Alpelisib and fulvestrant in PIK3CA-mutated hormone receptor-positive HER2-negative advanced breast cancer included in the French early access program

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Abstract

Background

SOLAR-1 and BYLIEVE trials documented the efficacy of the PI3K-inhibitor alpelisib in pre-treated *PIK3CA*-mutant, hormone receptor-positive, HER2-negative (HR+/HER2-) advanced breast cancer (ABC) patients. We report here real-life data of patients prospectively registered in the French alpelisib early access program (EAP).

Patients and methods:

The French EAP was opened to *PIK3CA*-mutant HR+/HER2- ABC patients treated with alpelisib and fulvestrant, managed per standard of care. Primary endpoint was PFS by local investigators using RECIST1.1.

Results

Eleven centers provided individual data on 233 consecutive patients. Patients had received a median number of 4 (range: 1–16) prior systemic treatments for ABC, including CDK4/6 inhibitor, chemotherapy, fulvestrant and everolimus in 227 (97.4%), 180 (77.3%), 175 (75.1%) and 131 (56.2%) patients, respectively. After a median follow-up of 7.1 months and 168 events, median PFS was 5.3 months (95%CI, 4.7-6.0). Among 186 evaluable patients, CBR at 6 months was 45.3% (95%CI, 37.8–52.8). In multivariable analysis, characteristics significantly associated with a shorter PFS were age < 60 years (HR = 1.5, 95%CI = 1.1–2.1), > 5 lines of prior treatments (HR = 1.4, 95%CI = 1.0–2.0) and the C420R *PI3KCA* mutation (HR = 4.1, 95%CI = 1.3–13.6). Most frequent grade 3/4 adverse events (AEs) were hyperglycemia, rash, fatigue and diarrhea occurring in 11.6, 9.9, 4.3 and 3% of patients, respectively. N = 91 (39.1%) patients discontinued alpelisib due to AEs.

Discussion

To our knowledge, this is the largest real-life assessment of alpelisib efficacy. Despite heavy pre-treatments, patients derived a clinically relevant benefit from alpelisib and fulvestrant. PFS was not overtly impaired by a prior use of either everolimus or fulvestrant. No new safety signal was found.

Introduction

Approximately 40% of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer display activating mutations in the phosphatidylinositol 3-kinase

(*PIK3CA*) gene, leading to the activation of the PI3K pathway [1,2]. *PIK3CA* mutations have been associated with a poor outcome and endocrine resistance in HR+/HER2- advanced breast cancer (ABC)[3,4].

Alpelisib is an orally bioavailable, α-selective PI3K inhibitor and degrader[5]. SOLAR-1, a phase 3 trial, investigated the efficacy of fulvestrant associated with alpelisib versus placebo [6] in endocrine-resistant HR-positive, HER2-negative ABC. In the cohort of patients with *PIK3CA*-mutated ABC, progression-free survival (PFS) was significantly improved in the alpelisib-fulvestrant group, as compared with the placebo–fulvestrant group (with 11 and 5.7 months median PFS, respectively). Despite a particular toxicity profile, adverse events were manageable. Of note, only few (5.9%) patients in SOLAR-1 received a prior CDK4/6 inhibitor [7]. The median PFS achieved by fulvestrant-alpelisib after a first line therapy with CDK4/6 inhibitor was later documented by the BYLieve phase 2 trial: the 127 patients pretreated with an aromatase inhibitor and a CDK4/6 inhibitor (cohort A) experienced a median PFS of 7.3 months on alpelisib and fulvestrant[8].

Based on the results of SOLAR-1, FDA approved alpelisib-fulvestrant for the treatment of post-menopausal patients with *PIK3CA*-mutated HR+/HER2- endocrine resistant ABC. In France, a temporary early access program (EAP) was opened on November 26th, 2018 to provide access to alpelisib-fulvestrant in *PIK3CA*-mutated HR+/HER2- ABC patients pretreated with at least two systemic treatments including an aromatase inhibitor and a CDK4/6 inhibitor. Following the decision of the European Medicine Agency to restrict the European label of alpelisib to patients who did not receive a prior CDK4/6 inhibitor, the French EAP was closed to new patients in 10.2020. In this retrospective analysis, we report the outcome of consecutive patients treated with alpelisib-fulvestrant through the French EAP in major French breast cancer centers.

