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Original article

Safety and efficacy of sirolimus combined with endocrine therapy in patients with advanced hormone receptor-positive breast cancer and the exploration of biomarkers

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ABSTRACT

Background: We performed a retrospective study on the efficacy and safety of sirolimus (an mTOR inhibitor) in hormone receptor (HR)-positive advanced breast cancer and searched for biomarkers to predict its efficacy.

Methods: All patients with HR-positive metastatic breast cancer treated with sirolimus plus endocrine therapy between December 2017 and July 2018 at the Cancer Hospital, Chinese Academy of Medical Sciences were consecutively and retrospectively reviewed. Mutations in circulating tumour DNA (ctDNA) were assayed for 1021 tumour-related genes via gene panel target capture-based next-generation sequencing.

Results: Thirty-six patients with metastatic breast cancer treated with sirolimus plus endocrine therapy were included. The progression-free survival (PFS) rates between the sirolimus group and everolimus group were similar, and the median PFS was 4.9 months and 5.5 months, respectively (hazard ratio 1.56, 95% CI 0.86–2.81, $P = 0.142$). The objective response rate in the 36 patients was 19.4%, and the clinical benefit rate was 41.7%. Lipid metabolism disorder was the most common adverse event (69.4%), and 13.9% of patients had stomatitis. Most (94.4%) adverse events were grade 1–2. Twenty patients (55.6%) underwent ctDNA analysis before receiving sirolimus therapy. For patients who received less than 3 lines of chemotherapy, those with PI3K/Akt/mTOR pathway alterations had a better response to sirolimus than those without alterations, with a median PFS of 7.0 months vs 4.3 months (hazard ratio = 0.01, 95% CI 0.00–0.34, $P = 0.010$).

Conclusions: Sirolimus is a potentially effective treatment option for patients with HR-positive advanced breast cancer.

1. Introduction

Hormone receptors (HRs), including oestrogen receptor (ER) and/or progesterone receptor, are expressed in approximately 70% of breast cancers [1]. Endocrine manipulation is the principal treatment for HR-positive breast cancer patients, both in the early and advanced stages of the disease [2]. However, intrinsic and acquired resistance to endocrine therapy is an immense challenge in the clinic [1,3].

The phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway is an important signal transduction pathway related to cell growth and survival [4–7]. The molecular cross-talk between this pathway and the ER may play a role in the resistance to hormone therapy observed in breast cancer

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[8]. Everolimus is currently the most commonly used mTOR inhibitor in cancer treatment strategies, and several phase II or III randomized trials have shown that everolimus can improve the outcomes of patients with HR-positive breast cancer [9,10].

However, a high percentage of patients discontinued everolimus because of adverse events related to poor tolerance, such as stomatitis, rash, fatigue, anorexia, diarrhoea, metabolic disorders with hyperglycaemia, non-infectious pneumonitis and haematologic disorders, and must reduce their dosage or terminate treatment, which not only affects treatment efficacy but also reduces the quality of life of patients, leading to great disappointment in the clinic [11–13].

Sirolimus is another specific mTOR antagonist that targets the PI3K/Akt/mTOR pathway and blocks downstream signalling elements. Sirolimus as well as everolimus was not approved by China Food and Drug Administration in breast cancer. Although sirolimus is now widely used as an immunosuppressant in organ transplantation, it has also been found to possess antiproliferative and angiogenic properties in many preclinical studies, including those on advanced breast cancer [14]. Some early-phase clinical studies have explored its safety in cancer patients [15,16], and its tolerability makes it an appealing alternative to everolimus. However, the efficacy of sirolimus in HR-positive advanced breast cancer is still unclear.

Further research is needed to identify a drug with the same efficacy as everolimus but with better safety. We therefore conducted a retrospective study on the efficacy and safety of sirolimus, off-label use, in HR-positive advanced breast cancer and searched for biomarkers to predict its efficacy.

