professor Patrick Neven* (*University Hospitals Leuven*) presented two interesting exploratory analyses of this trial. A first of these analyses indicated that particularly patients with poor prognostic features seemed to derive the highest survival benefit from the addition of abemaciclib to hormonal therapy.[4,5] The second analysis demonstrated that the addition of abemaciclib provides a PFS and OS advantage, irrespective of the treatment line.[6] Notwithstanding the fact that these findings come from exploratory analyses and, as such, need to be treated with care, *Prof Neven* underscores that *this type of analyses is very useful for physicians as they provide some sort of guidance when making treatment decisions in their daily clinical practice*.

MONARCH 2: significant clinical benefit from adding abemaciclib to fulvestrant in women with HR+/HER2- advanced breast cancer

In the phase III MONARCH 2 trial, 669 pre-, peri- or postmenopausal women with endocrine resistant HR+/HER2- advanced breast cancer were randomly assigned (2:1) to receive abemaciclib or placebo (150 mg, twice daily) on a continuous schedule in combination with fulvestrant (500 mg, per label). For this study, endocrine resistance was defined as having a disease relapse on (neo)adjuvant endocrine therapy (ET), or within one year from the end of the adjuvant ET or experiencing disease progression on first-line ET for advanced breast cancer. In order to be eligible for the study, patients had to be 18 years or older and have an ECOG performance status of 0 or 1. In addition, patients were not allowed to have received

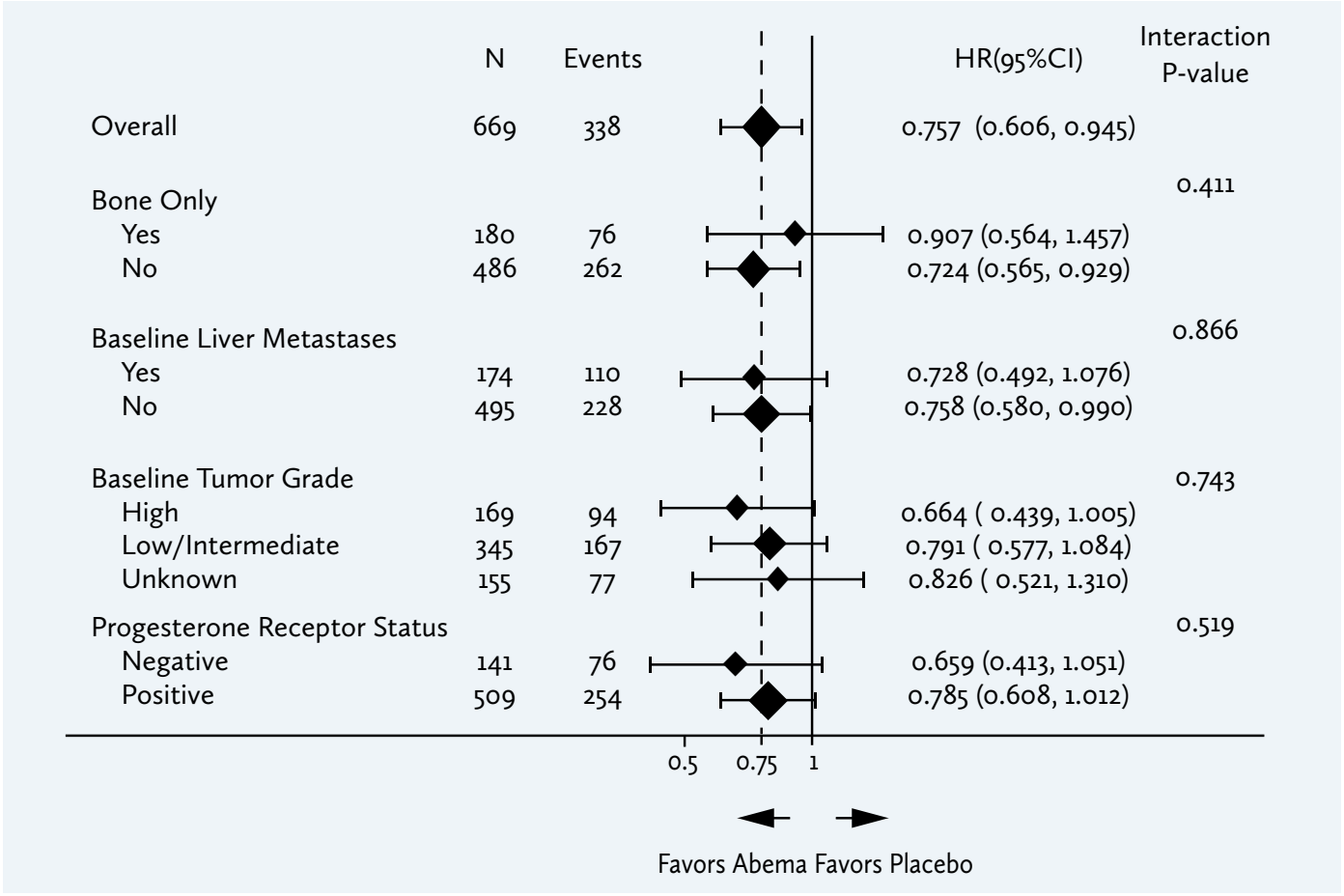

Figure 1. Overall survival in prognostic subgroups of the MONARCH 2 trial.[5]

more than one prior line of ET and they were not allowed to have been treated with chemotherapy in the advanced breast cancer setting. Patients were stratified according to metastatic site (visceral, bone only, other) and ET resistance (primary, secondary). The data cut-off for the presented analysis was June 20th, 2019, representing a median follow-up of 47.7 months. At that timepoint, 17% of the patients in the abemaciclib-fulvestrant arm and 4% of patients who only received fulvestrant remained on treatment.[2]