Patients And Methods

Patients and treatment

The French EAP was accessible to all patients and centers in France. To be eligible, the following criteria were mandatory: women aged 18 years and more; treated for a histologically proven HR + HER2- ABC (HR-positivity being defined by ≥ 10% tumor cells positive for either estrogen and/or progesterone receptor by immunohistochemistry); having received at least 2 prior lines of systemic therapy, including an aromatase inhibitor and a CDK4/6 inhibitor; activating *PI3KCA* mutation, per local sequencing of the primary and/or metastatic tumors and/or liquid biopsy. Patients with visceral crisis or inflammatory breast cancer were excluded. Patients had to have a fasting plasma glucose below 140 mg/dl (7.7 mmol/l) and glycated hemoglobin A_{1c} below 6.4%. All patients treated as part of the EAP were prospectively registered at their site in a national registry. Alpelisib was delivered to patients by their hospital pharmacy every month, at a starting dose of 300 mg daily. Fulvestrant was used at standard doses (500 mg intramuscularly on day 1 of each 28-day cycle and on day 15 of cycle 1). LH-RH agonists

were allowed per standard of care and investigator's opinion. Treatment and dose reductions were managed by oncologists, following drug labels.

Data collection

This study was approved by the Institut Curie review board; a waiver of informed consent was granted due to the retrospective nature of the work. A synopsis of this retrospective study was sent to French cancer centers, known for having significantly contributed to the alpelisib EAP. Eleven of these centers agreed to participate in the study: Institut Curie Paris and Saint Cloud Hospitals, Institut Paoli Calmettes, Centre Eugene Marquis, Institut de Cancérologie de l'Ouest, Gustave Roussy, Centre Antoine Lacassagne, Tenon Hospital, Brest University Hospital Center, Centre Georges-François Leclerc, American Hospital of Paris, Institut Sainte-Catherine.

Medical oncologists retrospectively collected data using electronic medical records for all patients enrolled in the EAP at their sites. Participating sites had to grade toxicities according to CTCAE v5.0, whereas tumor assessment by imaging had to be reported using RECIST v1.1 [9]. The list of collected data is available as **Supplementary Table 1**. Data cutoff was February 28th 2021. Pseudonymized individual data were further manually reviewed for quality and coherence at Institut Curie, and queries were issued whenever needed.

Endpoints and statistics

The primary endpoint was PFS. Secondary endpoints were overall survival (OS), objective response rate (ORR), 6 months clinical benefit rate (6mCBR) defined as the percentage of patients who have achieved a complete or partial response and/or experienced a stable disease for at least 6 months, and safety. The following prognostic factors for PFS were explored: median age at alpelisib initiation, performance status, histological subtypes, hormone receptors expression, disease stage at diagnosis, presence of visceral disease, number of metastatic sites, number and type of previous systemic treatments administered for metastatic disease and type of *PIK3CA* mutation – with no correction for multiple testing.

Descriptive statistics were used to summarize patients' characteristics. Progression-free survival was defined as the time from treatment initiation to disease progression or death, whichever came first. Patients discontinuing both alpelisib and fulvestrant for other reason than a PFS event were censored at time of discontinuation. Survival curves for PFS, median PFS and its 95% confidence interval (95%CI) were generated using the Kaplan-Meier method. Multivariate Cox proportional hazards models were constructed on the general population using a backward step-by-step manual selection procedure to identify independent prognosis factors. All factors significant at a conservative 10% level in univariate analysis were included in multivariate analysis. The final model was reached when including only factors at a $p = 0.05$ significance level. All analyses were performed using R version 3.3.2. Statistical significance was defined by a two-tailed $p < 0.05$.