2. Methods

2.1. Patients and sample collection

All patients with HR-positive metastatic breast cancer treated with sirolimus plus endocrine therapy between December 2017 and July 2018 at the Cancer Hospital, Chinese Academy of Medical Sciences were consecutively and retrospectively reviewed. The patients received sirolimus therapy because of their intolerance to everolimus or the unavailability of everolimus. Patients treated with HER2-targeted therapy or chemotherapy combined with sirolimus were excluded. The following data were collected for each patient enrolled in the present study: initial pathological type, age, receptor status, number of metastatic sites, visceral metastases, prior anticancer therapy history, treatment details, outcome and safety. The study was approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences. All participants provided written informed consent.

2.2. Treatment

The patients were administered with sirolimus at a dose of 2 mg per day in combination with endocrine therapy. Endocrine therapy was chosen by the treating physician according to prior treatments and the patient's clinical characteristics. Efficacy was assessed every two to three months or whenever the patient had symptoms and/or signs that indicated disease progression. The efficacy assessment was based on the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.

Safety assessments were retrospectively collected from patients' medical records and laboratory test results. Adverse events (AEs) were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

2.3. Biomarker analysis

Ten millilitres of peripheral blood was collected from patients who consented to participate in the biomarker analysis. A panel of 1021 genes (Supplementary Table S1) that are frequently mutated in breast cancer and other solid tumours were tested in cell-free DNA. DNA extraction, library preparation, hybrid capture, and sequencing were performed as previously described [17,18].

2.4. Statistical analysis

The chi-square test and Fisher's exact test were used to compare categorical variables. To compare the efficacy of sirolimus with that of everolimus, another mTOR inhibitor that is commonly used in

Table 1
Population characteristics before and after propensity score matching.

Characteristics	Unmatched comparison			Matched comparison		
	Everolimus (N = 120)	Sirolimus (N = 36)	*P*	Everolimus (N = 36)	Sirolimus (N = 36)	*P*
Median age/years (range)	53 (24–84)	53 (29–76)	0.701	54 (34–59)	53 (29–76)	0.709
Pathological type, No. (%)						
Infiltrating ductal carcinoma	112 (93.3%)	33 (91.7)	0.717	35 (97.2)	33 (91.7)	0.614
Infiltrating lobular carcinoma	8 (6.7)	3 (8.3)		1 (2.8)	3 (8.3)	
HER2 status, No. (%)						
Negative	104 (86.7%)	31 (86.1)	1.000	28 (77.8)	31 (86.1)	0.358
Positive	16 (13.3%)	5 (13.9)		8 (22.2)	5 (13.9)	
Number of metastatic sites, No. (%)						
1–2	66 (55.0%)	11 (30.6)	0.010	16 (44.4)	11 (30.6)	0.224
≥3	54 (45.0%)	25 (69.4)		20 (55.6)	25 (69.4)	
Visceral metastases, No. (%)						
Yes	54 (45.0%)	19 (52.8)	0.412	23 (63.9)	19 (52.8)	0.339
No	66 (55.0%)	17 (47.2)		13 (36.1)	17 (47.2)	
Number of chemotherapy lines, No. (%)						
0–2	68 (56.7%)	19 (52.8)	0.680	22 (61.1)	19 (52.8)	0.475
≥3	52 (43.3%)	17 (47.2)		14 (38.9)	17 (47.2)	
Number of endocrine therapy lines, No. (%)						
0–1	22 (18.3%)	7 (19.4)	0.881	13 (36.1)	7 (19.4)	0.097
≥2	98 (81.7%)	29 (80.6)		22 (61.1)	29 (80.6)	
The drug combined with previous used, No. (%)						
Yes	39 (32.5%)	12 (33.3)	0.926	8 (22.2)	12 (33.3)	0.293
No	81 (67.5)	24 (66.7)		28 (77.8)	24 (66.7)	

Abbreviations: HER2, human epidermal growth factor receptor-2.

Table 2
Best overall response (N = 36).

Best response	Number	Percentage (%)
Complete response (CR)	0	0
Partial response (PR)	7	19.4
Stable disease (SD)	16	44.4
Progressive disease (PD)	13	36.1
ORR	7	19.4
CBR	15	41.7

Abbreviations: ORR, objective response rate (ORR=CR + PR); CBR, clinical benefit rate (CBR=CR + PR + SD of 24 weeks or longer).