In MONARCH 2, the addition of abemaciclib to fulvestrant previously demonstrated a significant improvement in the primary outcome of PFS, by prolonging the median PFS from 9.3 to 16.9 months (HR[95%CI]: 0.536[0.445-0.645], p< 0.0001). In addition, abemaciclib-fulvestrant treated patients also experienced a significant and clinically meaningful OS benefit (median OS: 46.7 vs. 37.3 months, HR[95%CI]: 0.757 [0.606-0.945], p= 0.01).[2,3] Finally, also the time to chemotherapy (median 50.2 vs. 22.1 months, HR[95%CI]: 0.625[0.501-0.779]) and the median chemotherapy-free survival (CFS) (25.5 *vs.* 18.2 months (HR[95%CI]: 0.638[0.527-0.773]) were significantly longer in the abemaciclib arm.[3]

Interestingly, a previously reported exploratory analysis of MONARCH-2 indicated a particularly pronounced PFS benefit with the abemaciclib-fulvestrant combination in patients presenting with less favourable prognostic features. These poor prognostic factors were described by *Di Leo et al.* and include a high tumour grade, progesterone receptor negativity, the presence of liver metastases, and the occurrence of metastatic spread beyond the bone.[4] While

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this exploratory subgroup analysis demonstrated a consistent PFS benefit from abemaciclib-fulvestrant over placebo-fulvestrant across all the investigated subgroups, the hazard ratios for PFS in poor prognostic subgroups were lower than what was seen in the overall study population and in patients with more favourable prognostic characteristics.[3] At SABCS 2019, a second exploratory analysis was presented specifically looking at the secondary efficacy endpoints of OS, chemotherapy-free survival and time to chemotherapy in these poor prognostic subgroups.[5]

Exploratory results on OS and chemotherapy delay in poor prognostic subgroups

Similar to what was observed for PFS, patients with poor prognostic features seemed to experience a more pronounced OS benefit from the addition of abemaciclib to fulvestrant compared to patients with a better prognosis (*Figure 1*).[5] For example, in patients

with high-grade tumours the median OS was prolonged from 27.68 months with fulvestrant alone to 38.83 months with abemaciclib-fulvestrant combination, representing a 34% risk reduction (HR[95%CI]: 0.664[0.439-1.005]). In contrast, also patients with low or intermediate grade tumours experienced an OS improvement with abemaciclib (median OS increased from 41.72 to 48.82 months), but in these patients this only corresponded to a risk reduction of 21% (HR[95%CI]: 0.791[0.577-1.084]). Similar results were also observed for patients with progesterone negative vs. positive tumours (HR 0.659 vs. 0.758). Among women with baseline liver metastasis, a 28% reduction in the risk of death was observed for abemaciclib-fulvestrant vs. fulvestrant alone, with a median OS of 35.34 and 25.58 months, respectively (HR[95%CI]: 0.728[0.492-1.076]). Finally, also patients without bone-only disease at treatment initiation benefitted more from the abemaciclib-fulvestrant combination (median OS: 42.12 vs. 34.36 months; HR[95%CI]: 0.724[0.565-0.929]) than patients in the overall study population. *Prof. Neven explains: "Patients with less aggressive types of hormone-resistant breast cancer indeed seemed to have a less pronounced benefit from the addition of abemaciclib to fulvestrant. This can probably be explained by the fact that in these patients, hormone-therapy on its own has a good efficacy and that it was too early to see the additional benefits of abemaciclib. In contrast, for patients with more aggressive types of breast cancer, the endocrine therapy alone is not sufficiently protective and, as a result, these patients have a higher risk of disease relapse when they only receive fulvestrant. Therefore, at the time of analysis, patients with poor prognostic features who received the combination of abemaciclib and fulvestrant had a better outcome as compared to patients in the fulvestrant arm."*

Interestingly, in the subgroup of patients with bone-only metastasis, the OS was not yet reached after a median follow-up of 47.7 months (as compared to 47.31 months in the placebo arm; HR[95%-CI]: 0.907[0.564-1.457]). This subgroup thus seems to have a particularly favourable prognosis and continued follow-up is ongoing to further characterise the OS benefit. *"It is interesting to see that in patients with aggressive types of breast cancer, we see an early and strong response to abemaciclib, indicating that this is a very potent drug. On the other hand, as the data in patients with bone-only metastases seem to indicate, I believe that also patients with good prognostic features will eventually benefit from the addition of abemaciclib to fulvestrant. In these patients it is therefore key to prolong the follow-up as the benefit of abemaciclib may deepen at later time points."*

'IT IS INTERESTING TO SEE THAT IN PATIENTS WITH AGGRESSIVE TYPES OF BREAST CANCER, WE SEE AN EARLY AND STRONG RESPONSE TO ABEMACICLIB, INDICATING THAT THIS IS A VERY POTENT DRUG.'