Results

Patients’ and tumor characteristics

Out of a total number of 365 patients included in the French EAP (according to the ANSM public report of June 2, 2020) (9), 233 (63.8%) were included in the 11 participating centers and met the study eligibility criteria (Fig. 1). Baseline demographic and clinicopathological characteristics of patients are shown in Table 1. Median age was 61.7 years (range: 30.9–84.5 years). Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 82 patients (36.1%), 1 in 116 patients (51.1%), 2 or 3 in 29 patients (12.8%). Fifty-five (23.7%) patients had *de novo* stage IV disease. At baseline, 166 patients (71.2%) had visceral disease while 67 (28.8%) had bone-only metastatic disease. The median number of prior treatment lines was 4 (range 1–16): 180 patients (77.3%) had received chemotherapy, 175 (75.1%) fulvestrant alone or in combination, and 131 (56.2%) everolimus plus endocrine therapy. Table 2 displays the distribution of *PI3KCA* mutations, the most common being H1047R (38.6%), E545K (14.5%) and E542K (14.1%).

Table 1
Clinical characteristics and prognostic impact on progression-free survival

			Univariate analysis		Multivariate analysis	
Characteristics	N patients (%)	Median PFS [95%CI]	PFS HR [95%CI]	P value	PFS HR [95%CI]	P value
Performance status						
0	82 (36.1)	5.8 [4.9;7.5]	1			
1	116 (51.1)	5.0 [3.8;6.0]	1.3 [0.9;1.8]	NS		
2–3	29 (12.8)	4.9 [2.0;10.0]	1.2 [0.7;2.0]	NS		
Age						
< 60 years	107 (45.9)	4.3 [3.8;5.7]	1	NS	1.5 [1.1;2.1]	0.01
≥ 60 years	126 (54.1)	5.9 [5.0;6.9]	0.7 [0.5;0.97]		1	
De novo stage IV disease						
Yes	55 (23.7)	4.1 [3.2;6.6]	1.2 [0.8;1.7]	NS		
No	177 (76.3)	5.7 [4.9;6.3]	1			
Number of metastatic sites						
< 3	132 (56.7)	5.5 [4.7;6.3]	1			
≥ 3	101 (43.3)	5.0 [3.8;6.2]	1.1 [0.8;1.4]	NS		
Visceral metastases						
Yes	166 (71.2)	5.4 [4.4;6.2]	1 [0.7;1.4]	NS		
No	67 (28.8)	5.1 [3.8;7.1]	1			
Bone metastases						
Yes	191 (82)	5.1 [4.3;6.2]	0.9 [0.6;1.4]	NS		

NS: not significant

Median PFS are estimated by Cox under the proportion hazard assumption

			Univariate analysis		Multivariate analysis	
No	42 (18)	5.5 [4.1;6.4]	1			
Liver metastases						
Yes	122 (52.4)	5.7 [4.9;6.3]	0.9 [0.7;1.3]	NS		
No	111 (47.6)	4.7 [3.9;6.1]	1			
Locoregional involvement						
Yes	45 (19.3)	4.8 [2.9;7.9]	1.1 [0.7;1.6]	NS		
No	188 (80.7)	5.6 [4.7;6.2]	1			
Lung/pleural metastases						
Yes	86 (36.9)	5.5 [4.1;6.5]	0.9 [0.7;1.3]	NS		
No	147 (63.1)	5.3 [4.3;6.1]	1			
Prior systemic treatments						
1 to 4	125 (53.6)	5.8 [4.8;7.0]	1		1	
5 to 16	108 (46.4)	4.9 [3.8;6.0]	1.5 [1.1;2.1]	0.009	1.4 [1.0;2.0]	0.05
Prior fulvestrant						
Yes	175 (75.1)	5.4 [4.7;6.2]	1.1 [0.8;1.6]	NS		
No	58 (24.9)	5.1 [3.3;6.5]	1			
Prior everolimus						
Yes	131 (56.2)	5.8 [4.9;6.9]	0.8 [0.6;1.1]	NS		
No	102 (43.8)	4.7 [3.3;5.7]	1			
Prior chemotherapy						
Yes	180 (77.3)	4.9 [3.9;6.0]	1.5 [1.1;2.2]	0.02	1.3 [0.9;2.0]	NS

NS: not significant

Median PFS are estimated by Cox under the proportion hazard assumption

			Univariate analysis		Multivariate analysis	
No	53 (22.7)	5.8 [5.1;7.5]	1		1	
C420R PIK3CA **mutation**						
Yes	4 (1.8)	2.2 [1;NR]	5.0 [1.6;16.3]	0.007	4.1 [1.3;13.6]	0.02
No	216 (98.2)	5.5 [4.8;6.1]	1		1	
NS: not significant						
Median PFS are estimated by Cox under the proportion hazard assumption						