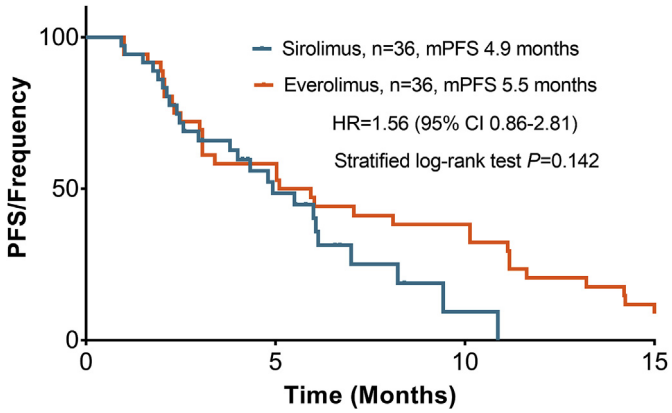

Fig. 1. Kaplan-Meier plot of PFS for HR-positive advanced breast cancer patients treated with sirolimus compared to everolimus. PFS, progression-free survival; HR, hormone receptor.

clinical practice, we retrospectively analysed 120 HR-positive advanced breast cancer patients treated with everolimus plus endocrine therapy at our institution. The data were reported in our previous article [17]. To compare the efficacy and safety of sirolimus with those of everolimus, we used the propensity score method (PSM) to match the important clinical features between the sirolimus group and the everolimus group. The Kaplan-Meier method was used to estimate progression-free survival (PFS), and the log-rank test was used to compare PFS between the treatment groups. Cox multivariate models were performed based on the univariate analysis results. All reported p values in the present study were two-sided, and significance was set at $P < 0.05$. All of the statistical analyses were performed using the Maftools package in R v3.6.0, SPSS version 23.0 (IBM Corporation, Armonk, NY) or GraphPad Prism 7.0 (La Jolla, CA).

3. Results

3.1. Patients

A total of 36 patients with metastatic breast cancer treated with sirolimus plus endocrine therapy were included. The clinicopathological characteristics of all patients at the initiation of sirolimus treatment are shown in Table 1. The median age was 54 years with a range of 34–59 years. Ten patients (27.8%) previously received everolimus before sirolimus treatment. Eight of the 10 patients (80%) discontinued everolimus treatment due to intolerance before the first tumour response evaluation, and two patients (20%) discontinued everolimus treatment due to disease progression. More than half of the patients (58.3%) received sirolimus combined with fulvestrant. Four patients (15.8%) were treated with sirolimus combined with tamoxifen or toremifene, and another 11 patients (30.6%) received aromatase inhibitor (AI) combined with sirolimus.

3.2. Efficacy analysis

Out of all 36 patients, 25 (69.4%) discontinued sirolimus treatment at the time of this report. The median PFS was 4.9 months (95% confidence interval [CI] 3.1–6.8 months). The best overall response data based on RECIST v1.1 are shown in Table 2. Partial response (PR) was observed in 7 patients (19.4%). Sixteen patients (44.4%) achieved stable disease (SD) as optimal efficacy, which was the most frequently observed response. Additionally, 13 patients (36.1%) showed progressive disease (PD) at the first assessment and

Table 3
Adverse events.