As indicated earlier, the addition of abemaciclib to fulvestrant also prolonged the time to the initiation of chemotherapy (HR[95%CI]: 0.625[0.501-0.779]) as well as the chemotherapy-free survival (HR[95%CI]: 0.638[0.527-0.773]). These effects were consistent across all investigated subgroups, including those patients with poor prognostic features.[5]

Professor Neven concludes: "Despite the fact that this is an exploratory analysis and that results should always be interpreted with care, to me the data of this subgroup analysis are of high clinical relevance. I believe that it certainly is a promising finding that mainly patients with liver metastases, a progesterone-receptor negative tumour or a high-grade tumour seem to benefit most from this treatment."

PFS and OS analyses in function of treatment line and response to ET

In a poster presented at ASCO 2020, Prof Neven presented a second exploratory analysis of MONARCH 2 looking at the treatment effect of abemaciclib in function of the treatment line in which patients received the CDK4/6 inhibitor and taking into account their prior response to ET.[6] As indicated earlier, all patients enrolled in MONARCH 2 were endocrine resistant and received the study drug as first or second line therapy for their advanced breast cancer. For the presented analysis, patients were divided into two subgroups: 1st line patients were patients who received the study drug as a first line treatment in the metastatic setting (i.e. these patients received ET in the neoadjuvant or adjuvant setting and progressed during ET or within 12 months after adjuvant ET), while 2nd line patients received the study drug as a second line option for their metastatic disease (i.e. the most recent ET for these patients was given in the metastatic setting). About 60% (N=398) of patients included in the MONARCH 2 trial were treated in the first-line metastatic setting. Of them, about a quarter (N=110) was classified as being primary endocrine resistant to adjuvant treatment. This was defined as having a relapse within 24 months after the start of the adjuvant ET. The rest of the patients in the first-line cohort was classified as being secondary endocrine resistant. In total, 256 patients, representing approximately 40% of the entire MONARCH 2 population, were allocated to the 2nd line subgroup. About a fifth (N= 56) of these patients experienced disease progression within the first 6 months of initiating ET for the treatment of metastatic disease. These patients were classified as being primary ET resistant, while patients who progressed beyond 6 months were seen as secondary ET resistant.[6]

Overall, the median PFS among patients in the 1st line cohort was reported at 15.45 months with the abemaciclib-fulvestrant combination as compared to 11.24 months with fulvestrant alone (HR[95%-CI]: 0.573[0.451-0.727]), representing a 43% reduced risk of disease progression or death for patients receiving abemaciclib. A closer look into this subgroup of patients learns that the largest PFS benefit obtained with abemaciclib was seen in patients with primary resistance (HR[95%CI]: 0.401[0.256-0.628]) and in patients with visceral disease (HR[95%CI]: 0.535[0.392-0.731]) (*Figure 2*).[6] Also in the 2nd line