Table 2
Types of *PIK3CA* mutations and prognostic impact for PFS NS: not significant; NE: not evaluable

***PIK3CA* mutation**	**N (%)**	**Median PFS [95%CI]**	**Univariate analysis PFS HR [95%CI]**	**Univariate analysis P value**
N345K				
Yes	3 (1.4)	6.1 [NE;NE]	0.9 [0.1;6.2]	NS
No	217 (98.6)	5.4 [4.7;6.0]	1	
C420R				
Yes	4 (1.8)	2.2 [1;NE]	5.0 [1.6;16.3]	0.007
No	216 (98.2)	5.5 [4.8; 6.1]	1	
E542K				
Yes	31(14.1)	5.0 [3.1;8.5]	0.9 [0.5;1.4]	NS
No	189 (85.9)	5.5 [4.7;6.0]	1	
E545A				
Yes	15 (6.8)	4.2 [2.9;6.3]	1.5 [0.9;2.6]	NS
No	205 (93.2)	5.5 [4.9;6.0]	1	
E545K				
Yes	32 (14.5)	6.7 [4.4;NE]	0.7 [0.4;1.1]	NS
No	188 (85.5)	5.1 [4.7;6.0]	1	
Q546R				
Yes	4 (1.8)	7.8 [5.0;NE]	0.3 [0.1;1.3]	NS
No	216 (98.2)	5.3 [4.7;6.0]	1	
H1047R				
Yes	85 (38.6)	5.4 [4.9;6.1]	1.1 [0.8;1.5]	NS
No	135 (61.4)	5.6 [3.7;6.3]	1	
H1047L				
Yes	13 (5.9)	3.3 [2.8;NE]	1.5 [0.8;2.9]	NS
No	207 (94.1)	5.5 [4.9;6.2]	1	

Median PFS are estimated by Cox under the proportion hazard assumption

PIK3CA mutation	N (%)	Median PFS [95%CI]	Univariate analysis PFS HR [95%CI]	Univariate analysis P value
Double mutants				
Yes	9 (4.1)	6.6 [4.4;NE]	0.6 [0.2;1.5]	NS
No	211 (95.9)	5.3 [4.7;6.0]	1	
Median PFS are estimated by Cox under the proportion hazard assumption				

Treatment efficacy

At data cutoff, median follow-up was 7.1 months (range: 0.2–19.5). With 168 PFS events, the median PFS was 5.3 months (95%CI, 4.7-6.0) (Fig. 2). Sixty-nine patients (29.6%) have died at database lock, with a median OS of 16.8 months (95%CI, 14.5-NR) (Fig. 3). Among 186 evaluable patients, best tumor responses were: complete response in 5 patients (2.7%), partial response in 66 patients (35.5%) and stable disease in 53 patients (28.5%). The overall response rate was 38.8% (95%CI, 31.8%-45.7%) and the 6mCBR was 45.3% (95%CI, 37.8%-52.8%) (Table 3).

Table 3
Clinical efficacy summary CBR: Clinical Benefit Rate, ORR: Overall Response Rate, SD: Stable Disease, PR: Partial Response, CR: Complete Response

CBR at 6 months [95%CI]	**45.3 [37.8;52.8]**
ORR [95%CI]	38.8 [31.8;45.7]
Best response: SD (N, %)	53 (28.5%)
Best response: PR (N, %)	66 (35.5%)
Best response: CR (N, %)	5 (2.7%)

Prognostic factors

Univariate and multivariate analyses for PFS are shown in Table 1. Adverse prognostic factors for PFS identified using univariate analysis were: age < 60 years (HR = 1.4, 95%CI[1.0-1.9]), prior chemotherapy for advanced disease (HR = 1.5 [1.1–2.2]) and > 5 prior treatment lines (HR = 1.5 [1.1–2.1]). Importantly, our analysis did not retrieve a significant impact of the prior use of either fulvestrant and/or everolimus. The C420R *PIK3CA* mutation, which was detected in only 4 patients (1.8%) significantly impaired PFS on univariate analysis (HR = 5.0 [1.6–16.3]).