	All, No. (%)	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)
Increased cholesterol	25 (69.4)	22 (61.1)	3 (8.3)	0 (0.0)	0 (0.0)
Increased triglycerides	17 (47.2)	17 (47.2)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	10 (27.8)	7 (19.4)	3 (8.3)	0 (0.0)	0 (0.0)
Leukopenia	9 (25.0)	7 (19.4)	2 (5.6)	0 (0.0)	0 (0.0)
Neutropenia	8 (22.2)	6 (16.7)	2 (5.6)	0 (0.0)	0 (0.0)
Increased ALT or AST	8 (22.2)	8 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)
Anaemia	7 (19.4)	7 (19.4)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	5 (13.9)	3 (8.3)	1 (2.8)	1 (2.8)	0 (0.0)
Albuminuria	5 (13.9)	3 (8.3)	2 (5.6)	0 (0.0)	0 (0.0)
Hyperglycaemia	5 (13.9)	5 (13.9)	0 (0.0)	0 (0.0)	0 (0.0)
Cough	3 (8.3)	2 (5.6)	0 (0.0)	1 (2.8)	0 (0.0)
Thrombocytopenia	3 (8.3)	3 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	2 (5.6)	1 (2.8)	1 (2.8)	0 (0.0)	0 (0.0)
Diarrhoea	2 (5.6)	1 (2.8)	1 (2.8)	0 (0.0)	0 (0.0)
Nausea	2 (5.6)	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Anorexia	2 (5.6)	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Weight loss	2 (5.6)	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Hypokalaemia	2 (5.6)	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Increased bilirubin	2 (5.6)	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonitis	2 (5.6)	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral oedema	1 (2.8)	0 (0.0)	1 (2.8)	0 (0.0)	0 (0.0)
Dyspnoea	1 (2.8)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	1 (2.8)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
Agrypnia	1 (2.8)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral nerve toxicity	1 (2.8)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
Palpitation	1 (2.8)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
Anaemia	1 (2.8)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4
Cox regression analyses of the associations between PFS and clinical characteristics.

Variable	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
HER2 status, positive vs negative	1.88 (0.64–5.51)	0.249		
The drug combined with previously used, no vs yes	0.60 (0.22–1.67)	0.325		
Previous everolimus treatment, no vs yes	0.39 (0.13–1.13)	0.083		
Prior endocrine therapy line (as continuous variable)	0.98 (0.67–1.44)	0.919		
The drug combined with, fulvestrant vs others	0.891 (0.38–2.09)	0.791		
Prior chemotherapy line (as continuous variable)	1.62 (1.28–2.05)	<0.001	1.53 (1.16–2.01)	0.002
Number of metastatic sites (as continuous variable)	1.37 (1.14–1.67)	0.001	1.05 (0.80–1.37)	0.736
Sites of metastasis, visceral vs nonvisceral	2.91 (1.12–7.59)	0.028	1.92 (0.63–5.82)	0.252

Abbreviations: PFS: progression-free survival. HER2: human epidermal growth factor receptor 2.

were considered de novo resistant to sirolimus. None of the patients achieved complete response (CR) in the present study. Overall, the objective response rate (ORR=CR + PR) of the 36 patients was 19.4%, and the clinical benefit rate (CBR=CR + PR + SD of 24 weeks or longer) was 41.7%.

We further compare the efficacy of sirolimus with that of everolimus. The PSM based on R v3.6.0 was used to balance the clinical characteristics between the sirolimus treatment group and everolimus treatment group. A total of 36 patients were matched (Table 1) according to prior chemotherapy line (0–2 vs ≥ 3), number of metastatic sites (1–2 vs ≥ 3) and sites of metastasis (visceral vs nonvisceral). The median PFS in the sirolimus treatment group and everolimus treatment group was 4.9 months and 5.5 months, respectively, this difference was nonsignificant (hazard ratio 1.56, 95% CI 0.86–2.81, $P = 0.142$, Fig. 1).

3.3. Safety and tolerability

All 36 patients enrolled in the present study were eligible for safety evaluation. The grades of all major treatment-related AEs are shown in Table 3. Lipid metabolism disorder was the most common AE. There were 25 patients (69.4%) and 17 patients (47.2%) with observed increased cholesterol and increased triglycerides, respectively. Other AEs that occurred in more than 20% of patients included fatigue, leukopenia, neutropenia, and increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels. Five patients (13.9%) had stomatitis, which was lower than the 67% (270/482) previously reported for patients treated with everolimus in BOLERO-2 ($P < 0.001$) [9]. Most (94.4%) of the AEs were grade 1–2, and only two patients (5.6%) experienced grade 3 AEs. One patient experienced grade 3 hyperglycaemia, and another patient experienced grade 3 anaemia. No grade 4 AEs or treatment-related deaths were observed in the present study.