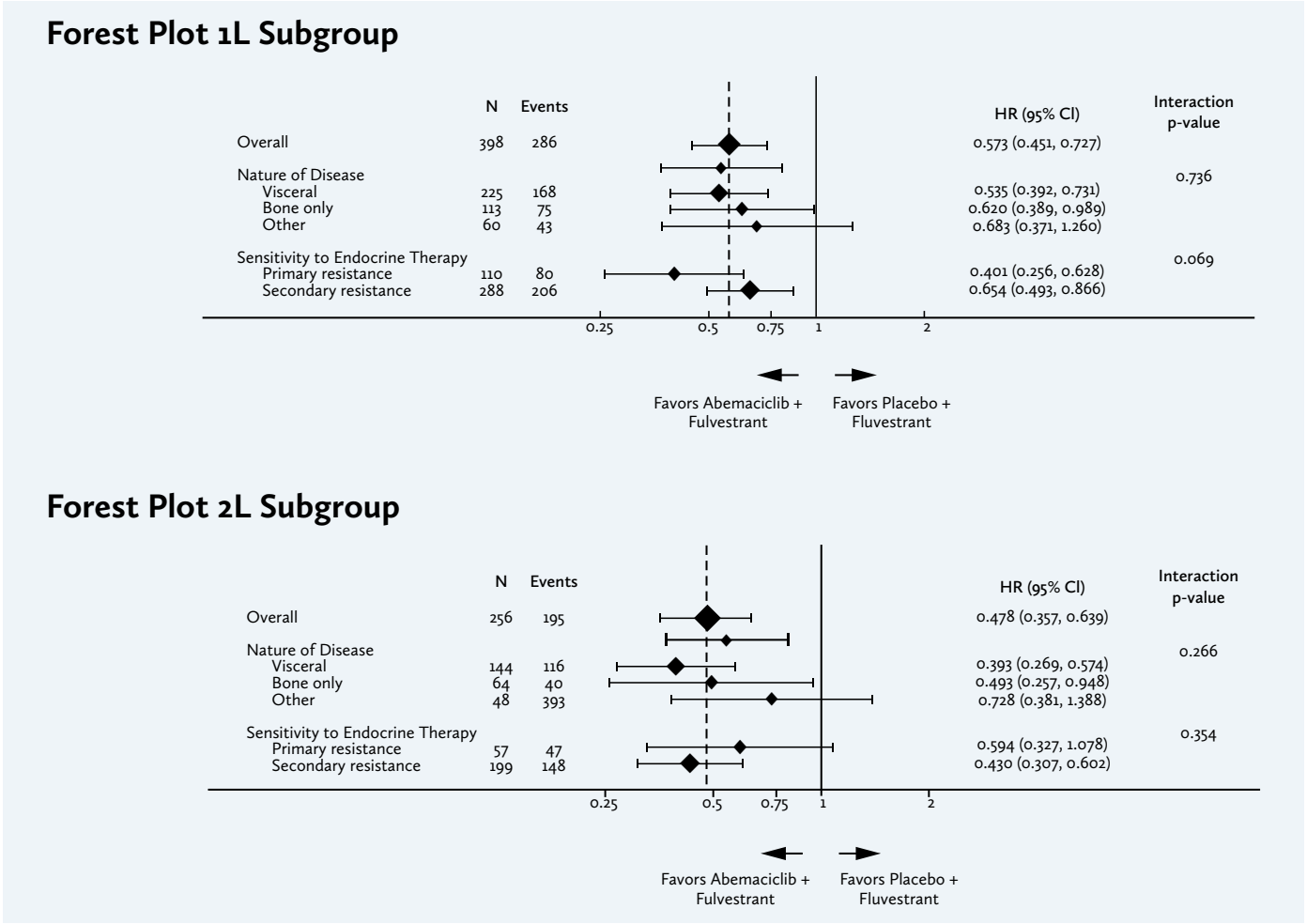

Figure 2. Progression free survival in function of treatment line in MONARCH 2.[6]

cohort abemaciclib provided a significant PFS advantage with a median PFS of 17.39 months with abemaciclib-fulvestrant *vs.* 7.36 months with the placebo-fulvestrant combination (HR[95%CI]: 0.478[0.357-0.639]). Among these patients, especially those presenting with visceral metastases experienced the largest PFS advantage with abemaciclib (HR[95%CI]: 0.393[0.269-0.574]) (*Figure 2*).[6]

In addition to significantly delaying disease progression, the combination of abemaciclib and fulvestrant also led to a prolongation in OS, irrespective of the treatment line. Patients in the 1st line subgroup who were treated in the abemaciclib arm had a median OS that was 6.4 months longer than the median OS seen with placebo-fulvestrant (43.63 *vs.* 37.25 months, HR[95%CI]: 0.851[0.638-1.135]). Similar to what was seen for PFS, also the OS benefit was most pronounced among 1st line patients with primary ET resistance (HR[95%CI]: 0.583[0.351-0.970]). Among patients in the 2nd line subgroup, abemaciclib-fulvestrant was associated with a median OS of 51.29 months, which was almost one year longer than the 39.72 months median OS for 2nd line patients treated with fulvestrant alone (HR[95%CI]: 0.656[0.461-0.935]). Also here the most pronounced effect was observed in patients with visceral disease (HR[95%CI]: 0.514[0.326-0.811]) (*Figure 3*).[6] *Prof. Neven comments: "Consistent with what we previously observed, also in this exploratory analysis it was clear that abemaciclib particularly benefited patients with more aggressive tumour types (e.g. patients with visceral disease). In addition, this analysis clearly indicates the clinical benefit of abemaciclib in women who proved to be primary resistant to ET given in the (neo)adjuvant setting."*

In addition to the significant improvement of PFS and OS, abemaciclib-fulvestrant also proved to be associated with a significantly longer time to second progression (PFS2) compared to fulvestrant alone (median 23.38 *vs.* 21.60 in 1st line group HR[95%C]: 0.757[0.591-0.970], 22.65 *vs.* 18.44 months in 2nd line group HR[95%CI]: 0.549[0.407-0.740]). This indicates that the use of abemaciclib does not compromise the efficacy of subsequent treatment lines. Finally, also the time to chemotherapy (TTC) and the chemotherapy-free survival (CFS) were longer with abemaciclib-fulvestrant than with fulvestrant-placebo both in the 1st and 2nd line subgroup. In this respect, the prolongation of TTC and CFS was found to be significantly greater in the 2nd line subgroup, compared to 1st line patients (interaction p-value 0.006 and 0.005, respectively). However, according to the authors, this result may have been driven by the large differences observed in the medians in the placebo arm (e.g. median TTC in placebo arm 27.65 and 12.92 months in 1st and 2nd line subgroup, respectively).