The independent adverse prognostic factors retrieved by multivariate analysis were: age < 60 years (HR = 1.5 [1.1–2.1]), > 5 prior treatment lines (HR = 1.4[1.0–2.0]) and the C420R *PI3KCA* mutation (HR = 4.1 [1.3–13.6]) (Table 1).

Safety

Alpelisib dose reduction occurred in 91 (39.1%) patients. Permanent discontinuation because of treatment toxicity occurred in 84 (36.9%) patients. Most frequent grade 3 or 4 toxicities observed were hyperglycemia in 27 patients (11.6%), rash in 23 (9.9%) patients, fatigue in 10 (4.3%) and diarrhea in 7 (3%) (Table 4). No toxic death was observed.

Table 4
Adverse events according to NCI CTCAE v 5.0 among 233 patients

	All grades, N (%)	Grades 3 and 4, N (%)
Fatigue	132 (56.7)	10 (4.3)
Hyperglycemia	124 (53.2)	27 (11.6)
Rash	94 (40.3)	23 (9.9)
Weight loss	80 (34.3)	2 (0.9)
Nausea	62 (26.6)	4 (1.7)
Diarrhea	55 (25.1)	7 (3)
Oral mucositis	52 (22.3)	4 (1.7)
Hypereosinophilia	22 (9.4)	0 (0)

Discussion

EAPs offer ethical, compliant, and controlled mechanisms of access to investigational drugs outside of the clinical trial space and before the commercial launch of the drug [10]. The prospective registration of participating patients and the tracability of alpelisib delivery by hospital pharmacies was considered as a unique opportunity to report real-life alpelisib data. Our retrospective study gathered the individual data of almost two-thirds of patients treated as part of the French EAP nationwide and is, to our knowledge, the most significant population-based study on alpelisib and fulvestrant in a post-CDK4/6 inhibitor setting.

In our multicentric real-life cohort of N=233 patients, the median PFS obtained under alpelisib and fulvestrant (5.3 months) must be weighed against clinical trial results obtained with either fulvestrant and alpelisib combination or single agent fulvestrant, in a post-CDK4/6 inhibitor setting. On the one hand, the median PFS in our study is numerically shorter than that observed in BYLieve trial cohort A (7.3 months, N=127 patients[8]). We posit that this difference is attributable by a much fitter and less heavily pretreated

population in BYLieve: 62% of patients in BYLieve had a performans status (PS)=0, vs 36% in our population; the median number of prior line of therapy was one in BYLieve, vs four in our study. In the primary alpelisib pivotal trial, SOLAR-1, the N=20 patients who received a prior CDK5/6 inhibitor displayed a similar median PFS of 5.5 months under alpelisib and fulvestrant [11]. On the other hand, in the recently reported EMERALD trial a median PFS of 1.9 months was observed in N=165 ER+/HER2- ABC patients treated with fulvestrant single agent as second- or third-line therapy after CDK4/6 inhibitor[12]. In addition to these median PFS data, response rates and 6mCBR reported in our study suggests that alpelisib and fulvestrant is an effective therapy for real-life endocrine treatment-resistant *PIK3CA*-mutant ER+/HER2- ABC patients.

An exploratory analysis of clinicopathological characteristics associated with shorter PFS on alpelisib and fulvestrant retrieved that the most heavily pre-treated patients had shorter PFS, suggesting that the full benefit of alpelisib could be obtained in the earliest lines of therapy for ABC. Patients younger than 60 years of age also experienced significantly shorter median PFS, although we found no difference in baseline characteristics with older patients (data not shown). Lastly, we observed that the 4 patients displaying a C420R *PIK3CA* mutation had a worse outcome. While the small number of patients precludes any definitive conclusion, mutations located in exon 4 and that impact the C2 domain (C420R and N345K) have been previously reported as associated with shorter OS in the METABRIC dataset (12). *In vitro* screening experiments also showed that the C420R *PIK3CA*-mutant EFM192A and JIMT-1 cell lines display limited sensitivity to alpelisib (14). Of note, most centers participating to the EAP did not sequence *PIK3CA* exon 4, explaining the underrepresentation of exon 4 mutations in our cohort: 1.7% (4/233 patients), while C420R and N3345K account for 7.5% of all activating *PIK3CA* mutations (15). Further research is therefore required to explore the potential impact of these exon 4 mutations on alpelisib efficacy.