We further analysed the safety and tolerability of the 8 patients who previously used everolimus and discontinued treatment because of AEs. None of the 8 patients had grade 3–4 AEs.

3.4. Risk factors for PFS

Based on univariate Cox regression analysis, patients treated with fewer previous chemotherapy lines (as a continuous variable) had better PFS (hazard ratio = 1.62, 95% CI 1.28–2.05, $P < 0.001$). Similarly, patients with fewer metastatic sites (as a continuous variable, hazard ratio = 1.37, 95% CI 1.14–1.67, $P = 0.001$) and

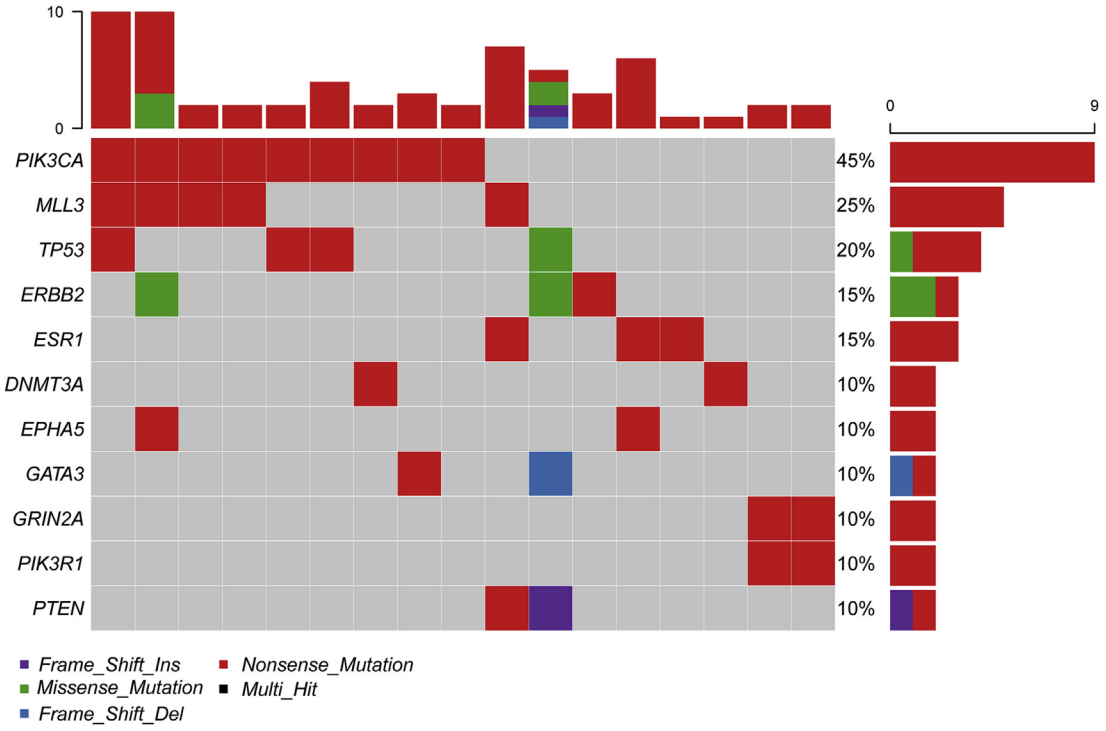

Fig. 2. The spectrum of hotspot mutations in 20 patients who underwent ctDNA analysis. ctDNA, circulating tumour DNA.