Commenting on these findings, Prof. Neven stated: *"To me, these results underline the importance of considering the ET resistance timeline. If a woman has done well on her ET in first line and only relapses after, for example, ten years, I believe that she can still be treated with*

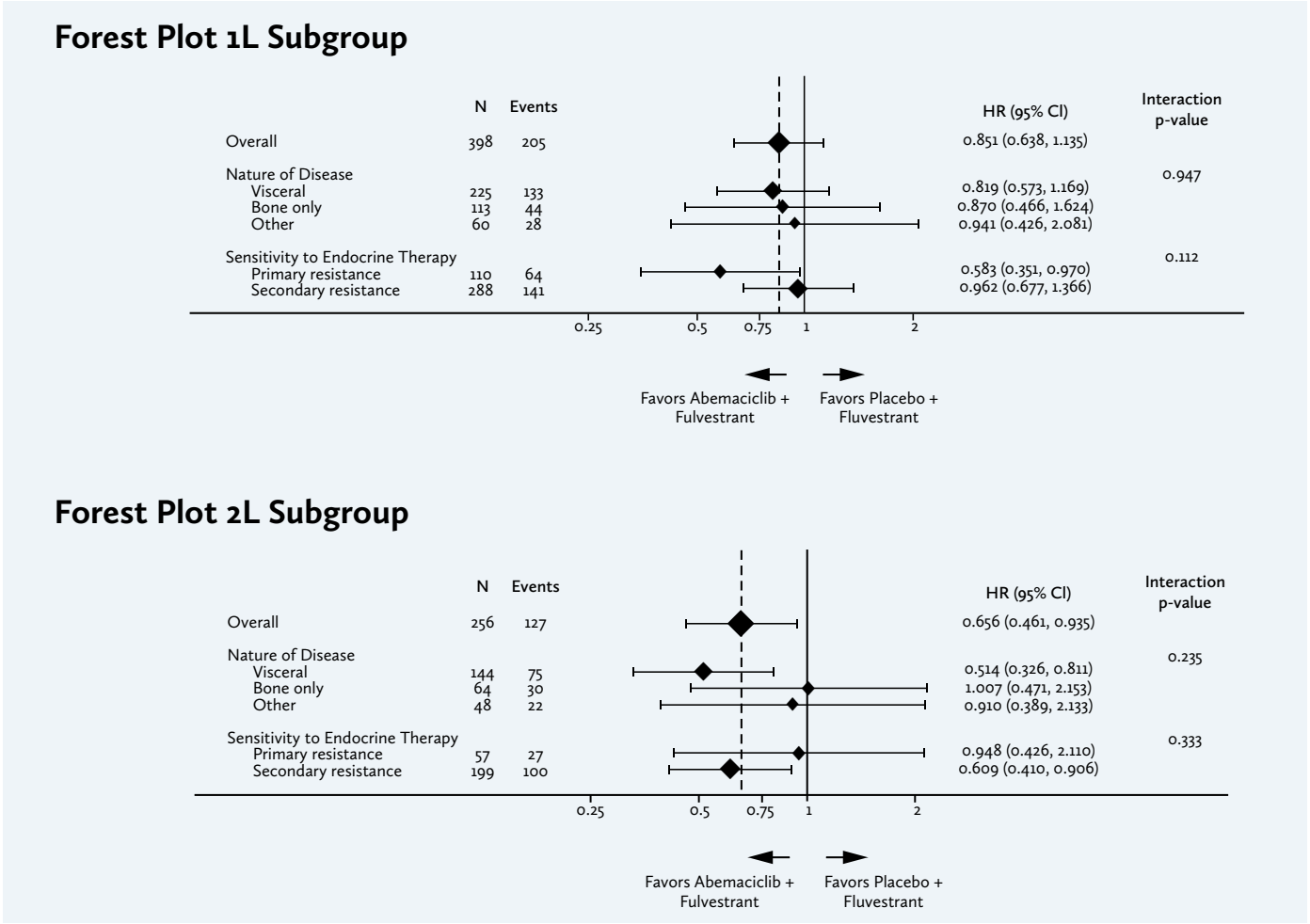

Figure 3. Overall Survival in function of treatment line in MONARCH 2.[6]

monotherapy in the first-line metastatic setting, on the condition that she presents with few disease symptoms. On the other hand, these data underline that patients with a quick relapse in the adjuvant or metastatic setting derive a pronounced benefit from a more intensive treatment consisting of a fulvestrant-abemaciclib combination. As such, these findings again underline that the treatment of women with HR+/HER2- advance breast cancer is no longer a one size fits all story, but that we should consider individual patient and disease factors in our treatment decisions."

"THESE DATA UNDERLINE THAT PATIENTS WITH A QUICK RELAPSE IN THE ADJUVANT OR METASTATIC SETTING DERIVE A PRONOUNCED BENEFIT FROM A MORE INTENSIVE TREATMENT CONSISTING OF A FULVESTRANT-ABEMACICLIB COMBINATION."