As part of the EAP, clinicians were requested to document and report treatment-related adverse events in a prospective manner. Interestingly, the frequency of any grade hyperglycemia (53%) appears very similar to that observed in SOLAR-1 (64%) and BYLIEVE (58%). Similarly, the proportion grade 3 or 4 rashes was consistent with that observed in BYLieve[8]. This may be explained by the application of prophylactic antihistamines recommended for the first 8 weeks of alpelisib treatment[13]. Our real-life study however reports a numerically higher rate of alpelisib discontinuation (37%) than in trials (SOLAR-1: 25%; BYLieve: 21%), which could be explained by the different clinical profile of treated patients and less stringent monitoring. Overall, our data suggest that alpelisib toxicity management seems feasible in real life, nothwithstanding the fact that our study was conducted in expert cancer centers, which may have participated to prior alpelisib trials. Yet, regarding the lack of documented significant OS and/or quality of life benefit, as illustrated by the score of 3 on ESMO-magnitude of clinical benefit scale (MCBS), such a tolerance profile makes the actual place of alpelisib in the management of ABC still discussable.

Limitations of this study stem from its retrospective nature, preventing any direct comparison with other studies and trials. Nevertheless, a strength of the EAP is that patients were prospectively registered and no patient was lost to follow-up, allowing robust outcomes analyses. This cohort is, to our knowledge, the

largest real-life dataset reported so far, and confirms the efficacy and manageability of alpelisib and fulvestrant in *PIK3CA*-mutant HR+/HER2- ABC patients.

Declarations

Data Availability Statements

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Any Prior presentations

Preliminary data have been published as an abstract and a poster at the 2021 ASCO Annual Meeting (abstract number: 1064)