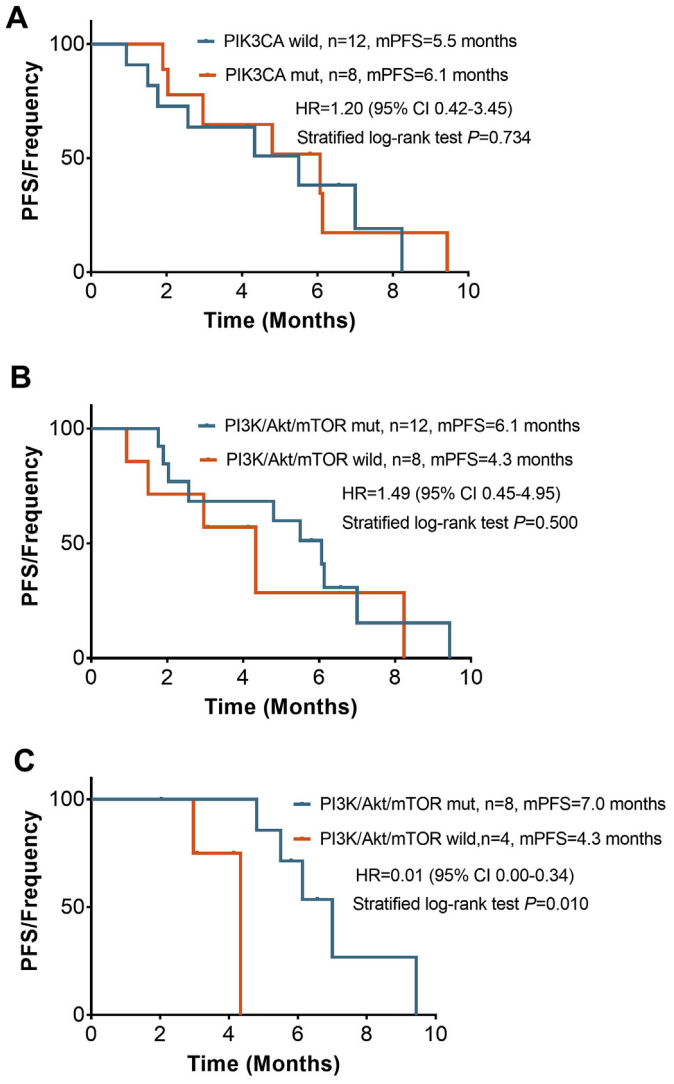

Fig. 3. Kaplan-Meier plot of PFS in all ctDNA analysis patients by PIK3CA mutation (A) and PI3K/Akt/mTOR pathway alteration (B). Kaplan-Meier plot of PFS by PI3K/Akt/mTOR pathway alteration in twelve patients who received less than 3 lines of prior chemotherapy (C). PFS, progression-free survival. ctDNA, circulating tumour DNA.

nonvisceral (vs visceral) metastases had better PFS (hazard ratio 2.91, 95% CI 1.12–7.59, $P < 0.001$). Interestingly, HER2 status, prior use of everoliums, combination with a previously used drug, prior endocrine therapy line and the use of combined drug regimens were not associated with the response to sirolimus in the present study ($P > 0.05$). Multivariate Cox regression analysis indicated that only the previous chemotherapy line was a poor predictor of sirolimus efficacy (hazard ratio = 1.53, 95% CI 1.16–2.01, $P = 0.002$). The univariate and multivariate Cox regression results are shown in Table 4.

3.5. ctDNA analysis

Twenty patients (55.6%) underwent ctDNA analysis before receiving sirolimus therapy. Seventeen (85%) of these patients had more than one somatic genomic alteration. Consistent with previous reports, PIK3CA, TP53, ERBB2 and ESR1 were the most frequently mutated genes (Fig. 2).

PIK3CA mutations were detected in 9 patients (45.0%); the most common mutation point was H1047R (28.6%), followed by D350G (14.3%), E726K (14.3%) and E542K (14.3%). Another four mutations—R93W, N345K, E545K and E453_L456del—were detected in only one patient (7.1%). We also analysed the mutation features at the signalling pathway level, and 13 patients (65.0%) were identified as having PI3K/Akt/mTOR pathway alterations.