Conclusions

MONARCH 2 established the combination of abemaciclib and fulvestrant as a standard of care for women with HR+/HER2- metastatic breast cancer. The OS benefit of abemaciclib and fulvestrant was consistent across all exploratory subgroups. However, in line with previously reported PFS data, the OS improvement was most pronounced in patients with less favourable prognostic features (i.e. high tumour grade, negative progesterone receptor status, liver metastases and without bone only metastases). Continued follow-up is ongoing to further characterise the OS benefit, particularly in subgroups with a more favourable prognosis (i.e. patients with bone only disease where a median OS value has not yet been reached). The PFS and OS benefit obtained with abemaciclib was also seen irrespective of the treatment line and irrespective of the type of ET resistance (primary or secondary). Interestingly, among patients treated with abemaciclib as a first-line treatment for their metastatic disease, the PFS and OS benefit was particularly pronounced in patients with an early disease relapse on adjuvant ET therapy (i.e. within 2 years). This observation further confirms the finding that particularly patients with a more aggressive tumour type seem to derive the largest clinical benefit of the CDK4/6 inhibitor.

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PP-AL-BE-0122 – SEPTEMBER 2020

Hospital price
150 mg x 56 tabl.: € 3.820,11
100 mg x 56 tabl.: € 3.820,11
50 mg x 56 tabl.: € 3.820,11

MINIMAL INFORMATIONS OF THE SPC ▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions. **1. NAME OF THE MEDICINAL PRODUCT** Verzenios 50 mg film-coated tablets Verzenios 100 mg film-coated tablets Verzenios 150 mg film-coated tablets **2. QUALITATIVE AND QUANTITATIVE COMPOSITION** Verzenios 50 mg film-coated tablets Each film-coated tablet contains 50 mg abemaciclib. *Excipients with known effect* Each film-coated tablet contains 14 mg of lactose monohydrate. Verzenios 100 mg film-coated tablets Each film-coated tablet contains 100 mg abemaciclib. Excipients with known effect Each film-coated tablet contains 28 mg of lactose monohydrate. Verzenios 150 mg film-coated tablets Each film-coated tablet contains 150 mg abemaciclib. *Excipients with known effect* Each film-coated tablet contains 42 mg of lactose monohydrate. For the full list of excipients, see section 6.1. **3. PHARMACEUTICAL FORM** Film-coated tablet (tablet). Verzenios 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. Verzenios 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. Verzenios 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. **4. CLINICAL PARTICULARS 4.1 Therapeutic indications** Verzenios is indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (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. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist. **4.2 Posology and method of administration** Verzenios therapy should be initiated and supervised by physicians experienced in the use of anticancer therapies. Posology *Verzenios in combination with endocrine therapy* The recommended dose of abemaciclib is 150 mg twice daily when used in combination with endocrine therapy. Please refer to the Summary of Product Characteristics of the endocrine therapy combination partner for the recommended posology. Verzenios should be taken continuously as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs. If a patient vomits or misses a dose of Verzenios, the patient should be instructed to take the next dose at its scheduled time; an additional dose should not be taken. *Dose adjustments* Management of some adverse reactions may require dose interruption and/or dose reduction as shown in Tables 1-6. **Table 1. Dose adjustment recommendations for adverse reactions**

	Verzenios dose combination therapy
Recommended dose	150 mg twice daily
First dose adjustment	100 mg twice daily
Second dose adjustment	50 mg twice daily

Table 2. Management recommendations for haematologic toxicities Complete blood counts should be monitored prior to the start of Verzenios therapy, every two weeks for the first two months, monthly for the next two months, and as clinically indicated. Before treatment initiation, absolute neutrophil counts (ANC) ≥1500/mm^3, platelets ≥100,000/mm^3, and haemoglobin ≥8 g/dL are recommended.

Toxicity[a, b]	**Management recommendations**
Grade 1 or 2	No dose adjustment required.
Grade 3	Suspend dose until toxicity resolves to Grade 2 or less. Dose reduction is not required.
Grade 3, recurrent; or Grade 4	Suspend dose until toxicity resolves to Grade 2 or less. Resume at next lower dose.
Patient requires administration of blood cell growth factors	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to Grade 2 or less. Resume at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.

[a] NCI Common Terminology Criteria for Adverse Events (CTCAE) b ANC: Grade 1: ANC < LLN - 1500/mm3; Grade 2: ANC 1000 - <1500/mm3; Grade 3: ANC 500 - <1000/mm3; Grade 4: ANC <500/mm3 LLN = lower limit of normal

Table 3. Management recommendations for diarrhoea Treatment with antidiarrhoeal agents, such as loperamide, should be started at the first sign of loose stools.

Toxicity[a]	**Management recommendations**
Grade 1	No dose adjustment required.
Grade 2	If toxicity does not resolve within 24 hours to Grade 1 or less, suspend dose until resolution. Dose reduction is not required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to Grade 1 or less. Resume at next lower dose.
Grade 3 or 4 or requires hospitalisation	

[a] NCI CTCAE **Table 4. Management recommendations for increased aminotransferases** Alanine aminotransferase (ALT) and aspartate aminostransferase (AST) should be monitored prior to the start of Verzenios therapy, every two weeks for the first two months, monthly for the next two months, and as clinically indicated.