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Figures

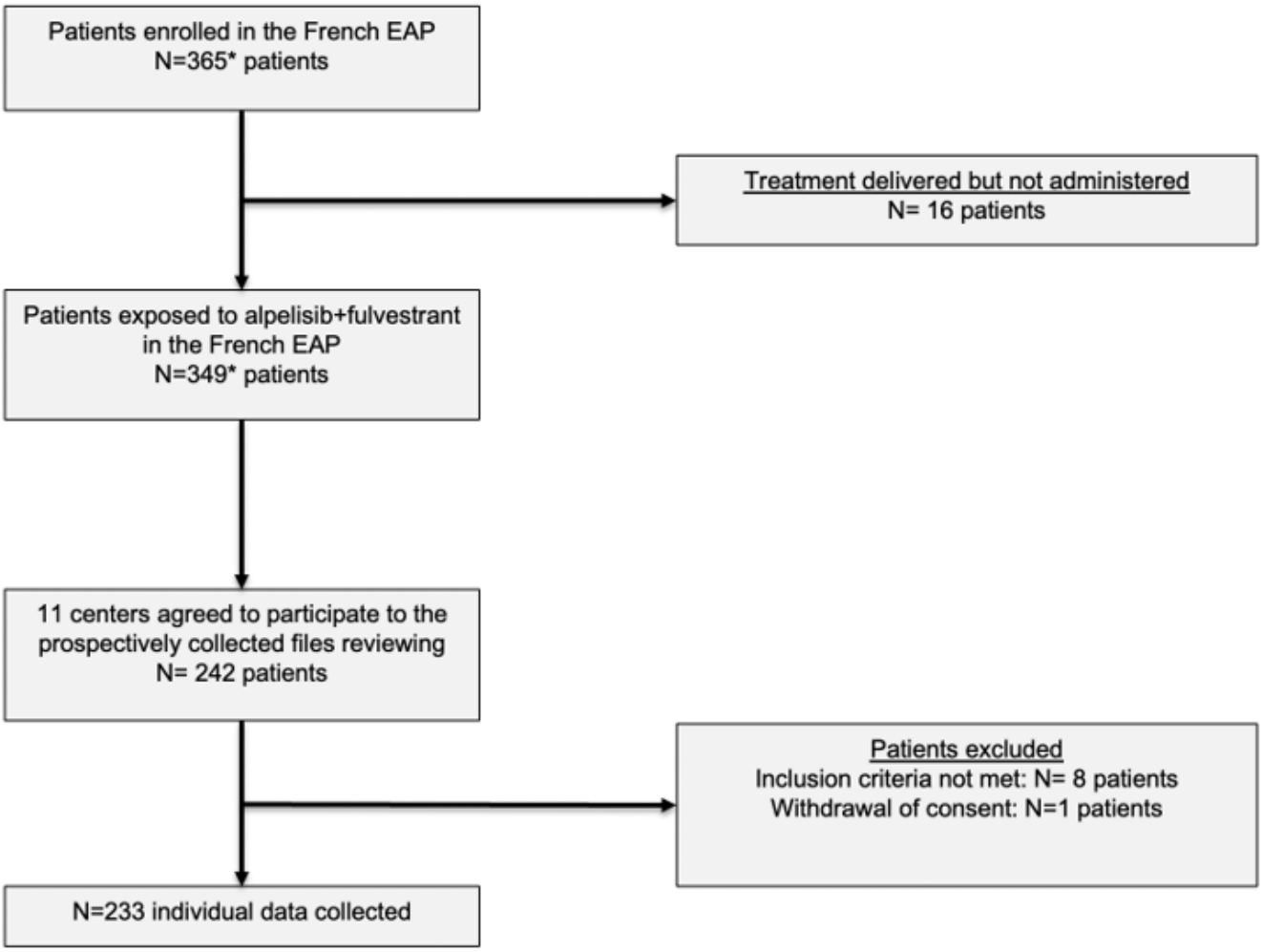

Figure 1

Patients' enrollment

* Source : https://ansm.sante.fr

Rapport de synthèse n°3 ALPELISIB 50 et 200 mg, comprimés pelliculés (BYL 719) Dans le cancer du sein.Période du 03/02/2020 au 02/06/2020 (17/12/2020).

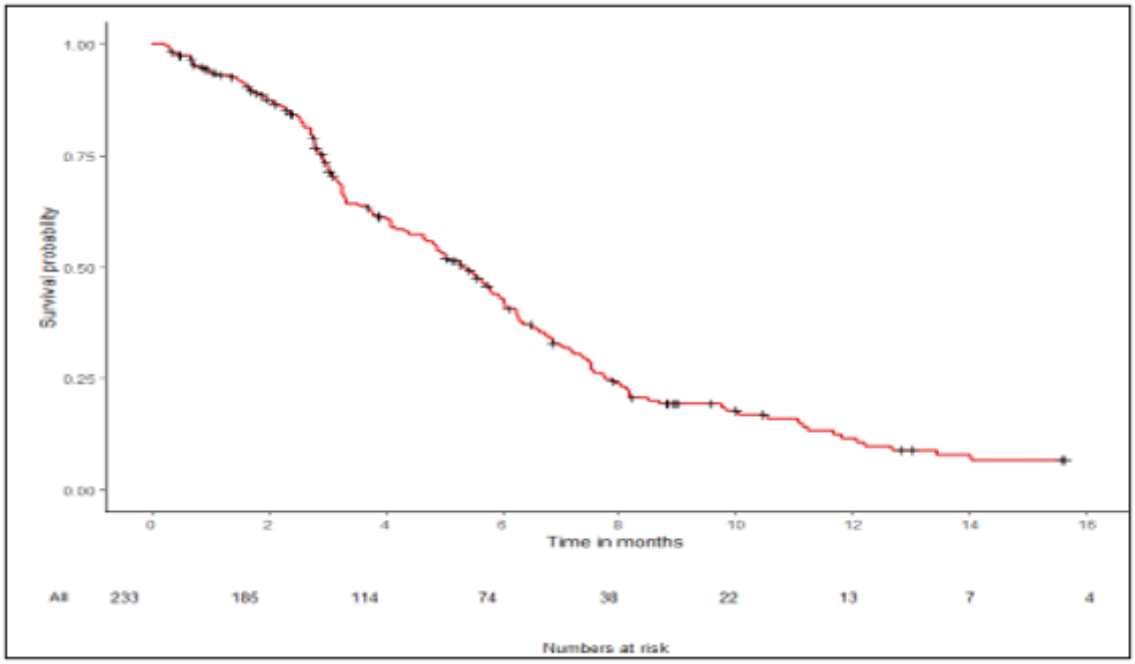

Figure 2

Median progression free survival in patients treated with alpelisib + fulvestrant

Kaplan-Meier plot of progression-free survival per local investigator assessment. Censoring date was date of last adequate tumor assessment before the cutoff date. Censoring is shown with crosses.