PFS was similar between patients with PIK3CA mutations (N = 8) and those with wild-type PIK3CA (N = 12), with a median PFS of 6.1 months and 5.5 months, respectively (hazard ratio = 1.20, 95% CI 0.42–3.45, $P = 0.734$, Fig. 3A). At the pathway level, patients with or without PI3K/AKT/mTOR pathway alterations also had similar PFS rates (N = 12 and 8, respectively), with median PFS values of 6.1 months for the mutant group and 4.3 months for the wild-type group (hazard ratio = 1.49, 95% CI 0.45–4.95, $P = 0.500$, Fig. 3B). Interestingly, for patients who received less than 3 lines of chemotherapy, those with PI3K/Akt/mTOR pathway alterations had a better response to sirolimus than those without alterations (N = 8 and 4, respectively), with a median PFS of 7.0 months vs 4.3 months (hazard ratio = 0.01, 95% CI 0.00–0.34, $P = 0.010$, Fig. 3C).

4. Discussion

Endocrine therapy is the cornerstone of treatment for HR-positive breast cancer patients; however, patients who respond to this therapy will eventually relapse. The identification of means to overcome resistance to endocrine therapies has been a promising research area for several decades. In the present study, patients treated with 2 mg/day sirolimus had a median PFS of 4.9 months, similar to that of everolimus. In addition, most had a high tumour burden and had received multiple anticancer therapy lines prior to sirolimus treatment, with 27.8% of patients previously having received everolimus. Despite this, 19.4% of patients achieved PR as the best response, and the CBR was 41.7%. Further analysis indicated that treatment with a previous chemotherapy line was an important factor impacting the efficacy of sirolimus. Unfortunately, we did not detect the blood concentration of sirolimus, which is a limitation of this study. Thus, the effective blood concentration of sirolimus for breast cancer patients warrants further investigation.

The adverse reactions of sirolimus reported in past studies vary greatly with the disease being treated [19]. In a phase I study of sirolimus in advanced cancer patients, the most common AEs were hyperglycaemia, hyperlipidaemia, lymphopenia, anaemia, and diarrhoea [15]. The AE spectrum of sirolimus in the present study is different from that of everolimus in previous reports [9,20]. Lipid metabolism disorder was the most frequent AE observed in the present study. Other common AEs included fatigue, leukopenia, neutropenia, and increased ALT or AST. However, most (94.4%) of the AEs of sirolimus were grade 1–2 AEs; only 2 patients experienced grade 3 hyperglycaemia and anaemia. The most common AE associated with everolimus is stomatitis. In our study, sirolimus-related stomatitis was observed in 19.3% of patents, which was lower than the 67% reported in BOLERO-2 [9]. The results of the present study indicated that the toxicity of 2 mg/day sirolimus was tolerable for advanced breast cancer patients. However, the AEs may be underestimated in retrospective studies and prospective randomized clinical studies are needed for further validation the result.

Since the development of mTOR inhibitors, considerable effort has been made to identify biomarkers that will allow more precise patient stratification. Although the findings from preclinical studies have suggested that the PIK3CA mutation is a predictor of mTOR inhibition efficacy, the results of clinical studies have been controversial [21]. Nevertheless, few studies have reported associations of PIK3CA mutation and PI3K/Akt/mTOR alterations with sirolimus efficacy. Thus, we explored the relationship between gene mutations in ctDNA and the efficacy of sirolimus and found

that a total of 45% of our patients had PIK3CA mutations, which was similar the findings reported in a previous study [22], but no association between PIK3CA mutations and the response to sirolimus was identified. However, patients who received less than 3 lines of prior chemotherapy and had PI3K/Akt/mTOR alterations were more likely to benefit from sirolimus than patients without pathway alterations. Notably, all of these analyses were retrospective and the cohort size was small, so the conclusions are hypothesis generating. Additional large-scale randomized, prospective clinical trials are needed in the future to investigate the association of PI3K/Akt/mTOR alterations and the efficacy of sirolimus.

5. Conclusions

Overall, sirolimus is a potentially effective treatment option with relatively mild toxicity for patients with HR-positive advanced breast cancer.

Contribution

Conception and design: Fei Ma, Binghe Xu.
Assembly of data: All authors.
Data analysis and interpretation: Zongbi Yi, Binliang Liu, Fei Ma, Binghe Xu.
Manuscript writing: All authors.
Final approval of manuscript: All authors.

Declaration of competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.04.004.

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Ethical approval

The study was approved by the institutional review board of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

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