Toxicity[a]	**Management recommendations**
Grade 1 (>ULN-3.0 x ULN) Grade 2 (>3.0-5.0 x ULN)	No dose adjustment required.
Persistent or Recurrent Grade 2, or Grade 3 (>5.0-20.0 x ULN)	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Elevation in AST and/or ALT >3 x ULN WITH total bilirubin >2 x ULN, in the absence of cholestasis	Discontinue abemaciclib.
Grade 4 (>20.0 x ULN)	Discontinue abemaciclib.

[a] NCI CTCAE ULN = upper limit of normal **Table 5. Management recommendations for interstitial lung disease (ILD)/ pneumonitis**

Toxicity[a]	**Management recommendations**
Grade 1 or 2	No dose adjustment required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	Discontinue abemaciclib.

[a] NCI CTCAE **Table 6. Management recommendations for non-haematologic toxicities (excluding diarrhoea, increased aminotransferases and interstitial lung disease (ILD)/pneumonitis)**

Toxicity[a]	**Management recommendations**
Grade 1 or 2	No dose adjustment required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures to baseline or Grade 1 within 7 days	Suspend dose until toxicity resolves to Grade 1 or less. Resume at next lower dose.
Grade 3 or 4	

[a] NCI CTCAE CYP3A4 inhibitors Concomitant use of strong CYP3A4 inhibitors should be avoided. If strong CYP3A4 inhibitors cannot be avoided, the abemaciclib dose should be reduced to 100 mg twice daily. In patients who have had their dose reduced to 100 mg abemaciclib twice daily and in whom coadministration of a strong CYP3A4 inhibitor cannot be avoided, the abemaciclib dose should be further reduced to 50 mg twice daily. In patients who have had their dose reduced to 50 mg abemaciclib twice daily and in whom coadministration of a strong CYP3A4 inhibitor cannot be avoided, the abemaciclib dose may be continued with close monitoring of signs of toxicity. Alternatively, the abemaciclib dose may be reduced to 50 mg once daily or discontinued. If the CYP3A4 inhibitor is discontinued, the abemaciclib dose should be increased to the dose used prior to the initiation of the CYP3A4 inhibitor (after 3 to 5 half-lives of the CYP3A4 inhibitor). Special populations Elderly No dose adjustment is required based on age (see section 5.2). Renal impairment No dose adjustments are necessary in patients with mild or moderate renal impairment. There are no data regarding abemaciclib administration in patients with severe renal impairment, end stage renal disease, or in patients on dialysis (see section 5.2). Abemaciclib should be administered with caution in patients with severe renal impairment, with close monitoring for signs of toxicity. Hepatic impairment No dose adjustments are necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. In patients with severe (Child Pugh C) hepatic impairment, a decrease in dosing frequency to once daily is recommended (see section 5.2). Paediatric population The safety and efficacy of abemaciclib in children and adolescents aged less than 18 years has not been established. No data are available. Method of administration Verzenios is for oral use. The dose can be taken with or without food. It should not be taken with grapefruit or grapefruit juice (see section 4.5). Patients should take the doses at approximately the same times every day. The tablet should be swallowed whole (patients should not chew, crush, or split tablets before swallowing). **4.3 Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.8 Undesirable effects Summary of the safety profile The most commonly occurring adverse reactions are diarrhoea, infections, neutropenia, anaemia, fatigue, nausea, vomiting and decreased appetite. Tabulated list of adverse reactions In the following table, adverse reactions are listed in order of MedDRA body system organ class and frequency. Frequency gradings are: very common (³1/10), common (³1/100 to <1/10), uncommon (³1/1,000 to <1/100), rare (³1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. **Table 7. Adverse reactions reported in phase 3 studies of abemaciclib in combination with endocrine therapy (N=768)**

System organ class *Frequency* *Preferred term*	**Abemaciclib plus endocrine therapy**[a]		
	All Grades Toxicity (%)	**Grade 3 Toxicity (%)**	**Grade 4 Toxicity (%)**
Infections and infestations			
Very common			
Infections[b]	43.6	5.2	1.0
Blood and lymphatic system disorders			
Very common			
Neutropenia	45.1	22.9	2.5
Leukopenia	25.7	8.5	0.3
Anaemia	30.1	7.0	0.1
Thrombocytopenia	14.3	2.2	1.0
Common			
Lymphopenia	7.3	3.0	0.1
Uncommon			
Febrile neutropenia	0.9	0.7	0.1
Metabolism and nutrition disorders			
Very common			
Decreased appetite	26.4	1.3	0
Nervous system disorders			
Very common			
Dysgeusia	14.3	0	0
Dizziness	12.9	0.5	0
Eye disorders			
Common			
Lacrimation increased	6.8	0.1	0
Vascular disorders			
Common			
Venous thromboembolism[c]	5.3	1.7	0.3
Respiratory, thoracic and mediastinal disorders *Common* Interstitial lung disease (ILD)/pneumonitis	3.4	0.4	0.1
Gastrointestinal disorders			
Very common			
Diarrhoea Vomiting Nausea	84.6 27.7 43.5	11.7 1.2 2.1	0 0 0
Skin and subcutaneous tissue disorders			
Very common			
Alopecia	20.7	0	0
Pruritus	13.5	0	0
Rash	12.9	1.0	0
Common			
Dry skin	9.0	0	0
Musculoskeletal and connective tissue disorders			
Common			
Muscular weakness	8.3	0.5	0
General disorders and administration site conditions			
Very common			
Fatigue	40.5	2.3	0
Pyrexia	10.7	0.1	0
Investigations			
Very common			
Alanine aminotransferase increased	15.1	4.8	0.3
Aspartate aminotransferase increased	14.2	2.9	0