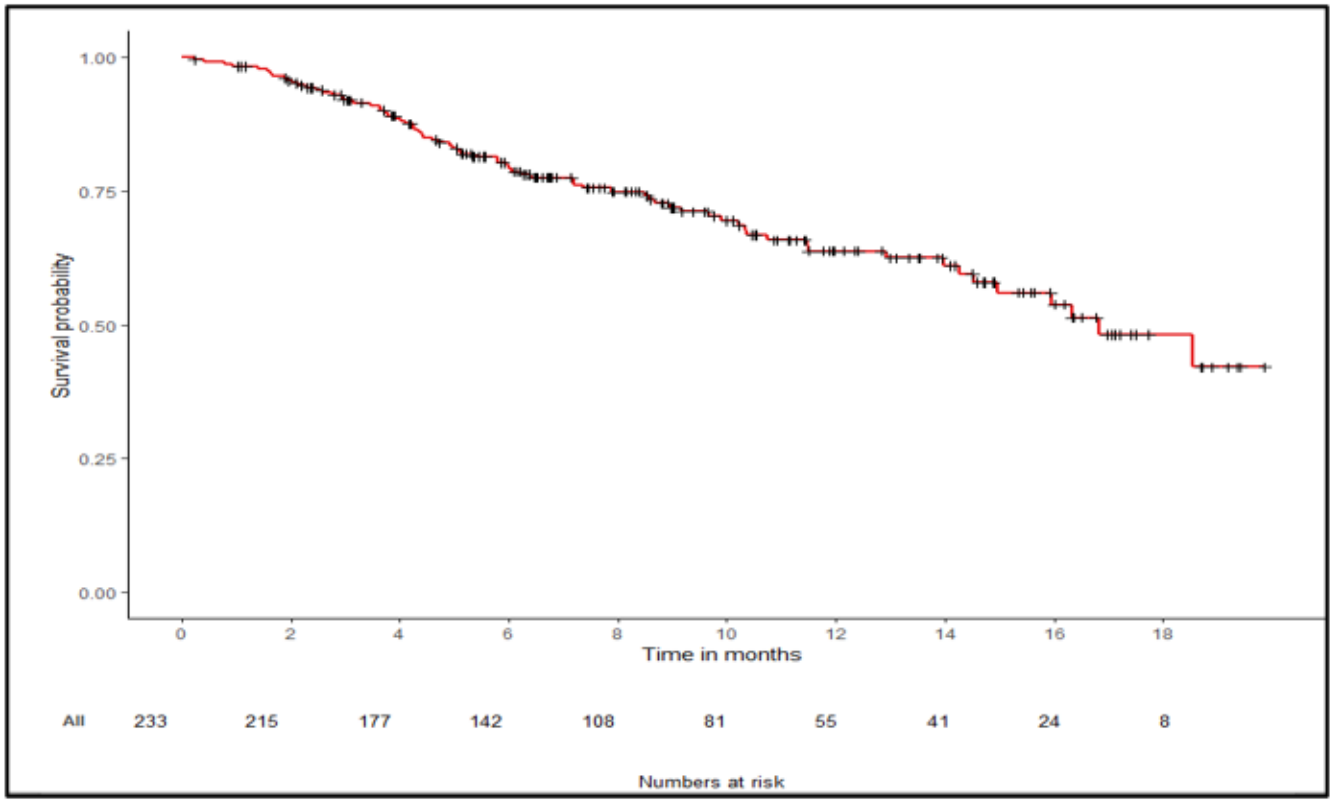

Figure 3

Median overall survival in patients treated with alpelisib + fulvestrant

Kaplan-Meier plot of overall survival per local investigator assessment. Censoring is shown with crosses.

Supplementary Files

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