[a] Abemaciclib in combination with letrozole, anastrozole, or fulvestrant. [b] Infections includes all PTs that are part of the System Organ Class Infections and infestations. [c] Venous thromboembolic events include DVT, pulmonary embolism, cerebral venous sinus thrombosis, subclavian, axillary vein thrombosis,DVT inferior vena cava and pelvic venous thrombosis Description of selected adverse reactions *Neutropenia* Neutropenia was reported frequently (45.1%). and a Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 28.2% of patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant. The median time to onset of Grade 3 or 4 neutropenia was 29 to 33 days, and median time to resolution was 11 to 15 days. Febrile neutropenia was reported in 0.9% patients. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia (see section 4.2). *Diarrhoea* Diarrhoea was the most commonly reported adverse reaction (see Table 7). Incidence was greatest during the first month of abemaciclib treatment and was lower subsequently. The median time to onset of the first diarrhoea event was approximately 6 to 8 days across studies, and the median duration of diarrhoea was 9 to 12 days (Grade 2) and 6 to 8 days (Grade 3) across studies. Diarrhoea returned to baseline or lesser grade with supportive treatment such as loperamide and/or dose adjustment (see section 4.2). *Increased aminotransferases* In patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant, ALT and AST elevations were reported frequently (15.1% and 14.2%, respectively). Grade 3 or 4 ALT or AST elevations (based on laboratory findings) were reported in 6.1% and 4.2% patients. The median time to onset of Grade 3 or 4 ALT elevation was 57 to 61 days, and median time to resolution was 14 days. The median time to onset of Grade 3 or 4 AST elevation was 71 to 185 days, and median time to resolution was 13 to 15 days. Dose modification is recommended for patients who develop Grade 3 or 4 ALT or AST increase (see section 4.2). *Creatinine* Although not an adverse reaction, abemaciclib has been shown to increase serum creatinine in 98.3% of patients (based on laboratory findings), 1.9% Grade 3 or 4 (based on laboratory findings). In patients receiving an aromatase inhibitor or fulvestrant alone, 78.4% reported an increase in serum creatinine (all laboratory grades). Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters without affecting glomerular function (as measured by iohexol clearance) (see section 4.5). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C. Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: Belgium: l'Agence fédérale des médicaments et des produits de santé, Division Vigilance, Boîte Postale 97, B- 1000 Bruxelles, Madou (www.afmps.be or adversedrugreactions@fagg-afmps.be) Luxembourg: **Centre Régional de Pharmacovigilance de Nancy**, Bâtiment de Biologie Moléculaire et de Biopathologie (BBB), CHR de Nancy – Hôpitaux de Brabois, Rue du Morvan, 54511 VANDOEUVRE LES NANCY CEDEX, tel. : (+33) 3 83 65 60 85/87, fax : (+33) 3 83 65 61 33, e-mail crpv@chru-nancy.fr or **Direction de la Santé, Division de la Pharmacie et des Médicaments**, Allée Marconi – Villa Louvigny, L- 2120 Luxembourg, tel. : (+352) 247-85592, fax : (+352) 247-95615, e-mail pharmacovigilance@ms.etat.lu. Link for the form: http://www.sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html **7. MARKETING AUTHORISATION HOLDER** Eli Lilly Nederland B.V., Papendorpseweg 83, 3528BJ Utrecht, The Netherlands. **8. MARKETING AUTHORISATION NUMBER(S)**
EU/1/18/1307/001 EU/1/18/1307/002 EU/1/18/1307/003 EU/1/18/1307/004 EU/1/18/1307/005
EU/1/18/1307/006 EU/1/18/1307/007 EU/1/18/1307/008 EU/1/18/1307/009 EU/1/18/1307/010
EU/1/18/1307/011 EU/1/18/1307/012 EU/1/18/1307/013 EU/1/18/1307/014 EU/1/18/1307/015
EU/1/18/1307/016 EU/1/18/1307/017 EU/1/18/1307/018 EU/1/18/1307/019 EU/1/18/1307/020
EU/1/18/1307/021 **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION** Date of first authorisation: 27 September 2018 **10. DATE OF REVISION OF THE TEXT** 16 January 2020 METHOD OF DELIVERY Medicinal product subject to restricted medical prescription. Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu